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(54) Title: NOVEL EXENDIN AGONIST COMPOUNDS		
(57) Abstract		
Novel exendin agonist compounds are provided. These compounds are useful in treating diabetes and conditions which would be benefited by lowering plasma glucose or delaying and/or slowing gastric emptying.		

DESCRIPTION

NOVEL EXENDIN AGONIST COMPOUNDS

Field of the Invention

The present invention relates to novel compounds which have activity as exendin agonists. These compounds are useful in the preparation of medicaments for treatment of Type I and II diabetes, in treatment of disorders which would be benefited by agents which lower plasma glucose levels and in treatment of disorders which would be benefited with agents useful in delaying and/or slowing gastric emptying.

BACKGROUND

The following description includes information that may be useful in understanding 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.

Exendin

The exendins are peptides that are found in the venom of the Gila-monster, a lizard endogenous to Arizona and Northern Mexico. Exendin-3 [SEQ. ID. NO. 1] is present in the venom of



Heloderma horridum, and exendin-4 [SEQ. ID. NO. 2] is present in the venom 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 amino acid sequence of exendin-3 is shown in Figure 1. The amino acid sequence of exendin-4 is shown in Figure 2. 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]NH₂ [SEQ. ID. NO. 3] (Goke, et al., J. Biol. Chem., 268:19650-55, 1993). GLP-1[7-36]NH₂, also known as proglucagon[78-107] or simply "GLP-1" as used most often herein, has an insulinotropic effect, stimulating insulin secretion from pancreatic β -cells; GLP-1 also inhibits glucagon secretion from pancreatic α -cells (Ørsov, et al., Diabetes, 42:658-61, 1993; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). The amino acid sequence of GLP-1 is shown in Figure 3. GLP-1 is reported to inhibit gastric emptying (Willms 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 (Ørsov, 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 has been cloned from a β -cell line (Thorens, Proc. Natl. Acad. Sci. USA 89:8641-45, 1992), hereinafter referred to as the "cloned GLP-1 receptor." Exendin-4 reportedly acts at GLP-1

receptors on insulin-secreting β TCl cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from stomach; the peptide is also reported 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 reportedly found 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).

Based on their insulinotropic activities, the use of exendin-3 and exendin-4 for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed (Eng, U.S. Patent No. 5,424,286).

Agents which serve to delay gastric emptying have found a place in medicine as diagnostic aids in gastro-intestinal radiologic examinations. For example, glucagon is a polypeptide hormone which is produced by the α cells of the pancreatic islets of Langerhans. It is a hyperglycemic agent which mobilizes glucose by activating hepatic glycogenolysis. It can to a lesser extent stimulate the secretion of pancreatic insulin. Glucagon is used in the treatment of insulin-induced hypoglycemia, for example, when administration of glucose intravenously is not possible. However, as glucagon reduces the motility of the gastro-intestinal tract it is also used as a diagnostic aid in gastro-intestinal radiological examinations. Glucagon has also been used in several studies to treat various painful gastro-intestinal disorders associated with spasm.

Daniel, et al. (Br. Med. J., 3:720, 1974) reported quicker symptomatic relief of acute diverticulitis in patients treated with glucagon compared with those who had been treated with analgesics or antispasmodics. A review by Glauser, et al. (J. Am. Coll. Emergency Physns, 8:228, 1979) described relief of acute esophageal food obstruction following glucagon therapy. In another study, glucagon significantly relieved pain and tenderness in 21 patients with biliary tract disease compared with 22 patients treated with placebo (M.J. Stower, et al., Br. J. Surg., 69:591-2, 1982).

Methods for regulating gastrointestinal motility using amylin agonists are described in International Application No. PCT/US94/10225, published March 16, 1995.

Methods for regulating gastrointestinal motility using exendin agonists are described in PCT/US 97/14199 (WO 98/05351).

Methods for reducing food intake using exendin agonists are described in U.S. Patent Application Serial No. 09/003,869, published as PCT/98/00449, entitled "Use of Exendin and Agonists Thereof for the Reduction of Food Intake".

Novel exendin agonist compounds are described in PCT Application Serial No. PCT/US98/16387 filed August 6, 1998, entitled "Novel Exendin Agonist Compounds".



Other novel exendin agonists are described in PCT Application Serial No. PCT/US98/24278, entitled "Novel Exendin Agonist Compounds".

SUMMARY OF THE INVENTION

According to one aspect, the present invention provides novel exendin agonist compounds which exhibit advantageous properties which include effects in slowing gastric emptying and lowering plasma glucose levels.

According to the present invention, provided are compounds of the formula (I) [SEQ. ID. NO. 4]:

Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀,
Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Ala Xaa₁₈, Xaa₂₀,
Xaa₂₁, Xaa₂₂, Xaa₂₃, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, Xaa₂₈-Z₁; wherein

Xaa₁ is His, Arg, Tyr, Ala, Norval, Val
or Norleu;

Xaa₂ is Ser, Gly, Ala or Thr;

Xaa₃ is Ala, Asp or Glu;

Xaa₄ is Ala, Norval, Val, Norleu or Gly;

Xaa₅ is Ala or Thr;

Xaa₆ is Phe, Tyr or naphthylalanine;

Xaa₇ is Thr or Ser;

Xaa₈ is Ala, Ser or Thr;

Xaa₉ is Ala, Norval, Val, Norleu, Asp or Glu;

Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;



Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala or Leu;
Xaa₂₂ is Phe, Tyr or naphthylalanine;
Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;
Xaa₂₆ is Ala or Leu;
Xaa₂₇ is Ala or Lys;
Xaa₂₈ is Ala or Asn;
Z₁ is -OH,
-NH₂,
Gly-Z₂,
Gly Gly-Z₂,
Gly Gly Xaa₃₁-Z₂,
Gly Gly Xaa₃₁ Ser-Z₂,
Gly Gly Xaa₃₁ Ser Ser-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Ser -Z₂;
wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently
Pro, homoproline, 3Hyp, 4Hyp, thioproline,
N-alkylglycine, N-alkylpentylglycine or
N-alkylalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈,
Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉,
Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇ and Xaa₂₈ are Ala; and
provided also that, if Xaa₁ is His, Arg or Tyr, then at least
one of Xaa₃, Xaa₄ and Xaa₅ is Ala.

Also included within the scope of the present invention are
pharmaceutically acceptable salts of the compounds of formula
(I) and pharmaceutical compositions including said compounds and
salts thereof.

Also within the scope of the present invention are narrower
genera of peptide compounds of various lengths, for example,
genera of compounds which do not include peptides having a
length of 28, 29 or 30 amino acid residues, respectively.

Additionally, the present invention includes narrower
genera of peptide compounds having particular amino acid
sequences, for example, compounds of formula [I] [SEQ. ID.
NO. 111]:

Xaa₁ Xaa₂ Xaa₃ Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃
Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀ Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅
Xaa₂₆ Xaa₂₇ Xaa₂₈-Z₁; wherein



Xaa₁ is His or Ala;
Xaa₂ is Gly or Ala;
Xaa₃ is Ala, Asp or Glu;
Xaa₄ is Ala or Gly;
Xaa₅ is Ala or Thr;
Xaa₆ is Phe or naphthylalanine;
Xaa₇ is Thr or Ser;
Xaa₈ is Ala, Ser or Thr;
Xaa₉ is Ala, Asp or Glu;
Xaa₁₀ is Ala, Leu or pentylglycine;
Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Met or pentylglycine;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala or Leu;
Xaa₂₂ is Phe or naphthylalanine;
Xaa₂₃ is Ile, Val or tert-butylglycine;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp or Phe;
Xaa₂₆ is Ala or Leu;
Xaa₂₇ is Ala or Lys;
Xaa₂₈ is Ala or Asn;
Z₁ is -OH,
-NH₂,

Gly-Z₂,
 Gly Gly-Z₂,
 Gly Gly Xaa₃₁-Z₂,
 Gly Gly Xaa₃₁ Ser-Z₂,
 Gly Gly Xaa₃₁ Ser Ser-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈
 Ser-Z₂;

Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently Pro,
 homoproline, thioproline, or
 N-methylalalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₅, Xaa₆, Xaa₈, Xaa₁₀,
 Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁,
 Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₂₈ are Ala; and provided that, if
 Xaa₁ is His, Arg or Tyr, then at least one of Xaa₃, Xaa₄, and Xaa₅
 is Ala; and pharmaceutically acceptable salts thereof.

Also provided are peptide compounds of the formula (II)

[SEQ. ID. NO. 94]:

Xaa₁ Xaa₂ Xaa₃ Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀
 Xaa₁₁ Xaa₁₂ Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀
 Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅ Xaa₂₆ X₁-Z₁; wherein
 Xaa₁ is His, Arg, Tyr, Ala, Norval, Val, Norleu or 4-
 imidazopropionyl;
 Xaa₂ is Ser, Gly, Ala or Thr;



Xaa₃ is Ala, Asp. or Glu;
 Xaa₄ is Ala, Norval, Val, Norleu or Gly;
 Xaa₅ is Ala or Thr;
 Xaa₆ is Phe, Tyr or naphthylalanine;
 Xaa₇ is Thr or Ser;
 Xaa₈ is Ala, Ser or Thr;
 Xaa₉ is Ala, Norval, Val, Norleu, Asp or Glu;
 Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;
 Xaa₁₁ is Ala or Ser;
 Xaa₁₂ is Ala or Lys;
 Xaa₁₃ is Ala or Gln;
 Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;
 Xaa₁₅ is Ala or Glu;
 Xaa₁₆ is Ala or Glu;
 Xaa₁₇ is Ala or Glu;
 Xaa₁₈ is Ala or Val;
 Xaa₂₀ is Ala or Arg;
 Xaa₂₁ is Ala, Leu or Lys-NH⁺-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalyleyl-alkanoyl;
 Xaa₂₂ is Phe, Tyr or naphthylalanine;
 Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
 Xaa₂₄ is Ala, Glu or Asp;
 Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;
 Xaa₂₆ is Ala or Leu;
 X₁ is Lys Asn, Asn Lys, Lys-NH⁺-R Asn, Asn Lys-NH⁺-R, Lys-NH⁺-R
 Ala, Ala Lys-NH⁺-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylalkanoyl
 Z₁ is -OH,
 -NH₂,



Gly-Z₂,
 Gly Gly-Z₂,
 Gly Gly Xaa₃₁-Z₂,
 Gly Gly Xaa₃₁ Ser-Z₂,
 Gly Gly Xaa₃₁ Ser Ser-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Ser-Z₂;

wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently
 selected from the group consisting of Pro,
 homoproline, 3Hyp, 4Hyp, thioproline,
 N-alkylglycine, N-alkylpentylglycine and
 N-alkylalanine; and
 Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈,
 Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉,
 Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, are Ala; and provided also that,
 if Xaa₁ is His, Arg, Tyr, or 4-imidazopropionyl then at least
 one of Xaa₃, Xaa₄, and Xaa₅ is Ala.

Also within the scope of the present invention are
 pharmaceutically acceptable salts of the compounds of formula
 (II) and pharmaceutical compositions including said compounds
 and salts thereof.

Preferred compounds of formula (II) include those wherein
 Xaa₁ is His, Ala, Norval or 4-imidazopropionyl. Preferably,



Xaa₁ is His, or 4-imidazopropionyl or Ala, more preferably His or 4-imidazopropionyl.

Preferred compounds of formula (II) include those wherein Xaa₂ is Gly.

Preferred compounds of formula (II) include those wherein Xaa₄ is Ala.

Preferred compounds of formula (II) include those wherein Xaa₉ is Ala.

Preferred compounds of formula (II) include those wherein Xaa₁₄ is Leu, pentylglycine or Met.

Preferred compounds of formula (II) include those wherein Xaa₂₅ is Trp or Phe.

Preferred compounds of formula (II) include those wherein Xaa₆ is Ala, Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.

Preferred compounds of formula (II) include those wherein Z₁ is -NH₂.

Preferred compounds of formula (II) include those wherein Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

Preferred compounds of formula (II) include those wherein Xaa₃₉ is Ser or Tyr, preferably Ser.

Preferred compounds of formula (II) include those wherein Z₂ is -NH₂.

Preferred compounds of formula (II) include those 42 wherein Z₁ is -NH₂.

Preferred compounds of formula (II) include those wherein Xaa₂₁ is Lys-NH^F-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

Preferred compounds of formula (II) include those wherein X_1 is Lys Asn, Lys-NH^R-R Asn, or Lys-NH^R-R Ala where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

Preferred compounds of formula (II) include those having an amino acid sequence selected from SEQ. ID. NOS. 95-110.

Definitions

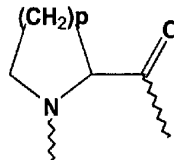
In accordance with the present invention and as used herein, the following terms are defined to have the following meanings, unless explicitly stated otherwise.

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-aminoisobutyric 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, pipercolic acid and thioproline. 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.

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.

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 substituent; or (2)



wherein p is 1, 2 or 3 representing the azetidinedicarboxylic acid, proline or pipercolic acid residues, respectively.

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.

"Pharmaceutically acceptable salt" includes salts of the compounds of the present invention 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 of the present invention are useful in both free base and salt form, with both forms being considered as being within the scope of the present invention.

In addition, the following abbreviations stand for the following:

- "ACN" or "CH₃CN" 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 hexafluorophosphate.
- "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

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the amino acid sequence for exendin-3 [SEQ. ID. NO. 1].

Figure 2 depicts the amino acid sequence for exendin-4 [SEQ. ID. NO. 2].

Figure 3 depicts the amino acid sequence for GLP-1[7-36]NH₂ (GLP-1) [SEQ. ID. NO. 3].

Figure 4 depicts the amino acid sequences for certain compounds of the present invention, Compounds 1-89 [SEQ. ID. NOS. 5 to 93].

Figure 5 depicts the effect on lowering blood glucose of various concentrations of Compound 1 [SEQ. ID. NO. 5].

Figure 6 depicts a comparison of effects on gastric emptying of various concentrations of Compound 1 [SEQ. ID. NO. 5].

Figure 7 depicts the amino acid sequences for certain compounds of the present invention, Compound Nos. 90-105 [SEQ. ID. NOS. 95-110].

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, provided are compounds of the formula (I) [SEQ. ID. NO. 4]:

Xaa₁ Xaa₂ Xaa₃ Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀
Xaa₁₁ Xaa₁₂ Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀
Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅ Xaa₂₆ Xaa₂₇ Xaa₂₈-Z₁; wherein
Xaa₁ is His, Arg, Tyr, Ala, Norval, Val
or Norleu;
Xaa₂ is Ser, Gly, Ala or Thr;
Xaa₃ is Ala, Asp or Glu;
Xaa₄ is Ala, Norval, Val, Norleu or Gly;
Xaa₅ is Ala or Thr;
Xaa₆ is Phe, Tyr or naphthylalanine;
Xaa₇ is Thr or Ser;
Xaa₈ is Ala, Ser or Thr;
Xaa₉ is Ala, Norval, Val, Norleu, Asp or Glu;
Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;
Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala, Leu or Lys-NH^R where R is Lys, Arg, C₁-C₁₀
straight chain or branched alkanoyl or cycloalyleyl-alkanoyl;
Xaa₂₂ is Phe, Tyr or naphthylalanine;
Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa₂₆ is Ala or Leu;

Xaa₂₇ is Ala or Lys;

Xaa₂₈ is Ala or Asn;

Z₁ is -OH,

-NH₂,

Gly-Z₂,

Gly Gly-Z₂,

Gly Gly Xaa₃₁-Z₂,

Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Xaa₃₉-Z₂;

wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇ and Xaa₂₈ are Ala; and provided also that, if Xaa₁ is His, Arg or Tyr, then at least one of Xaa₃, Xaa₄ and Xaa₉ is Ala. Also within the scope of the present invention are pharmaceutically acceptable salts of formula (I) and pharmaceutical compositions including said compounds and salts thereof.

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 of formula (I) include those identified in Examples 1-89 ("Compounds 1-89," respectively) [SEQ. ID. NOS. 5 to 93], as well as those corresponding compounds identified in Examples 104 and 105.

Preferred such exendin agonist compounds include those wherein Xaa₁ is His, Ala or Norval. More preferably Xaa₁ is His or Ala. Most preferably Xaa₁ is His.

Preferred are those compounds of formula (I) wherein Xaa₂ is Gly.

Preferred are those compounds of formula (I) wherein Xaa₃ is Ala.

Preferred are those compounds of formula (I) wherein Xaa₄ is Ala.

Preferred are those compounds of formula (I) wherein Xaa₅ is Ala.

Preferred are those compounds of formula (I) wherein Xaa₁₄ is Leu, pentylglycine or Met.

Preferred compounds of formula (I) are those wherein Xaa₂₅ is Trp or Phe.

Preferred compounds of formula (I) are those where Xaa₆ is Ala, Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.

Preferred are compounds of formula (I) wherein Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently selected from Pro, homoproline, thioproline and N-alkylalanine.

Preferably Z₁ is -NH₂.

Preferably Z_2 is $-NH_2$.

According to one aspect, preferred are compounds of formula (I) wherein Xaa_1 is Ala, His or Tyr, more preferably Ala or His; Xaa_2 is Ala or Gly; Xaa_6 is Phe or naphthylalanine; Xaa_{14} is Ala, 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; and Xaa_{39} is Ser or Tyr, more preferably Ser. More preferably Z_1 is $-NH_2$.

According to an especially preferred aspect, especially preferred compounds include those of formula (I) wherein: Xaa_1 is His or Ala; Xaa_2 is Gly or Ala; Xaa_3 is Ala, Asp or Glu; Xaa_4 is Ala or Gly; Xaa_5 is Ala or Thr; Xaa_6 is Phe or naphthylalanine; Xaa_7 is Thr or Ser; Xaa_8 is Ala, Ser or Thr; Xaa_9 is Ala, 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, Met 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 or Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38} Xaa_{39} - 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} ,

Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₂₈ are Ala; and provided also that, if Xaa₁ is His, Arg or Tyr, then at least one of Xaa₃, Xaa₄, and Xaa₅ is Ala. Especially preferred compounds of formula (I) include those having the amino acid sequence of SEQ. ID. NOS. 5-93

According to an especially preferred aspect, provided are compounds of formula (I) where Xaa₁ is Ala, Leu, Ile, Val or pentylglycine, more preferably Leu or pentylglycine, and Xaa₂₅ is Ala, Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will be less susceptible to oxidative degradation, both *in vitro* and *in vivo*, as well as during synthesis of the compound.

Also within the scope of the present invention are narrower genera of peptide compounds of various lengths, for example, genera of compounds which do not include peptides having a length of 28, 29 or 30 amino acid residues, respectively.

Additionally, the present invention includes narrower genera of peptide compounds having particular amino acid sequences, for example, compounds of formula [I] [SEQ. ID. NO. 111]:

Xaa₁, Xaa₂, Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₇, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Ala, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₂, Xaa₂₃, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, Xaa₂₈-Z₁; wherein

Xaa₁ is His or Ala;

Xaa₂ is Gly or Ala;

Xaa₃ is Ala, Asp or Glu;

Xaa₄ is Ala or Gly;



Xaa₅ is Ala or Thr;
Xaa₆ is Phe or naphthylalanine;
Xaa₇ is Thr or Ser;
Xaa₈ is Ala, Ser or Thr;
Xaa₉ is Ala, Asp or Glu;
Xaa₁₀ is Ala, Leu or pentylglycine;
Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Met or pentylglycine;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala or Leu;
Xaa₂₂ is Phe or naphthylalanine;
Xaa₂₃ is Ile, Val or tert-butylglycine;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp or Phe;
Xaa₂₆ is Ala or Leu;
Xaa₂₇ is Ala or Lys;
Xaa₂₈ is Ala or Asn;
Z₁ is -OH,
-NH₂,
Gly-Z₂,
Gly Gly-Z₂,
Gly Gly Xaa₃₁-Z₂,
Gly Gly Xaa₃₁ Ser-Z₂,

Xaa₇ is Thr or Ser;
Xaa₈ is Ala, Ser or Thr;
Xaa₉ is Ala, Norval, Val, Norleu, Asp or Glu;
Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;
Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala, Leu or Lys-NH^ε-R where R is Lys, Arg, C^ε-10 straight chain or branched alkanoyl or cycloalyleyl-alkanoyl;
Xaa₂₂ is Phe, Tyr or naphthylalanine;
Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;
Xaa₂₆ is Ala or Leu;
X₁ is Lys Asn, Asn Lys, Lys-NH^ε-R Asn, Asn Lys-NH^ε-R, Lys-NH^ε-R Ala, Ala Lys-NH^ε-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylalkanoyl
Z₁ is -OH,
-NH₂,
Gly-Z₂,
Gly Gly-Z₂,
Gly Gly Xaa₃₁-Z₂,
Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Xaa₃₉-Z₂;
wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine and N-alkylalanine; and
Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, are Ala; and provided also that, if Xaa₁ is His, Arg, Tyr, or 4-imidazopropionyl then at least one of Xaa₃, Xaa₄ and Xaa₉ is Ala.

Also within the scope of the present invention are pharmaceutically acceptable salts of the compounds of formula (II) and pharmaceutical compositions including said compounds and salts thereof.

Preferred compounds of formula (II) include those wherein Xaa₁ is His, Ala, Norval or 4-imidazopropionyl. Preferably, Xaa₁ is His, or 4-imidazopropionyl or Ala, more preferably His or 4-imidazopropionyl.

Preferred compounds of formula (II) include those wherein Xaa₂ is Gly.

Preferred compounds of formula (II) include those wherein Xaa₄ is Ala.

Preferred compounds of formula (II) include those wherein Xaa₉ is Ala.

Preferred compounds of formula (II) include those wherein Xaa₁₄ is Leu, pentylglycine or Met.

Preferred compounds of formula (II) include those wherein Xaa₂₅ is Trp or Phe.

Preferred compounds of formula (II) include those wherein Xaa₆ is Ala, Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.

Preferred compounds of formula (II) include those wherein Z₁ is -NH₂.

Preferred compounds of formula (II) include those wherein Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

Preferred compounds of formula (II) include those wherein Xaa₃₉ is Ser or Tyr, preferably Ser.

Preferred compounds of formula (II) include those wherein Z₂ is -NH₂.

Preferred compounds of formula (II) include those 42 wherein Z₁ is -NH₂.

Preferred compounds of formula (II) include those wherein Xaa₂₁ is Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

Preferred compounds of formula (II) include those wherein X₁ is Lys Asn, Lys-NH^e-R Asn, or Lys-NH^e-R Ala where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.

Preferred compounds of formula (II) include those having an amino acid sequence selected from SEQ. ID. NOS. 95-110.

The compounds referenced above form salts with various inorganic and organic acids and bases. Such salts include salts prepared with organic and inorganic acids, for example, HCl, HBr, H₂SO₄, H₃PO₄, trifluoroacetic acid, acetic acid, formic acid, methanesulfonic acid, toluenesulfonic acid, maleic acid, fumaric acid and camphorsulfonic acid. Salts prepared with bases include ammonium salts, alkali metal salts, e.g. sodium and potassium salts, and alkali earth salts, e.g. calcium and magnesium salts. Acetate, hydrochloride, and trifluoroacetate salts are preferred. The salts may be formed by conventional means, as by 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.

Utility

The compounds described above are useful in view of their pharmacological properties. In particular, the compounds of the invention are exendin agonists, and possess activity as agents to regulate gastric motility and to slow gastric emptying, as evidenced by the ability to reduce post-prandial glucose levels in mammals.

The compounds of the present invention are useful in in vitro and in vivo scientific methods for investigation of exendins and exendin agonists for example in methods such as those described in Examples A-E below.

Preparation of Compounds

The compounds of the present invention 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.

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).

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).

Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters Delta Prep 3000 system. A C4, C8 or C18 preparative column (10 μ , 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 (5 μ , 0.46 x 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH₃CN) 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 and on a VG-Trio machine.

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.

Formulation and Administration

Compounds of the invention are useful in view of their exendin-like effects, and may conveniently be provided in the form of formulations suitable for parenteral (including intravenous, intramuscular and subcutaneous) or nasal, buccal or oral administration. In some cases, it will be convenient to provide an exendin agonist and another anti-gastric-emptying agent, such as glucagon, an amylin, or an amylin agonist, in a single composition or solution for administration together. In other cases, it may be more advantageous to administer another anti-emptying agent separately from said exendin agonist. In yet other cases, it may be beneficial to provide an exendin agonist either co-formulated or separately with other glucose

lowering agents such as insulin. 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).

Compounds useful in the invention can be provided as parenteral compositions for injection or infusion. 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 5.6 to 7.4. 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 other form of delivery.

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.

The claimed compounds 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.

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.

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, or transmucosally.

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).

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.

For use by the physician, the compounds will be provided in dosage unit form containing an amount of an exendin agonist,

with or without another anti-emptying agent. Therapeutically effective amounts of an exendin agonist for use in the control of gastric emptying and in conditions in which gastric emptying is beneficially slowed or regulated are those that decrease post-prandial blood glucose levels, preferably to no more than about 8 or 9 mM or such that blood glucose levels are reduced as desired. In diabetic or glucose intolerant individuals, plasma glucose levels are higher than in normal individuals. In such individuals, beneficial reduction or "smoothing" of post-prandial blood glucose levels, may be obtained. As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the patient's physical condition, the blood sugar level or level of inhibition of gastric emptying to be obtained, and other factors.

Such pharmaceutical compositions are useful in causing gastric hypomotility in a subject and may be used as well in other disorders where gastric motility is beneficially reduced.

The effective daily anti-emptying dose of the compounds will typically be in the range of 0.001 or 0.005 to about 5 mg/day, preferably about 0.01 or 0.05 to 2 mg/day and more preferably about 0.05 or 0.1 to 1 mg/day, for a 70 kg patient. 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. Administration should begin at the first sign of symptoms or shortly after diagnosis of diabetes mellitus. Administration may be by injection, preferably subcutaneous or intramuscular. Administration may also be by other routes, for example, by oral, buccal or nasal

routes, however dosages should be increased about 5-10 fold, over injection doses.

Generally, in treating or preventing elevated, inappropriate, or undesired post-prandial blood glucose levels, the compounds of this invention may be administered to patients in need of such treatment in a dosage ranges similar to those given above, however, the compounds are administered more frequently, for example, one, two, or three times a day.

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 patients, 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.

To assist in understanding the present invention the following Examples are included which describe the results of a series of experiments. 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 1Preparation of Compound 1

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-NH₂ [SEQ. ID.
NO. 5]

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%.

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

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 2

Preparation of Compound 2

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-NH₂ [SEQ. ID.
NO. 6]

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 Compound 1. 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 3Preparation of Compound 3

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-NH₂ [SEQ. ID. NO.
7]

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 Compound 1. 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 4Preparation of Compound 4

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-NH₂ [SEQ. ID. NO.
8]

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 Compound 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 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 5

Preparation of Compound 5

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-NH₂ [SEQ. ID. NO.
9]

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. 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 6Preparation of Compound 6

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-NH₂ [SEQ. ID. NO.
10]

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. 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 7Preparation of Compound 7

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-NH₂ [SEQ. ID.
NO. 11]

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. 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 8

Preparation of Compound 8

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-NH₂ [SEQ. ID.
NO. 12]

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. 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 9Preparation of Compound 9

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-NH₂ [SEQ. ID.
NO. 13]

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. 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 10Preparation of Compound 10

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-NH₂ [SEQ. ID.
NO. 14]

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. 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 11

Preparation of Compound 11

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-NH₂ [SEQ. ID. NO.
15]

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. 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 12Preparation of Compound 12

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-NH₂ [SEQ. ID.
NO. 16]

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. 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 13Preparation of Compound 13

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-NH₂ [SEQ. ID.
NO. 17]

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. 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 14

Preparation of Compound 14

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-NH₂ [SEQ. ID.
NO. 18]

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. 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 15Preparation of Compound 15

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-NH₂ [SEQ. ID.
NO. 19]

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. 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 16Preparation of Compound 16

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-NH₂ [SEQ.
ID. NO. 20]

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. 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 17

Preparation of Compound 17

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-NH₂ [SEQ.
ID. NO. 21]

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. 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 18Preparation of Compound 18

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-NH₂ [SEQ. ID.
NO. 22]

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. 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 19Preparation of Compound 19

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-NH₂ [SEQ. ID.
NO. 23]

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. 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 20

Preparation of Compound 20

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-NH₂ [SEQ. ID.
NO. 24]

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. 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 21Preparation of Compound 21

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-NH₂ [SEQ. ID.
NO. 25]

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. 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 22Preparation of Compound 22

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-NH₂ [SEQ. ID.
NO. 26]

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 Compound 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 3170.6.

EXAMPLE 23

Preparation of Compound 23

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-NH₂ [SEQ. ID.
NO. 27]

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. 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 24Preparation of Compound 24

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-NH₂ [SEQ. ID.
NO. 28]

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. 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 25Preparation of Compound 25

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-NH₂ [SEQ. ID.
NO. 29]

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. 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 26

Preparation of Compound 26

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-NH₂ [SEQ. ID.
NO. 30]

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. 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 27Preparation of Compound 27

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-NH₂ [SEQ. ID.
NO. 31]

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. 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 28Preparation of Compound 28

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-NH₂
[SEQ. ID. NO. 32]

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. 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 29

Preparation of Compound 29

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-NH₂
[SEQ. ID. NO. 33]

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. 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 30Preparation of Compound 30

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-NH₂ [SEQ. ID.
NO. 34]

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. 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 31Preparation of Compound 31

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-NH₂ [SEQ. ID.
NO. 35]

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. 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 32

Preparation of Compound 32

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-NH₂ [SEQ. ID.
NO. 36]

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. 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 33Preparation of Compound 33

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-NH₂ [SEQ. ID.
NO. 37]

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. 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 34Preparation of Compound 34

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-NH₂ [SEQ. ID.
NO. 38]

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. 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 35

Preparation of Compound 35

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-NH₂ [SEQ. ID.
NO. 39]

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. 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 36Preparation of Compound 36

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-NH₂ [SEQ. ID.
NO. 40]

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. 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 37Preparation of Compound 37

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-NH₂ [SEQ. ID.
NO. 41]

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. 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 38

Preparation of Compound 38

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-NH₂
[SEQ. ID. NO. 42]

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. 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 39Preparation of Compound 39

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-NH₂
[SEQ. ID. NO. 43]

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. 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 40Preparation of Compound 40

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-NH₂ [SEQ. ID. NO.
44]

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. 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 41

Preparation of Compound 41

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-NH₂ [SEQ. ID. NO.
45]

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. 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 42Preparation of Compound 42

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-NH₂ [SEQ. ID.
NO. 46]

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. 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 43Preparation of Compound 43

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-NH₂ [SEQ. ID.
NO. 47]

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. 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 44

Preparation of Compound 44

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-NH₂ [SEQ. ID. NO.
48]

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. 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 45Preparation of Compound 45

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-NH₂ [SEQ. ID.
NO. 49]

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. 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 46Preparation of Compound 46

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-NH₂ [SEQ. ID. NO.
50]

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. 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 47

Preparation of Compound 47

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-NH₂ [SEQ. ID. NO.
51]

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. 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 48Preparation of Compound 48

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-NH₂ [SEQ. ID. NO.
52]

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. 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 49Preparation of Compound 49

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-NH₂ [SEQ. ID.
NO. 53]

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. 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 50

Preparation of Compound 50

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-NH₂ [SEQ. ID.
NO. 54]

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. 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 51Preparation of Compound 51

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-NH₂ [SEQ. ID. NO.
55]

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. 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 52Preparation of Compound 52

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-NH₂
[SEQ. ID. NO. 56]

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. 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 53

Preparation of Compound 53

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-NH₂
[SEQ. ID. NO. 57]

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. 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 54

Preparation of Compound 54

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-NH₂ [SEQ. ID. NO.
58]

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. 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 55

Preparation of Compound 55

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-NH₂ [SEQ. ID.
NO. 59]

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. 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 56

Preparation of Compound 56

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-NH₂ [SEQ.
ID. NO. 60]

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. 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 57

Preparation of Compound 57

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-NH₂ [SEQ.
ID. NO. 61]

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. 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 58

Preparation of Compound 58

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-NH₂ [SEQ. ID. NO.
62]

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. 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 59

Preparation of Compound 59

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-NH₂ [SEQ. ID. NO.
63]

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. 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 60

Preparation of Compound 60

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-NH₂ [SEQ. ID.
NO. 64]

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. 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 61

Preparation of Compound 61

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-NH₂ [SEQ. ID.
NO. 65]

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. 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 62

Preparation of Compound 62

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-NH₂ [SEQ. ID.
NO. 66]

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. 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 63

Preparation of Compound 63

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-NH₂ [SEQ. ID.
NO. 67]

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. 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 64

Preparation of Compound 64

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-NH₂ [SEQ. ID.
NO. 68]

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. 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 65

Preparation of Compound 65

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-NH₂ [SEQ. ID.
NO. 69]

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. 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 66

Preparation of Compound 66

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-NH₂ [SEQ. ID.
NO. 70]

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. 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 67

Preparation of Compound 67

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-NH₂ [SEQ. ID.
NO. 71]

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. 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 68

Preparation of Compound 68

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-NH₂ [SEQ. ID. NO. 72]

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. 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 69

Preparation of Compound 69

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-NH₂ [SEQ. ID. NO. 73]

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. 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 70

Preparation of Compound 70

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-NH₂ [SEQ. ID. NO. 74]

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. 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 71

Preparation of Compound 71

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-NH₂ [SEQ. ID. NO. 75]

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. 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 72

Preparation of Compound 72

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-NH₂ [SEQ. ID. NO. 76]

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. 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 73

Preparation of Compound 73

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-NH₂ [SEQ. ID. NO. 77]

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. 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 74

Preparation of Compound 74

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-NH₂ [SEQ. ID. NO. 78]

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. 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 75

Preparation of Compound 75

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-NH₂ [SEQ. ID. NO. 79]

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. 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 76

Preparation of Compound 76

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-NH₂ [SEQ. ID. NO. 80]

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. 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 77

Preparation of Compound 77

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-
NH₂ [SEQ. ID. NO. 81]

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. 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 78

Preparation of Compound 78

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-
NH₂ [SEQ. ID. NO. 82]

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. 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 79

Preparation of Compound 79

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-NH₂
[SEQ. ID. NO. 83]

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. 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 80

Preparation of Compound 80

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-NH₂
[SEQ. ID. NO. 84]

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. 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 81

Preparation of Compound 81

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-NH₂ [SEQ. ID.
NO. 85]

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. 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 82

Preparation of Compound 82

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-NH₂ [SEQ. ID. NO. 86]

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 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 83

Preparation of Compound 83

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-NH₂ [SEQ. ID. NO. 87]

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 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 84

Preparation of Compound 84

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-NH₂ [SEQ. ID. NO. 88]

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 85Preparation of Compound 85

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-NH₂ [SEQ. ID. NO. 89]

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. 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 86Preparation of Compound 86

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-NH₂ [SEQ. ID. NO. 90]

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. 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 87

Preparation of Compound 87

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-NH₂
[SEQ. ID. NO. 91]

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. 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 88Preparation of Compound 88

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-NH₂ [SEQ. ID. NO. 92]

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. 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 89Preparation of Compound 89

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-NH₂ [SEQ. ID. NO. 93]

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. 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 90

Preparation of Peptide having SEQ. ID. NO. 95

Compound No. 90, 4-imidazolylpropionyl-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-NH^ooctanoyl Asn-NH₂ [SEQ. ID. NO. 95], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. Instead of using a protected amino acid for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of residues 2-28 on the resin. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in CAN). 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 3361.7

EXAMPLE 91

Preparation of Peptide having SEQ. ID. NO. 96

Compound No. 91, 4-imidazolylpropionyl-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-NH^ooctanoyl Asn-NH₂ [SEQ. ID. NO. 96], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. Instead of using a protected amino acid for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of residues 2-28 on the resin. 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 3304.6

EXAMPLE 92

Preparation of Peptide having SEQ. ID. NO. 97

Compound No. 92, 4-imidazolylpropionyl-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-NH^ooctanoyl Ash Gly Gly-NH₂ [SEQ. ID. NO. 97], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. Instead of using a protected amino acid for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of residues 2-30 on the resin. 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 3475.8

EXAMPLE 93

Preparation of Peptide having SEQ. ID. NO. 98

Compound No. 93, 4-imidazolylpropionyl-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-NH^ooctanoyl Asn Gly Gly-NH₂ [SEQ. ID. NO. 98], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. Instead of using a protected amino acid for the final coupling at position 1, 4-imidazolylpropionic acid

is coupled directly to the N-terminus of residues 2-30 on the resin. 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 3418.7

EXAMPLE 94

Preparation of Peptide having SEQ. ID. NO. 99

Compound No. 94, 4-imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl-NH₂ [SEQ. ID. NO. 99], 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. Fmoc-Lys-NH^ooctanoyl acid is used for the initial coupling onto the resin at position 28. Instead of using a protected amino acid for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of protected residues 2-28 on the resin. 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 3361.7

EXAMPLE 95Preparation of Peptide having SEQ. ID. NO. 100

Compound No. 95, 4-imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl-NH₂ [SEQ. ID. NO. 100], 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. Fmoc-Lys-NH^ooctanoyl acid is used for the initial coupling onto the resin at position 28. Instead of using a protected amino acid for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of residues 2-28 on the resin. 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 3304.6

EXAMPLE 96Preparation of Peptide having SEQ. ID. NO. 101

Compound 96, 4-imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 101], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 28. Instead of using a protected amino acid for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of protected residues 2-30 on the resin. 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 3475.8

EXAMPLE 97

Preparation of Peptide having SEQ. ID. NO. 102

Compound No. 97, 4-imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 102], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 28. Instead of using protected His for the final coupling at position 1, 4-imidazolylpropionic acid is coupled directly to the N-terminus of residues 2-30 on the resin. 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 3418.7

EXAMPLE 98

Preparation of Peptide having SEQ. ID. NO. 103

Compound No. 98, 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-NH^ooctanoyl Asn-NH₂ [SEQ. ID. NO. 103], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. 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 3334.6

EXAMPLE 99

Preparation of Peptide having SEQ. ID. NO. 104

Compound No. 99, 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-NH^ooctanoyl Asn-NH₂ [SEQ. ID. NO. 104], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. 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 3277.6

EXAMPLE 100

Preparation of Peptide having SEQ. ID. NO. 105

Compound No. 100, 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-NH^ooctanoyl Asn Gly Gly-NH₂ [SEQ. ID. NO. 105], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. 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 3442.8

EXAMPLE 101Preparation of Peptide having SEQ. ID. NO. 106

Compound No. 101, 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-NH^ooctanoyl Asn Gly Gly-NH₂ [SEQ. ID. NO. 106], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 27. 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 3391.7

EXAMPLE 102Preparation of Peptide having SEQ. ID. NO. 107

Compound No. 102, 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 Asn Lys-NH^ooctanoyl-NH₂ [SEQ. ID. NO. 107], 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. Fmoc-Lys-NH^ooctanoyl acid is used for the initial coupling onto the resin at position 28. 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 3334.6

EXAMPLE 103

Preparation of Peptide having SEQ. ID. NO. 108

Compound No. 103, 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 Asn Lys-NH^ooctanoyl-NH₂ [SEQ. ID. NO. 108], 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. Fmoc-Lys-NH^ooctanoyl acid is used for the initial coupling onto the resin at position 28. 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 3277.6

EXAMPLE 104Preparation of Peptide having SEQ. ID. NO. 109

Compound No. 104, 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 Asn Lys-NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 109], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position 28. 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 3442.8

EXAMPLE 105Preparation of Peptide having SEQ. ID. NO. 110

Compound No. 105, 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 Asn Lys-NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 110], 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. Fmoc-Lys-NH^ooctanoyl acid is used for coupling at position

28. 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 3391.7

EXAMPLE 106

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for Compounds 1-67, 73-79, 80-81, 86-89 and 90-105.

C-terminal carboxylic acid peptides corresponding to amidated Compounds 1-67, 73-79, 80-81, 86-89 and 90-105 are assembled on the so called Wang resin (p-alkoxybenzylalcohol 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 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 107

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for Compounds 68-72, 79 and 82-85.

C-terminal carboxylic acid peptides corresponding to amidated Compounds 68-72, 79 and 82-85 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 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).

EXAMPLES A TO EReagents Used

GLP-1[7-36]NH₂ (GLP-1) was purchased from Bachem (Torrance, CA). All other peptides were prepared using synthesis methods such as those described therein. All chemicals were of the highest commercial grade. The cAMP SPA immunoassay was purchased from Amersham. The radioligands were purchased from New England Nuclear (Boston, MA). RINm5f cells (American Type Tissue Collection, Rockville, MD) were grown in DME/F12 medium containing 10% fetal bovine serum and 2mM L-glutamine. Cells

were grown at 37°C and 5% CO₂/95% humidified air and medium was replaced every 2 to 3 days. Cells were grown to confluence then harvested and homogenized using on a Polytron homogenizer. Cell homogenates were stored frozen at -70°C until used.

EXAMPLE A

GLP-1 Receptor Binding Studies

Receptor binding was assessed by measuring displacement of [¹²⁵I]GLP-1 or [¹²⁵I]exendin(9-39) from RINm5f membranes. Assay buffer contained 5 µg/ml bestatin, 1 µg/ml phosphoramidon, 1 mg/ml bovine serum albumin (fraction V), 1 mg/ml bacitracin, and 1 mM MgCl₂ in 20 mM HEPES, pH 7.4. To measure binding, 30 µg membrane protein (Bradford protein assay) was resuspended in 200 µl assay buffer and incubated with 60 pM [¹²⁵I]GLP-1 or [¹²⁵I]exendin(9-39) and unlabeled peptides for 120 minutes at 23°C in 96 well plates (Nagle Nunc, Rochester, NY). Incubations were terminated by rapid filtration with cold phosphatebuffered saline, pH 7.4, through polyethyleneimine-treated GF/B glass fiber filters (Wallac Inc., Gaithersburg, MD) using a Tomtec Mach II plate harvester (Wallac Inc., Gaithersburg, MD). Filters were dried, combined with scintillant, and radioactivity determined in a Betaplate liquid scintillant counter (Wallac Inc.).

Peptide samples were run in the assay as duplicate points at 6 dilutions over a concentration range of 10⁻⁶M to 10⁻¹²M to generate response curves. The biological activity of a sample is expressed as an IC₅₀ value, calculated from the raw data using an iterative curve-fitting program using a 4-parameter

logistic equation (Prizm™, GraphPAD Software). The results are shown in Table I.

TABLE I

<u>Compound</u>	<u>IC₅₀ (nM)</u>
Exendin-4 [SEQ. ID. NO. 2]	0.7
Compound 1 [SEQ. ID. NO. 5]	26.1
Compound 2 [SEQ. ID. NO. 6]	14.42
Compound 3 [SEQ. ID. NO. 7]	41.65
Compound 4 [SEQ. ID. NO. 8]	4.96

EXAMPLE B

Cyclase Activation Study

Assay buffer contained 10 μ M GTP, 0.75 mM ATP, 2.5 mM MgCl₂, 0.5mM phosphocreatine, 12.5 U/ml creatine kinase, 0.4 mg/ml aprotinin, 1 μ M IBMX in 50 mM HEPES, pH 7.4. Membranes and peptides were combined in 100 ml of assay buffer in 96 well filter-bottom plates (Millipore Corp., Bedford, MA). After 20 minutes incubation at 37°C, the assay was terminated by transfer of supernatant by filtration into a fresh 96 well plate using a Millipore vacuum manifold. Supernatant cAMP contents were quantitated by SPA immunoassay.

Peptide samples were run in the assay as triplicate points at 7 dilutions over a concentration range of 10⁻⁶M to 10⁻¹²M to generate response curves. The biological activity of a

particular sample was expressed as an EC₅₀ value, calculated as described above. Results are tabulated in Table II.

TABLE II

<u>Compound</u>	<u>EC₅₀ (nM)</u>
Exendin-4 [SEQ. ID. NO. 2]	0.23
Compound 1 [SEQ. ID. NO. 5]	>1,000
Compound 2 [SEQ. ID. NO. 6]	>10,000
Compound 3 [SEQ. ID. NO. 7]	>10,000
Compound 4 [SEQ. ID. NO. 8]	>10,000

EXAMPLE C

Determination of Blood Glucose Levels in db/db Mice

C57BLKS/J-m-db mice at least 3 months of age were utilized for the study. The mice were obtained from The Jackson Laboratory and allowed to acclimate for at least one week before use. Mice were housed in groups of ten at 22° ± 1°C with a 12:12 light:dark cycle, with lights on at 6 a.m. All animals were deprived of food for 2 hours before taking baseline blood samples. Approximately 70 µl of blood was drawn from each mouse via eye puncture, after a light anesthesia with metophane. After collecting baseline blood samples, to measure plasma glucose concentrations, all animals receive subcutaneous injections of either vehicle (10.9% NaCl), exendin-4 or test compound (1 µg) in vehicle. Blood samples were drawn again, using the same procedure, after exactly one hour from the injections, and plasma glucose concentrations were measured.

For each animal, the % change in plasma value, from baseline value, was calculated. The percent decrease in plasma glucose after one hour is shown in Table III.

TABLE III

<u>Test Compound</u>	<u>% drop in glucose</u>	
Exendin-4 [SEQ. ID. NO. 2]	39%	(n = 78)
Compound 1 [SEQ. ID. NO. 5]	40%	(n = 4)
Compound 2 [SEQ. ID. NO. 6]	41%	(n = 5)
Compound 3 [SEQ. ID. NO. 7]	32%	(n = 5)
Compound 4 [SEQ. ID. NO. 8]	42%	(n = 5)

EXAMPLE DDose Response Determination of Blood Glucose Levels in
db/db Mice

C57BLKS/J-m-db/db mice, at least 3 months of age were utilized for the study. The mice were obtained from The Jackson Laboratory and allowed to acclimate for at least one week before use. Mice were housed in groups of ten at 22°C ± 1°C with a 12:12 light:dark cycle, with lights on at 6 a.m.

All animals were deprived of food for 2 hours before taking baseline blood samples. Approximately 70 µl of blood was drawn from each mouse via eye puncture, after a light anesthesia with metophane. After collecting baseline blood samples, to measure plasma glucose concentrations, all animals receive subcutaneous injections of either vehicle, exendin-4 or test compound in concentrations indicated. Blood samples were drawn again, using

the same procedure, after exactly one hour from the injections, and plasma glucose concentrations were measured.

For each animal, the % change in plasma value, from baseline value, was calculated and a dose dependent relationship was evaluated using Graphpad Prism™ software.

Figure 5 depicts the effects of varying doses of exendin-4 [SEQ. ID. NO. 2] and Compound 1 [SEQ. ID. NO. 5] on plasma glucose levels. Exendin-4 had an ED₅₀ of 0.01 µg per mouse and Compound 1 had an ED₅₀ of 0.42 µg per mouse.

EXAMPLE E

Gastric Emptying

The following study was carried out to examine the effects of exendin-4 and an exendin agonist compound of the present invention on gastric emptying in rats. This experiment followed a modification of the method of Scarpignato, et al., Arch. Int. Pharmacodyn. Ther. 246:286-94, 1980.

Male Harlan Sprague Dawley (HSD) rats were used. All animals were housed at 22.7 ± 0.8 C in a 12:12 hour light:dark cycle (experiments being performed during the light cycle) and were fed and watered *ad libitum* (Diet LM-485, Teklad, Madison, WI). Exendin-4 was synthesized according to standard peptide synthesis methods. The preparation of Compound 1 [SEQ. ID. NO. 5] is described in Example 1.

The determination of gastric emptying by the method described below was performed after a fast of ~20 hours to ensure that the stomach contained no chyme that would interfere with spectrophotometric absorbance measurements.

Conscious rats received by gavage, 1.5ml of an acaloric gel containing 1.5% methyl cellulose (M-0262, Sigma Chemical Co, St Louis, MO) and 0.05% phenol red indicator. Twenty minutes after gavage, rats were anesthetized using 5% halothane, the stomach exposed and clamped at the pyloric and lower esophageal sphincters using artery forceps, removed and opened into an alkaline solution which was made up to a fixed volume. Stomach content was derived from the intensity of the phenol red in the alkaline solution, measured by absorbance at a wavelength of 560 nm. In separate experiments on 7 rats, the stomach and small intestine were both excised and opened into an alkaline solution. The quantity of phenol red that could be recovered from the upper gastrointestinal tract within 20 minutes of gavage was $89 \pm 4\%$; dye which appeared to bind irrecoverably to the gut luminal surface may have accounted for the balance. To account for a maximal dye recovery of less than 100%, percent of stomach contents remaining after 20 min were expressed as a fraction of the gastric contents recovered from control rats sacrificed immediately after gavage in the same experiment. Percent gastric contents remaining = (absorbance at 20 min)/(absorbance at 0 min) x 100.

In baseline studies, with no drug treatment, gastric emptying over 20 min was determined. In dose-response studies, rats were treated with 0.01, 0.1, 0.3, 1, 10 and 100 μg of exendin-4, and 0.1, 0.3, 1, 10 and 100 μg of Compound 1 [SEQ. ID. NO. 5].

The results, shown in Figure 6, demonstrate that the exendin agonists, exendin-4 and Compound 1, are potent

inhibitors of gastric emptying. The EC_{50} for exendin-4 was 0.27 μg . The EC_{50} for Compound 1 was 55.9 μg .

We claim:

1. A peptide compound of the formula [I] [SEQ. ID. NO. 4]:

Xaa₁ Xaa₂ Xaa₃ Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈ Xaa₉ Xaa₁₀
Xaa₁₁ Xaa₁₂ Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Ala Xaa₁₉ Xaa₂₀
Xaa₂₁ Xaa₂₂ Xaa₂₃ Xaa₂₄ Xaa₂₅ Xaa₂₆ Xaa₂₇ Xaa₂₈-Z₁; wherein

Xaa₁ is His, Arg, Tyr, Ala, Norval, Val
or Norleu;
Xaa₂ is Ser, Gly, Ala or Thr;
Xaa₃ is Ala, Asp or Glu;
Xaa₄ is Ala, Norval, Val, Norleu or Gly;
Xaa₅ is Ala or Thr;
Xaa₆ is Phe, Tyr or naphthylalanine;
Xaa₇ is Thr or Ser;
Xaa₈ is Ala, Ser or Thr;
Xaa₉ is Ala, Norval, Val, Norleu, Asp or Glu;
Xaa₁₀ is Ala, Leu, Ile, Val, pentylglycine or Met;
Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;

Xaa₂₁ is Ala or Leu;
 Xaa₂₂ is Phe, Tyr or naphthylalanine;
 Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
 Xaa₂₄ is Ala, Glu or Asp;
 Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;
 Xaa₂₆ is Ala or Leu;
 Xaa₂₇ is Ala or Lys;
 Xaa₂₈ is Ala or Asn;
 Z₁ is -OH,

-NH₂,

Gly-Z₂,

Gly Gly-Z₂,

Gly Gly Xaa₃₁-Z₂,

Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Ser-Z₂;

wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently
 selected from the group consisting of Pro,
 homoproline, 3Hyp, 4Hyp, thioproline,
 N-alkylglycine, N-alkylpentylglycine and
 N-alkylalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈,
 Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉,



Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₂₈ are Ala; and provided also that, if Xaa₁ is His, Arg or Tyr, then at least one of Xaa₃, Xaa₄ and Xaa₉ is Ala; and pharmaceutically acceptable salts thereof;

2. A compound according to claim 1 wherein Xaa₁ is His, Ala or Norval.

3. A compound according to claim 1 wherein Xaa₁ is Ala.

4. A compound according to claim 2 wherein Xaa₁ is Ala.

5. A compound according to claim 1 wherein Xaa₁ is His.

6. A compound according to claim 2 wherein Xaa₁ is His.

7. A compound according to claim 1 wherein Xaa₂ is Gly.

8. A compound according to claim 2 wherein Xaa₂ is Gly.

9. A compound according to claim 1 wherein Xaa₃ is Ala.

10. A compound according to claim 2 where Xaa₃ is Ala.

11. A compound according to claim 1 wherein Xaa₄ is Ala.

12. A compound according to claim 2 where Xaa₄ is Ala.

13. A compound according to claim 1 wherein Xaa₉ is Ala.

14. A compound according to claim 2 where Xaa₉ is Ala.
15. A compound according to any of claims 8-14 wherein Xaa₁₄ is Leu, pentylglycine or Met.
16. A compound according to claim 15 wherein Xaa₂₅ is Trp or Phe.
17. A compound according to claim 16 wherein Xaa₆ is Ala, Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.
18. A compound according to claim 17 wherein Z₁ is -NH₂.
19. A compound according to claim 17 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
20. A compound according to claim 1 wherein Xaa₃₉ is Ser or Tyr.
21. A compound according to claim 17 wherein Xaa₃₉ is Ser or Tyr.
22. A compound according to claim 1 wherein Xaa₃₉ is Ser.
23. A compound according to claim 17 wherein Xaa₃₉ is Ser.

24. A compound according to claim 1 wherein Z_2 is $-NH_2$.

25. A compound according to any of claims 19, 21 or 23 wherein Z_2 is $-NH_2$.

26. A compound according to claim 1 wherein Z_1 is $-NH_2$.

27. A compound according to claim 1 wherein Xaa_{31} , Xaa_{36} , Xaa_7 and Xaa_{38} are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.

28. A compound according to claim 1 which has an amino acid sequence selected from SEQ. ID. NOS. 5 to 93.

29. A peptide compound of the formula [I] [SEQ. ID. NO. 111]:

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_{18} 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 or Ala;

Xaa_2 is Gly or Ala;

Xaa_3 is Ala, Asp or Glu;

Xaa_4 is Ala or Gly;

Xaa_5 is Ala or Thr;

Xaa_6 is Phe or naphthylalanine;

Xaa_7 is Thr or Ser;

Xaa_8 is Ala, Ser or Thr;



Xaa₉ is Ala, Asp or Glu;
Xaa₁₀ is Ala, Leu or pentylglycine;
Xaa₁₁ is Ala or Ser;
Xaa₁₂ is Ala or Lys;
Xaa₁₃ is Ala or Gln;
Xaa₁₄ is Ala, Leu, Met or pentylglycine;
Xaa₁₅ is Ala or Glu;
Xaa₁₆ is Ala or Glu;
Xaa₁₇ is Ala or Glu;
Xaa₁₉ is Ala or Val;
Xaa₂₀ is Ala or Arg;
Xaa₂₁ is Ala or Leu;
Xaa₂₂ is Phe or naphthylalanine;
Xaa₂₃ is Ile, Val or tert-butylglycine;
Xaa₂₄ is Ala, Glu or Asp;
Xaa₂₅ is Ala, Trp or Phe;
Xaa₂₆ is Ala or Leu;
Xaa₂₇ is Ala or Lys;
Xaa₂₈ is Ala or Asn;
Z₁ is -OH,
-NH₂,
Gly-Z₂,
Gly Gly-Z₂,
Gly Gly Xaa₃₁-Z₂,
Gly Gly Xaa₃₁ Ser-Z₂,
Gly Gly Xaa₃₁ Ser Ser-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,
Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂
 Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈
 Ser-Z₂;

Xaa₃₁, Xaa₃₆, Xaa₃₇, and Xaa₃₈ are independently Pro,
 homoproline, thioproline, or
 N-methylalanine; and

Z₂ is -OH or -NH₂;

provided that no more than three of Xaa₃, Xaa₅, Xaa₆, Xaa₈, Xaa₁₀,
 Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁,
 Xaa₂₄, Xaa₂₅, Xaa₂₆, Xaa₂₇, and Xaa₂₈ are Ala; and provided that, if
 Xaa₁ is His, Arg or Tyr, then at least one of Xaa₃, Xaa₅, and Xaa₉
 is Ala; and pharmaceutically acceptable salts thereof.

30. A compound according to claim 29 which has an amino
 acid sequence selected from SEQ. ID. NOS. 5-9.

31. A composition comprising a compound of any of claims 1
 to 29 in a pharmaceutically acceptable carrier.

32. A composition comprising a compound of claim 30 in a
 pharmaceutically acceptable carrier

33. The use of a compound according to claim 1 in the
 preparation of a medicament for the treatment of diabetes
 mellitus.

34. The use of a compound according to claim 28 in the
 preparation of a medicament for the treatment of diabetes
 mellitus.



35. The use of a compound according to claim 29 in the preparation of a medicament for the treatment of diabetes mellitus.

36. The use of claim 33 wherein the medicament further comprises a therapeutically effective amount of an insulin.

37. The use of claim 34 wherein the medicament further comprises a therapeutically effective amount of insulin.

38. The use of claim 35 wherein the medicament further comprises a therapeutically effective amount of an insulin.

39. The use of a compound according to claim 1 in the preparation of a medicament for the treatment of a hyperglycemic condition in a mammal.

40. The use of a compound according to claim 28 in the preparation of a medicament for the treatment of a hyperglycemic condition in a mammal.

41. The use of a compound according to claim 29 in the preparation of a medicament for the treatment of a hypoglycemic condition in a mammal.



Xaa₂₁ is Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkyl alkanoyl Ala, Leu or;

Xaa₂₂ is Phe, Tyr or naphthylalanine;

Xaa₂₃ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;

Xaa₂₄ is Ala, Glu or Asp;

Xaa₂₅ is Ala, Trp, Phe, Tyr or naphthylalanine;

Xaa₂₆ is Ala or Leu;

X₁ is Lys Asn, Asn Lys, Lys-NH^e-R Asn, Asn Lys-NH^e-R, Lys-NH^e-R Ala, Ala Lys-NH^e-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkylalkanoyl

Z₁ is -OH,

-NH₂,

Gly-Z₂,

Gly Gly-Z₂,

Gly Gly Xaa₃₁-Z₂,

Gly Gly Xaa₃₁ Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇-Z₂,

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈-Z₂ or

Gly Gly Xaa₃₁ Ser Ser Gly Ala Xaa₃₆ Xaa₃₇ Xaa₃₈ Xaa₃₉-Z₂;

wherein

Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently

selected from the group consisting of Pro,

homoproline, 3Hyp, 4Hyp, thioproline,

N-alkylglycine, N-alkylpentylglycine and

N-alkylalanine; and

Z₂ is -OH or -NH₂.

provided that no more than three of Xaa₃, Xaa₄, Xaa₅, Xaa₆, Xaa₈, Xaa₉, Xaa₁₀, Xaa₁₁, Xaa₁₂, Xaa₁₃, Xaa₁₄, Xaa₁₅, Xaa₁₆, Xaa₁₇, Xaa₁₉, Xaa₂₀, Xaa₂₁, Xaa₂₄, Xaa₂₅, Xaa₂₆, are Ala; and provided also that, if Xaa₁ is His, Arg, Tyr, or 4-imidazopropionyl then at least one of Xaa₃, Xaa₄ and Xaa₉ is Ala; and pharmaceutically acceptable salts thereof.

43. A compound according to claim 42 wherein Xaa₁ is His, Ala, Norval or 4-imidazopropionyl.

44. A compound according to claim 43 wherein Xaa₁ is His or 4-imidazopropionyl.

45. A compound according to claim 43 wherein Xaa₁ is Ala.

46. A compound according to claim 43 wherein Xaa₁ is His.

47. A compound according to claim 43 wherein Xaa₁ is 4-imidazopropionyl.

48. A compound according to claim 42 wherein Xaa₂ is Gly.

49. A compound according to any of claims 43-47 wherein Xaa₂ is Gly.

50. A compound according to claim 42 wherein Xaa₃ is Ala.

51. A compound according to any of claims 43-47 where Xaa₃ is Ala.

52. A compound according to claim 42 wherein Xaa₄ is Ala.
 53. A compound according to any of claims 43-47 where Xaa₄ is Ala.
 54. A compound according to claim 42 wherein Xaa₄ is Ala.
 55. A compound according to any of claim 43-47 where Xaa₄ is Ala.
 56. A compound according to claim 42 wherein Xaa₁₄ is Leu, pentylglycine or Met.
 57. A compound according to claim 42 wherein Xaa₂₅ is Trp or Phe.
 58. A compound according to claim 42 wherein Xaa₆ is Ala, Phe or naphthylalanine; Xaa₂₂ is Phe or naphthylalanine; and Xaa₂₃ is Ile or Val.
 59. A compound according to claim 42 wherein Z₁ is -NH₂.
 60. A compound according to claim 42 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
 61. A compound according to claim 42 wherein Xaa₃₉ is Ser or Tyr.
-

62. A compound according to claim 58 wherein Xaa₃₉ is Ser or Tyr.
63. A compound according to claim 42 wherein Xaa₃₉ is Ser.
64. A compound according to claim 58 wherein Xaa₃₉ is Ser.
65. A compound according to claim 42 wherein Z₂ is -NH₂.
66. A compound according to any of claims 50, 52 or 54 wherein Z₂ is -NH₂.
67. A compound according to claim 42 wherein Z₁ is -NH₂.
68. A compound according to claim 42 wherein Xaa₃₁, Xaa₃₆, Xaa₃₇ and Xaa₃₈ are independently selected from the group consisting of Pro, homoproline, thioproline and N-alkylalanine.
69. A compound according to claim 42 wherein X₁ is Lys Asn, Lys-NH^ε-R Asn, or Lys-NH^ε-R Ala where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl.
70. A compound according to claim 42 wherein Xaa₂₁ is Lys-NH^ε-R where R is Lys, Arg, C₁-C₁₀ straight chain or branched alkanoyl or cycloalkyl-alkanoyl

71. A compound according to claim 42 which has an amino acid sequence selected from SEQ ID NOS: 95-110.

72. A composition comprising a compound of claim 42 in a pharmaceutically acceptable carrier.

5 73. A composition comprising a compound of claim 71 in a pharmaceutically acceptable carrier.

74. A peptide compound as claimed in claim 1 substantially as hereinbefore described with reference to any one of the examples.

10 75. A peptide compound as claimed in claim 28 substantially as hereinbefore described with reference to any one of the examples.

76. A peptide compound as claimed in claim 29, substantially as hereinbefore described with reference to any one of the examples.

77. A peptide compound as claimed in claim 1, substantially as hereinbefore described with reference to the accompanying drawings.

15 78. A peptide compound as claimed in claim 28, substantially as hereinbefore described with reference to the accompanying drawings.

79. A peptide compound as claimed in claim 29, substantially as hereinbefore described with reference to the accompanying drawings.

20 80. A composition comprising the compound of any one of claims 74 or 77, together with a pharmaceutically acceptable carrier.

81. A composition comprising the compound of any one of claims 75 or 78, together with a pharmaceutically acceptable carrier.

82. A composition comprising the compound of any one of claims 76 or 79, together with a pharmaceutically acceptable carrier.

25 83. A method for the treatment of diabetes mellitus, comprising administering a therapeutically effective amount of the compound of any one of claims 1, 28, 29, 74 to 79, or the composition of any one of claims 31, 32 or 80-82.

84. The method of claim 83 wherein the medicament further comprises a therapeutically effective amount of an insulin.

30 85. A method for the treatment of a hyperglycemic condition in a mammal, comprising administering a therapeutically effective amount of the compound of any one of claims 1, 28, 74-75 or 77-78.

86. A method for the treatment of a hypoglycemic condition in a mammal, comprising administering a therapeutically effective amount of the compound of any one of claims 29, 76 or 79.



87. Use of the compound of any one of claims 74-79 for the manufacture of a medicament for the treatment of diabetes mellitus.

88. Use of the compound of any one of claims 74-75 or 77-78 for the manufacture of a medicament for the treatment of a hyperglycemic condition in a mammal.

89. Use of the compound of any one of claims 76 or 79 for the manufacture of a medicament for the treatment of a hypoglycemic condition in a mammal.

90. A peptide compound as claimed in claim 42, substantially as hereinbefore described with reference to any one of the examples.

91. A peptide compound as claimed in claim 42, substantially as hereinbefore described with reference to the accompanying drawings.

Dated 18 November, 2002
Amylin Pharmaceuticals, Inc.

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON



FIGURE 7

Cmp
No.

- 90 4-Imidazolylpropionyl-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-NH^ooctanoyl Asn-NH₂ [SEQ. ID. NO. 95]
- 91 4-Imidazolylpropionyl-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-NH^ooctanoyl Asn-NH₂ [SEQ. ID. NO. 96]
- 92 4-Imidazolylpropionyl-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-NH^ooctanoyl Asn Gly Gly-NH₂ [SEQ. ID. NO. 97]
- 93 4-Imidazolylpropionyl-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-NH^ooctanoyl Asn Gly Gly-NH₂ [SEQ. ID. NO. 98]
- 94 4-Imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl-NH₂ [SEQ. ID. NO. 99]
- 95 4-Imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl-NH₂ [SEQ. ID. NO. 100]

- 96 4-Imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 101]
- 97 4-Imidazolylpropionyl-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 Asn Lys-NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 102]
- 98 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-NH^ooctanoyl
Asn-NH₂ [SEQ. ID. NO. 103]
- 99 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-NH^ooctanoyl
Asn-NH₂ [SEQ. ID. NO. 104]
- 100 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-NH^ooctanoyl
Asn Gly Gly-NH₂ [SEQ. ID. NO. 105]
- 101 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-NH^ooctanoyl
Asn Gly Gly-NH₂ [SEQ. ID. NO. 106]
- 102 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 Asn Lys-
NH^ooctanoyl-NH₂ [SEQ. ID. NO. 107]

- 103 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 Asn Lys-
NH^ooctanoyl-NH₂ [SEQ. ID. NO. 108]
- 104 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 Asn Lys-
NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 109]
- 105 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 Asn Lys-
NH^ooctanoyl Gly Gly-NH₂ [SEQ. ID. NO. 110]

GLP-1 (GLP-1(7-36)NH₂)

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
5 10 15
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg-NH₂
20 25 30

FIGURE 3

Amino Acid Position	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	
Compound 72	Ala	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Ala	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 73	Ala	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 74	His	Gly	Ala	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 75	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 76	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 77	Ala	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 78	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 79	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 80	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 81	Ala	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 82	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 83	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 84	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 85	Ala	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 86	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 87	His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 88	Ala	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			
Compound 89	Ala	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Glu	Leu	Phe	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro	NH2			

Figure 4

Glucose lowering effect in db/db mice at 1 hr time point

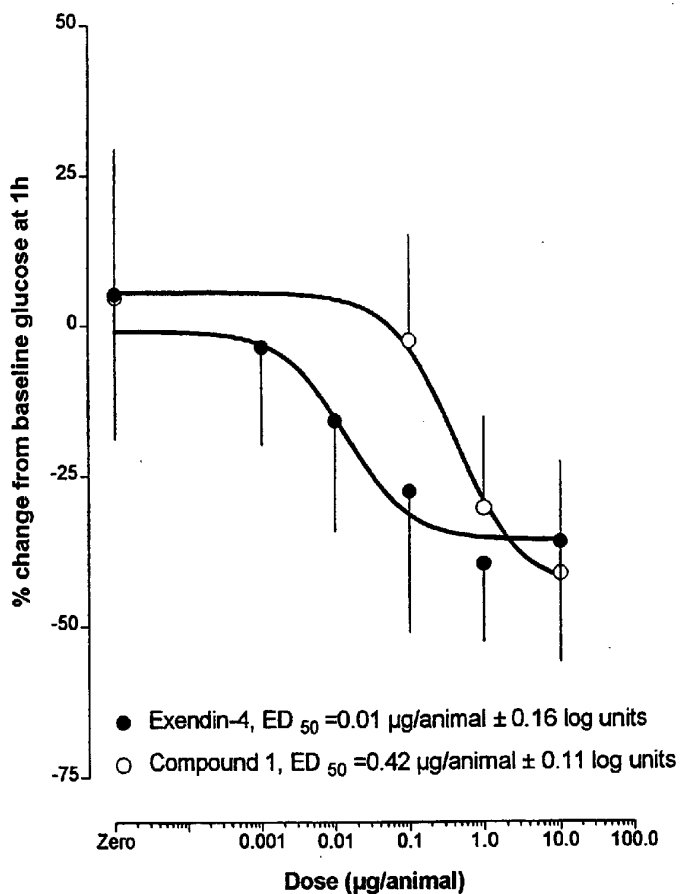


Figure 5

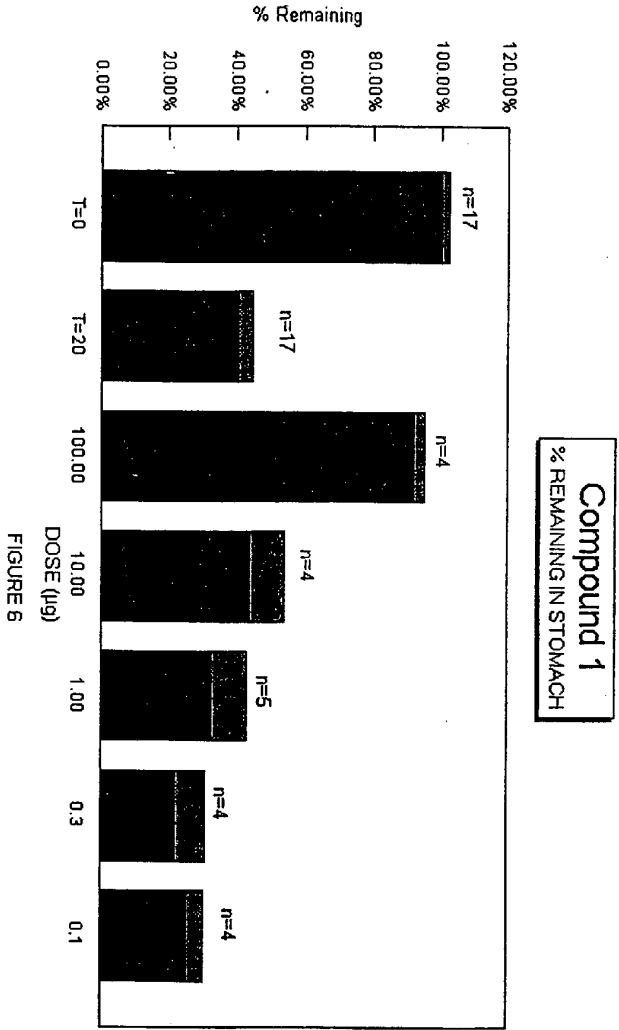


FIGURE 6

FIGURE 6