NOVEL COMPOUNDS AND THEIR EFFECTS ON FEEDING BEHAVIOUR

1. FIELD OF THE INVENTION

This application relates to the use of agents to control appetite, feeding, food intake, energy expenditure and calorie intake, treat excess weight, obesity and to prevent and treat the co-morbidities of obesity.

2. BACKGROUND OF THE INVENTION

According to the World Health Organisation (WHO), obesity represents a global epidemic in which more than one billion adults are overweight, of which at least 300 million are clinically obese. Furthermore, WHO estimate that 250,000 deaths per year in Europe, and more than 2.5 million deaths worldwide are weight related (World Health Organisation, Global Strategy on Diet, Physical Activity and Health, 2004).

The cause of obesity is complex and multi-factorial. Increasing evidence suggests that obesity is not a simple problem of self-control but is a complex disorder involving appetite regulation and energy metabolism. In addition, obesity is associated with a variety of conditions associated with increased morbidity and mortality in a population. Although the etiology of obesity is not definitively established, genetic, metabolic, biochemical, cultural and psychosocial factors are believed to contribute. In general, obesity has been described as a condition in which excess body fat puts an individual at a health risk.

There is strong evidence that obesity is associated with increased morbidity and mortality. Disease risk, such as cardiovascular disease risk and type 2 diabetes disease risk, increases independently with increased body mass index (BMI). Indeed, this risk has been quantified as a five percent increase in the risk of cardiac disease for females, and a seven percent increase in the risk of cardiac disease for males, for each point of a BMI greater than 24.9 (see Kenchaiah et al., N. Engl. J. Med. 347:305, 2002; Massie, N. Engl. J. Med. 347:358, 2002). In addition, there is substantial evidence that weight loss in obese or overweight persons reduces important disease risk factors. A weight loss of 10% of the initial body weight in both overweight and obese adults has been associated with a decrease in risk factors such as hypertension, hyperlipidemia, and hyperglycemia.

Although diet and exercise provide a simple process to decrease weight gain and promote weight loss, overweight and obese individuals often cannot sufficiently control these factors to lose weight effectively. Pharmacotherapy is available; several weight loss drugs have been approved by the US Food and Drug Administration that can be used as part of a comprehensive weight loss program. However, many of these drugs have serious adverse side effects. An example of a widely used appetite suppressant is sibutramine (reviewed by McNeely, W et al., Drugs, 1998, 56(6), 1093-1124). Sibutramine's primary and secondary metabolites are pharmacologically active and they are thought to induce enhancement of satiety and thermogenesis by inhibiting serotonin and noradrenaline reuptake. When less invasive methods have failed, and the patient is at high risk for obesity related morbidity or mortality, weight loss surgery is an option in carefully selected patients with clinically severe obesity. However, these treatments are high-risk, and suitable for use in only a limited number of patients (Wolfe and Morton, JAMA, 2005, 294,1960-1963). It is not only obese subjects who wish to lose weight. People with weight within the recommended range, for example, in the upper part of the recommended range, may wish to reduce their weight, to bring it closer to the ideal weight.

Oxyntomodulin (hereafter oxm) is a 37 amino acid peptide member of the glucagon superfamily (Sherwood et al, Endocrine Reviews, 2000, 21(6): 619-670) comprising the entire 29 amino acid sequence of glucagon, with an eight amino acid carboxy terminal extension, resulting from the tissue-specific processing of the pre-pro-glucagon precursor in the brain and gut (Holst, Ann Rev Physiol, 1997, 59:257-271). Administration of oxm to rats via intracerebroventricular injection and injection into the paraventricular and arcuate nuclei of the hypothalamus inhibits refeeding after a fast (Dakin et al, Endocrinology, 2001, 142:4244-4250; Dakin et al, Endocrinology, 2004, 145:2687-2695). Chronic central administration resulted in reduced weight gain consistent with a reduction in food intake (Dakin et al, Am J Physiol Endocrinol Metab, 2002, 283:E1173-E1177). Twice daily peripheral injections also resulted in reduced body weight gain and adiposity (Dakin et al, Endocrinology, 2004, 145:2687-2695).

WO 03/022304 discloses the use of oxm in its native form and analogues thereof as a medicament for use in control of appetite, feeding, food intake, energy expenditure and calorie intake, particularly in the field of obesity. Studies in humans have shown that intravenously infused oxm is an effective appetite suppressant (Cohen et al, J. Clin. Endocrinol Metab, 2003, 88(10): 4696-4701). In a study of the effects of oxm on weight loss in humans it was found that subcutaneous injections of 1.8 mg (approximately 400 nmol) of

oxm to human volunteers three times daily (30 mins before meals) for 28 days resulted in a significant reduction of body weight (Wynne et al, Diabetes, 2005, 54: 2390-2395).

Peptides are widely used in medical practice, although when native peptides or analogues thereof are used in therapy it is generally found that they have a high clearance rate and/or are sensitive to degradation. In particular, a high clearance or rapid degradation of a therapeutic agent is inconvenient in cases where it is desired to maintain a high blood level over a prolonged period of time since repeat administrations will then be necessary, decreasing patient compliance and increasing the cost of the therapy.

A need remains for agents that can be used to effect weight loss in overweight and obese subjects, and/or to treat patients with other conditions involving excess weight, for example diabetes and eating disorders. There is especially a need for agents structurally similar to oxm that show greater potency and/or a protracted or more therapeutically useful profile of action and/or a lower clearance rate than native oxm.

3. SUMMARY OF THE INVENTION

Compounds of the invention are novel peptide analogues of oxm (hereafter "oxm analogues") in which one or more amino acids or parts of the oxm sequence have been replaced by one or more particular substituent amino acids or sequences. Accordingly, the invention provides a peptide comprising the amino acid sequence:

Xaa1 Xaa2 Xaa3 Gly4 Thr5 Phe6 Thr7 Ser8 Asp9 Tyr10 Ser11 Lys12 Tyr13 Leu14

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 Trp25 Leu26

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 Lys33 Asn34 Asn35 Ile36 Ala37;

wherein:

Xaa1 is His1 or D-His1,
Xaa2 is Ser2 or Ala2,
Xaa3 is Gln3 or Asp3;

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is:

Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,

Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
or Asp15 Ser16 Arg17 Arg18 Ala19 Gln20 Asp21 Phe22 Val23 Gln24;

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is:

Met27 Asn28 Thr29 Lys30 Arg31 Asn32,
Lys27 Asn28 Ala29 Gly30 Pro31 Ser32,
or Lys27 Asn28 Gly29 Gly30 Pro31 Ser32

or a peptide as set out above in which residue Asn34 is replaced with Asp34;

or a peptide as set out above in which Xaa3 is Glu3;

with the proviso that if
Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is
Asp15 Ser16 Arg17 Arg18 Ala19 Gln20 Asp21 Phe22 Val23 Gln24,

then Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is not
Met27 Asn28 Thr29 Lys30 Arg31 Asn32

(SEQ ID NO: 356).

In one embodiment, the invention provides a peptide comprising the amino acid sequence:

Xaa1 Xaa2 Xaa3 Gly4 Thr5 Phe6 Thr7 Ser8 Asp9 Tyr10 Ser11 Lys12 Tyr13 Leu14

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 Trp25 Leu26

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 Lys33 Asn34 Asn35 Ile36 Ala37;

wherein:

Xaa1 is His1 or D-His1,
Xaa2 is Ser2 or Ala2,
Xaa3 is Gln3 or Asp3;

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is:

Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,

Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
or Asp15 Ser16 Arg17 Arg18 Ala19 Gln20 Asp21 Phe22 Val23 Gln24;

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is:

Met27 Asn28 Thr29 Lys30 Arg31 Asn32,
Lys27 Asn28 Ala29 Gly30 Pro31 Ser32,
or Lys27 Asn28 Gly29 Gly30 Pro31 Ser32

with the proviso that if
Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is
Asp15 Ser16 Arg17 Arg18 Ala19 Gln20 Asp21 Phe22 Val23 Gln24,

then Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is not
Met27 Asn28 Thr29 Lys30 Arg31 Asn32.

The peptides of the invention are potent and long-lasting appetite suppressants.

4. BRIEF DESCRIPTION OF THE FIGURES

Figure 1 discloses 355 specific peptide sequences falling within the scope of the invention.

Figures 2 to 41 show the results of Examples 1 to 19.

Figure 2 relates to Example 1.

Figure 3 relates to Example 2.

Figure 4 relates to Example 3 (PEPTIDE NO: 94).

Figure 5 relates to Example 3 (PEPTIDE NO: 82).

Figure 6 relates to Example 3 (PEPTIDE NO: 58).

Figure 7 relates to Example 3 (PEPTIDE NO: 52).

Figure 8 relates to Example 4 (PEPTIDE NO: 164).

Figure 9 relates to Example 4 (PEPTIDE NO: 167).

Figure 10 relates to Example 5 (PEPTIDE NO: 100).

Figure 11 relates to Example 5 (PEPTIDE NO: 148).

Figure 12 relates to Example 6 (PEPTIDE NO: 60).

Figure 13 relates to Example 6 (PEPTIDE NO: 178).

Figure 14 relates to Example 7 (PEPTIDE NO: 155).

Figure 15 relates to Example 8 (PEPTIDE NO: 142).

Figure 16 relates to Example 8 (PEPTIDE NO: 172).

Figure 17 relates to Example 8 (PEPTIDE NO: 184).

Figure 18 relates to Example 9 (PEPTIDE NO: 4).

Figure 19 relates to Example 9 (PEPTIDE NO: 108).

Figure 20 relates to Example 9 (PEPTIDE NO: 195).

Figure 21 relates to Example 9 (PEPTIDE NO: 136).

Figure 22 relates to Example 10 (PEPTIDE NO: 142).

Figure 23 relates to Example 10 (PEPTIDE NO: 22).

Figure 24 relates to Example 10 (PEPTIDE NO: 153).

Figure 25 relates to Example 10 (PEPTIDE NO: 199).

Figure 26 relates to Example 11 (PEPTIDE NO: 210).

Figure 27 relates to Example 11 (PEPTIDE NO: 211).

Figure 28 relates to Example 11 (PEPTIDE NO: 213).

Figure 29 relates to Example 11 (PEPTIDE NO: 214).

Figure 30 relates to Example 12 (PEPTIDE NO: 201).

Figure 31 relates to Example 12 (PEPTIDE NO: 202).

Figure 32 relates to Example 13 (PEPTIDE NO: 203).

Figure 33 relates to Example 14 (PEPTIDE NO: 204).

Figure 34 relates to Example 14 (PEPTIDE NO: 205).

Figure 35 relates to Example 15 (PEPTIDE NO: 206).

Figure 36 relates to Example 15 (PEPTIDE NO: 207).

Figure 37 relates to Example 15 (PEPTIDE NO: 209).

Figure 38 relates to Example 16 (PEPTIDE NO: 215).

Figure 39 relates to Example 17 (PEPTIDE NO: 216).

Figure 40 relates to Example 18 (PEPTIDE NO: 355).

Figure 41 relates to Example 19 (PEPTIDE NO: 130).

5. DEFINITIONS

In order to facilitate review of the various embodiments of this disclosure, the following explanations of specific terms are provided:

Animal: Living multi-cellular vertebrate organisms, a category that includes, for example, mammals and birds. The term mammal includes both human and non-human mammals. Similarly, the term "subject" includes both human and non-human subjects, including veterinary subjects.

Appetite: A natural desire, or longing for food. In one embodiment, appetite is measured by a survey to assess the desire for food. Increased appetite generally leads to increased feeding behavior.

Appetite Suppressants: Compounds that decrease the desire for food. Commercially available appetite suppressants include, but are not limited to, amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine fenfluramine, dexfenfluramine, sibutramine, rimonabant and fluoxetine.

Body Mass Index (BMI): A mathematical formula for measuring body mass, also sometimes called Quetelet's Index. BMI is calculated by dividing weight (in kg) by height^2 (in meters^2). The recommended classifications for BMI in humans, adopted by the Expert Panel on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults, and endorsed by leading organizations of health professionals, are as follows: Underweight <18.5 kg/m^2; Normal weight 18.5–24.9 kg/m^2; Overweight 25–29.9 kg/m^2; Obesity (Class 1) 30–34.9 kg/m^2; Obesity (Class 2) 35–39.9 kg/m^2; Extreme obesity (Class 3) ≥40 kg/m^2 (Practical Guide to the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The North American Association for the Study of Obesity (NAASO) and the National Heart, Lung, and Blood Institute (NHLBI) 2000). In one embodiment, a BMI of greater than 25 kg/m^2 can be used to identify a subject in need of a treatment for excess weight or obesity. Ideal body weight will vary among species and individuals based on height, body build, bone structure, and sex.

Conservative substitutions: The replacement of an amino acid residue by another similar residue in a polypeptide. Typical but not limiting conservative substitutions are the replacements, for one another, among the aliphatic amino acids Ala, Val, Leu and Ile;

interchange of Ser and Thr containing hydroxy residues, interchange of the acidic residues Asp and Glu, interchange between the amide-containing residues Asn and Gln, interchange of the basic residues Lys and Arg, interchange of the aromatic residues Phe and Tyr, and interchange of the small-sized amino acids Ala, Ser, Thr, Met and Gly. Additional conservative substitutions include the replacement of an amino acid by another of similar spatial or steric configuration, for example the interchange of Asn for Asp, or Gln for Glu.

Table 1: Non-limiting examples of conservative amino acid substitutions

Original Residue	Conservative Substitutions
Ala	Gly, Val, Leu, Ile, Ser, Thr, Met
Arg	Lys
Asn	Asp, Gln, His
Asp	Glu, Asn
Cys	Ser
Gln	Asn, His, Lys, Glu
Glu	Asp, Gln
Gly	Ala, Ser, Thr, Met
His	Asn, Gln
Ile	Ala, Leu, Val, Met
Leu	Ala, Ile, Val, Met,
Lys	Arg
Met	Leu, Ile, Ala, Ser, Thr, Gly
Phe	Leu, Tyr, Trp
Ser	Thr, Cys, Ala, Met, Gly
Thr	Ser, Ala, Ser, Met, Gly
Trp	Tyr, Phe
Tyr	Trp; Phe
Val	Ala, Ile, Leu

Non-conservative substitutions: The replacement, in a polypeptide, of an amino acid residue by another residue which is not biologically similar. For example, the replacement of an amino acid residue with another residue that has a substantially different charge, a substantially different hydrophobicity or a substantially different spatial or steric configuration.

The phrase "alternative amino acid" encompasses alternative amino acids that are the result of both conservative and non-conservative substitutions. In addition to the twenty commonly occurring amino acids that are typically found in naturally occurring polypeptides, rare amino acids, for example, canavanine, ornithine and 5-hydroxytryptophane, and artificial amino acids, that is to say amino acids not normally found *in vivo*, for example t-butylglycine, may

be used as "alternative amino acids" in accordance with the invention. Any chiral form of an amino acid may be used.

Diabetes: A failure of cells to transport endogenous glucose across their membranes either because of an endogenous deficiency of insulin and/or a defect in insulin sensitivity. Diabetes is a chronic syndrome of impaired carbohydrate, protein, and fat metabolism owing to insufficient secretion of insulin or to target tissue insulin resistance. It occurs in two major forms: insulin-dependent diabetes mellitus (IDDM, type I) and non-insulin dependent diabetes mellitus (NIDDM, type II) which differ in etiology, pathology, genetics, age of onset, and treatment.

The two major forms of diabetes are both characterised by an inability to deliver insulin in an amount and with the precise timing that is needed for control of glucose homeostasis. Diabetes type I, or insulin dependent diabetes mellitus (IDDM) is caused by the destruction of pancreatic β cells, which results in insufficient levels of endogenous insulin. Diabetes type II, or non-insulin dependent diabetes, results from a defect in both the body's sensitivity to insulin, and a relative deficiency in insulin production.

Food intake: The amount of food consumed by an individual subject. Food intake can be measured by volume or by weight. For example, food intake may be the total amount of food consumed by an individual subject. Or, food intake may be the amount of proteins, fat, carbohydrates, cholesterol, vitamins, minerals, or any other food component, of the individual subject. "Protein intake" refers to the amount of protein consumed by an individual. Similarly, "fat intake," "carbohydrate intake," "cholesterol intake," "vitamin intake," and "mineral intake" refer to the amount of fat, carbohydrates, cholesterol, vitamins, or minerals consumed by an individual subject respectively.

Normal Daily Diet: The average food intake for an individual of a given species. A normal daily diet can be expressed in terms of caloric intake, protein intake, carbohydrate intake, and/or fat intake. A normal daily diet in humans generally comprises the following: about 2,000, about 2,400, or about 2,800 to significantly more calories. In addition, a normal daily diet in humans generally includes about 12 g to about 45 g of protein, about 120 g to about 610 g of carbohydrate, and about 11 g to about 90 g of fat. A low calorie diet would be no more than about 85%, and preferably no more than about 70%, of the normal caloric intake of a human individual.

In animals, the caloric and nutrient requirements vary depending on the species and size of the animal. For example, in cats, the total caloric intake per pound, as well as the percent distribution of protein, carbohydrate and fat varies with the age of the cat and the reproductive state. A general guideline for cats, however, is 40 cal/lb/day (18.2 cal/kg/day). About 30% to about 40% should be protein, about 7% to about 10% should be from carbohydrate, and about 50% to about 62.5% should be derived from fat intake. One of skill in the art can readily identify the normal daily diet of an individual of any species.

Obesity: A condition in which excess body fat may put a person at health risk (see Barlow and Dietz, *Pediatrics* 102:E29, 1998; National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI), *Obes. Res.* 6 (suppl. 2):51S-209S, 1998). Excess body fat is a result of an imbalance of energy intake and energy expenditure. For example, the Body Mass Index (BMI) may be used to assess obesity. In one commonly used convention, a BMI of 25.0 kg/m^2 to 29.9 kg/m^2 is overweight, while a BMI of 30 kg/m^2 or greater is obese.

In another convention, waist circumference is used to assess obesity. Excess abdominal fat is an important, independent assessment of the risks associated with obesity or being overweight. Waist circumference measurement is particularly useful in patients who are categorised as normal or overweight. It is not usually necessary to measure waist circumference in individuals with BMIs $\geq$ 35 kg/m^2 since it adds little to the predictive power of the disease risk classification of BMI. Men who have waist circumferences greater than 40 inches (102 cm), and women who have waist circumferences greater than 35 inches (90 cm), are at higher risk of diabetes, dyslipidemia, hypertension, and cardiovascular disease because of excess abdominal fat. Individuals with waist circumferences greater than these values should be considered one risk category above that defined by their BMI.

Strong evidence shows that obesity affects both the morbidity and mortality of individuals. For example, an overweight or obese individual is at increased risk for heart disease, non-insulin dependent (type 2) diabetes, hypertension, stroke, cancer (e.g. endometrial, breast, prostate, and colon cancer), dyslipidemia, gall bladder disease, sleep apnea, reduced fertility, and osteoarthritis, amongst others (see Lyznicki et al., *Am. Fam. Phys.* 63:2185, 2001).

Overweight: An individual who weighs more than their ideal body weight. An overweight individual can be obese, but is not necessarily obese. For example, an overweight individual is any individual who desires to decrease their weight. In one convention, an overweight individual is an individual with a BMI of 25.0 kg/m^2 to 29.9 kg/m^2.

Pegylation: the process of reacting a poly(alkylene glycol), preferably an activated poly(alkylene glycol) to form a covalent bond. A facilitator may be used, for example an amino acid, e.g. lysine. Although "pegylation" is often carried out using poly(ethylene glycol) or derivatives thereof, such as methoxy poly(ethylene glycol), the term is not limited herein to the use of methoxy poly(ethylene glycol) but also includes the use of any other useful poly(alkylene glycol), for example poly(propylene glycol). Pegylated shall be defined accordingly.

Peripheral Administration: Administration outside of the central nervous system. Peripheral administration does not include direct administration to the brain. Peripheral administration includes, but is not limited to intravascular, intramuscular, subcutaneous, inhalation, oral, rectal, transdermal, buccal, sub-lingual or intra-nasal administration

Polypeptide: A polymer in which the monomers are amino acid residues which are joined together through amide bonds. When the amino acids are alpha-amino acids, either the L-optical isomer or the D-optical isomer can be used, the L-isomers being preferred. Throughout this specification, an alpha-amino acid will be assumed to be the L-isomer if it not explicitly stated to be the D-isomer. The terms "polypeptide" or "protein" as used herein encompass any amino acid sequence and include modified sequences such as glycoproteins. The term "polypeptide" covers naturally occurring proteins, as well as those which are recombinantly or synthetically produced. The term "polypeptide fragment" refers to a portion of a polypeptide, for example such a fragment which exhibits at least one useful sequence in binding a receptor. The term "functional fragments of a polypeptide" refers to all fragments of a polypeptide that retain an activity of the polypeptide. Biologically functional peptides can also include fusion proteins, in which the peptide of interest is fused to another peptide(s).

Therapeutically effective amount: A dose sufficient to prevent advancement, or to cause regression of a disorder, or which is capable of relieving a sign or symptom of a disorder, or which is capable of achieving a desired result. In several embodiments, a therapeutically effective amount of a compound of the invention is an amount sufficient to inhibit or halt weight gain, or an amount sufficient to decrease appetite, or an amount sufficient to reduce caloric intake or food intake or increase energy expenditure, or an amount sufficient to reduce weight, or to reduce the risk of mortality or morbidity from conditions associated with the disorder.

6. DETAILED DESCRIPTION

The inventors have found that, surprisingly, oxm analogues of the invention are effective appetite suppressants and/or have a more sustained effect than native oxm on food intake, and/or have a more potent effect than native oxm on food intake.

The human oxm sequence (which is the same as the rat and hamster) is as follows:

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn Arg Asn Asn Ile Ala (SEQ ID NO: 357)

The peptides of the invention also have a longer half-life or clearance time or improved resistance to degradation as compared with oxm. Increased duration of appetite suppression can be particularly important to avoid the effect known as "escape". A short duration appetite suppressant may reduce appetite for the time covered by one meal and, in that meal, the subject typically eats less food. If, however, the appetite suppressant has a short half-life or rapid clearance time or is then metabolized or otherwise removed from the circulation of the subject, then by the time of the next mealtime, the subject can regain its "normal" appetite. In view of the subject having eaten a small meal at the previous mealtime, the subject may in fact have an increased appetite by the time of the subsequent meal. If the subject satisfies that appetite, it is possible for the food intake over the two meals, in total, to be no lower than the food intake would have been without the appetite suppressant. That is to say that the subject may have "escaped" from the effects of the appetite suppressant. "Escape" can be reduced by using additional doses of appetite suppressant, or by using an appetite suppressant with a longer duration of action. If the subject has a reduced appetite for longer, then the degree to which it can make up the missed food from one meal in the next meal is reduced as there is a practical limit to the total capacity for food in a particular meal. Repeated or continuous administration of a compound over a period of time, for example over a period of days or weeks, will lead to extended appetite suppression and reduced potential for escape from the effects of the appetite suppression.

The improved activity and/or duration of action of the oxm analogues as compared with oxm offers various advantages. For example, effective suppression of appetite at lower dosages will be permitted (with the lower dosage and/or lower peak levels, offering the prospect of reduced side effects (including nausea) and reduction in the cost of treatment), or usage at relatively high dosages will be better tolerated by the patient enabling quicker and/or greater weight loss. Certain of the compounds of the invention used in the Examples herein exhibit a pattern of appetite suppression indicative of a 'flatter blood curve', that is to say they have improved pharmacokinetids, by virture of displaying either or both of (i) a more gradual onset

of the appetite suppressant activity than oxm and thereby potentially avoid an initial sharp peak (which may be associated with nausea); and (ii) a potentially longer duration of action.

Further advantages of many compounds of the invention include that the compounds have improved storage characteristics and are amenable to large scale synthesis, for example some compounds of the invention do not contain sequence motifs associated with the formation of aspartimide species, and/or are less prone to reduced stability.

In one embodiment, the invention provides a peptide wherein

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is:

Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
or Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24.

(SEQ ID NO: 359).

In particular embodiments, a peptide of the invention is one wherein

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is:
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
or Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24.

In a further embodiment, a peptide of the invention is one wherein

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is:
Asp15 Ser16 Arg17 Arg18 Ala19 Gln20 Asp21 Phe22 Val23 Gln24.

In a further embodiment, a peptide of the invention comprises Xaa1 Xaa2 Xaa3 selected from the group consisting of:

His1 Ser2 Gln3,

D-His1 Ser2 Gln3,
D-His1 Ala2 Gln3, and
D-His1 Ala2 Asp3.

(SEQ ID NO: 360).

In a further embodiment, a peptide of the invention is one wherein

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is:
Lys27 Asn28 Ala29 Gly30 Pro31 Ser32,
Lys27 Asn28 Gly29 Gly30 Pro31 Ser32,
or Met27 Asn28 Thr29 Lys30 Arg31 Asn32.

In a further embodiment, a peptide of the invention is one wherein

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is:

Lys27 Asn28 Ala29 Gly30 Pro31 Ser32,
or Lys27 Asn28 Gly29 Gly30 Pro31 Ser32

(SEQ ID NO: 361).

In one embodiment, a peptide of the invention is one wherein

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is:
Lys27 Asn28 Ala29 Gly30 Pro31 Ser32.

In particular, the peptide of the invention may have an amino acid sequence selected from the group comprising:

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 1)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 2)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 3)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 4)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 5)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 6)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 7)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 8)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 9)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 10)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 11)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 12)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 13)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 14)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 15)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 16)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 17)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 18)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 19)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 20)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 21)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 22)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 23)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 24)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 25)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 26)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 27)

HisSer Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 28)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 29)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 30)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 31)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 32)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 33)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 34)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 35)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 36)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 37)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 38)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 39)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 40)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 41)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 42)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 43)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 44)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 45)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 46)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 47)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 48)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 49)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 50)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 51)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 52)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 53)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 54)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 55)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 56)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 57)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 58)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 59)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 60)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 61)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 62)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 63)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 64)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 65)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 66)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 67)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 68)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 69)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 70)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 71)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 72)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 73)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 74)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 75)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 76)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 77)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 78)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 79)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 80)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 81)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 82)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 83)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 84)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 85)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 86)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 87)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 88)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 89)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 90)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 91)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 92)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 93)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 94)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 95)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 96)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 97)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 98)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 99)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 100)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 101)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 102)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 103)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 104)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 105)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 106)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 107)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 108)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 109)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 110)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 111)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 112)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 113)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 114)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 115)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 116)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 117)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 118)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 119)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 120)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 121)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 122)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 123)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 124)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 125)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 126)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 127)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 128)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 129)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 130)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 131)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 132)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 133)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 134)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 135)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 136)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 137)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 138)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 139)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 140)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 141)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 142)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 143)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 144)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 145)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 146)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 147)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 148)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 149)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 150)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 151)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 152)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 153)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 154)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 155)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 156)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 157)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 158)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 159)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 160)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 161)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 162)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 163)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 164)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 165)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 166)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 167)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 168)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 169)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 170)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 171)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 172)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 173)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 174)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 175)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 176)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 177)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 178)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 179)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 180)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 181)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 182)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 183)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 184)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 185)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 186)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 187)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 188)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 189)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 190)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 191)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 192)

For example, the peptide of the invention may have the amino acid sequence

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 193)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 194)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 195)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 196)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 197)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 198)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 199)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 200)

Optionally, the peptide of the invention has an extension moiety –A-B-C at the C-terminus. Accordingly, the peptide of the invention may have an additional extension moiety of sequence -A-B-C,

wherein:

A is absent or 1, 2, 3 or 4 Ala residues or 1, 2, 3 or 4 Glu residues
B is absent or 1, 2, 3 or 4 Ala residues or 1, 2, 3 or 4 Glu residues

provided that A and B do not both comprise Ala residues, and that A and B do not both comprise Glu residues; and

C is Lys, or Lys with an acid selected from capric acid, lauric acid, myristic acid, palmitic acid, stearic acid and arachidic acid, attached via its –COOH group to the $-NH_2$ group of the Lys side chain by means of a peptide bond.

In one embodiment, groups A or B or both A and B are absent. In an embodiment when A and B are both present, A is Glu and B is Ala. For example, in one embodiment A is one Glu residue, and B is one Ala residue.

In one embodiment, C is a Lys residue without substitution.

In one embodiment, C is a Lys residue with a fatty acid attached via its –COOH group to the -NH2 group of the Lys side chain by means of a peptide bond. For example, the fatty acid may be selected from

- capric acid
- lauric acid
- myristic acid,
- palmitic acid,
- stearic acid, and
- arachidic acid. (icosanoic acid)

In further emobodiments, the C-terminal extension moiety –A-B-C is:

Lys38,
Lys38-caproyl
Lys38-lauroyl,
Lys38-myristoyl,
Lys38-palmitoyl,
Lys38-stearoyl,
Lys38-arachidoyl,
Glu38 Ala39 Lys40,
Glu38 Ala39 Lys40-caproyl,
Glu38 Ala39 Lys40-lauroyl,
Glu38 Ala39 Lys40-myristoyl,
Glu38 Ala39 Lys40-palmitoyl,
Glu38 Ala39 Lys40-stearoyl,
or Glu38 Ala39 Lys40-arachidoyl.

The arachidoyl group is also known as the icosanoyl group.

Exemplary compounds comprising the C-termainal extension moiety –A-B-C may be selected from the group comprising:

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 201)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 202)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala Lys (SEQ ID NO: 203)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 204)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 205)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-myristoyl (SEQ ID NO: 206)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-palmitoyl (SEQ ID NO: 207)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-stearoyl (SEQ ID NO: 208)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-arachidoyl (SEQ ID NO: 209)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys (SEQ ID NO: 210)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 211)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 212)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-palmitoyl (SEQ ID NO: 213)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-arachidoyl (SEQ ID NO: 214)

As mentioned above, the native human oxm sequence (which is the same as the rat and hamster) is as follows:

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn Arg Asn Asn Ile Ala (SEQ ID NO: 357)

The native bovine oxm sequence (which is the same as the porcine) is as follows:

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 358)

That is to say that it is the same as the human sequence except that Arg33 in the human peptide is replaced by Lys33 in the bovine peptide. The present invention provides analogues of oxyntomodulin as set out above. The invention further provides peptides that are analogues in which the Lys33 residue of the peptide recited above is replaced with Arg33.

In an embodiment, the invention provides a peptide of the invention in which residue Asn34 is replaced with Asp34. Certain peptides with Asn34 replaced by Asp34 are shown as PEPTIDES No 215 to 292 in Figure 1. In a further embodiment, the invention provides a

peptide in which residue Gln3 or Asp3 is replaced with Glu3. Certain peptides with Glu3 are shown as PEPTIDES No 293 to 355 in Figure 1.

The invention further comprises embodiments incorporating the sequences disclosed in the attached examples and/or figures.

Derivatives

A compound of the invention may comprise a structure set forth above, modified by well known processes including amidation, glycosylation, carbamylation, alkylation, acylation, for example acetylation, sulfation, phosphorylation, cyclization, lipidization, protein (for example albumin) conjugation and pegylation. Analogues of the invention may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

A compound of the invention may be a fusion protein, whereby the analogue of oxyntomodulin is fused to another protein or polypeptide (the fusion partner) using recombinant methods known in the art. Alternatively, such a fusion protein may be synthetically synthesized by any known method. Such a fusion protein comprises the analogue of oxyntomodulin. Any suitable peptide or protein can be used as the fusion partner (e.g., serum albumin, carbonic anhydrase, glutathione-S-transferase, single chain antibodies, antibodies, antibody fragments or thioredoxin, etc.). For example, a compound of the invention could be fused to an immunoglobulin light chain variable domain that has binding specificity for serum albumin, as described in WO 05/118642. Preferred fusion partners will not have an adverse biological activity in vivo.

Such fusion proteins, including hybrid polypeptides, may be made by linking the carboxy-terminus of the fusion partner to the amino-terminus of the analogue of oxyntomodulin or vice versa, directly, or via a linker that preferably does not involve the loss of activity of components. Where present, the linker may be chemically stable, or labile, for example a cleavable linker may be used to link the analogue of oxyntomodulin to one or more fusion partners. A resulting cleavable fusion protein may be cleaved in vivo such that an active form of a compound of the invention is released. Examples of such cleavable linkers include, but are not limited to, the linkers D-D-D-D-Y, G-P-R, A-G-G and H-P-F-H-L, which can be cleaved by enterokinase, thrombin, ubiquitin cleaving enzyme and renin, respectively. See, e.g., U.S. Patent No. 6,410,707.

Alternatively a compound of the invention may be a fusion protein, whereby the structure of the compound of the invention is attached to a fusion partner via disulphide bond(s) resulting in a covalent linkage between at least one Cys residue of the compound of the invention, and at least one Cys residue of the fusion partner.

When a protein is used as a fusion partner, it is preferably chosen so as not to exhibit undesirable antigenicity. Undesirable antigenicity may be avoided by chosing a protein which is allogenic to the animal to which the compound is to be administered.

A compound of the invention may be a physiologically functional derivative of a compound of the invention. The term "physiologically functional derivative" is used herein to denote a chemical derivative of a compound of the invention having the same physiological function as the corresponding unmodified compound of the invention. For example, a physiologically functional derivative may be convertible in the body to a compound of the invention. According to the present invention, examples of physiologically functional derivatives include esters, amides, and carbamates; preferably esters and amides.

Pharmaceutically acceptable esters and amides of the compounds of the invention may comprise a C_{1-6} alkyl-, C_{5-10} aryl-, C_{5-10} ar-C_{1-6} alkyl-, or amino acid-ester or -amide attached at an appropriate site, for example at an acid group.

Acyl side chains may be advantageous, for example, by their lipophilic nature causing the moiety to bind with albumin, thus causing a greatly reduced rate of clearance from a subject and so increasing half life and duration of effect. Whilst the acyl side chains may be lower acyl, for example C_1- C_9 acyl, especially C_{1-6} acyl, they are preferred to be C_{4-40}, in particular C_{8-25} acyl, especially C_{16} or C_{18} acyl. Palmitoyl is especially preferred as an acyl side chain as is lauroyl. Acyl side chains may be added at any position on the peptide back bone. An acyl substituent may be attached to an amino acid residue in such a way that a carboxyl group of the acyl substituent forms an amide bond with an amino group of the amino acid residue. Alternatively, an acyl substituent may be attached to an amino acid residue in such a way that an amino group of the acyl substituent forms an amide bond with a carboxyl group of the amino acid residue. In a further preferred embodiment, the present invention relates to an oxm derivative wherein an acyl substituent is attached to the parent peptide by means of a spacer. For example, the acyl substituent may be attached to the oxm moiety by means of a spacer in such a way that a carboxyl group of the spacer forms an amide bond with an amino group of the oxm moiety. It is especially preferred to add an acyl side chain (optionally via a

spacer) at a position in the peptide back bone where a lysine residue is found. This is because lysine, having a four carbon atom side chain terminating at an epsilon-amino group, is particularly suitable for easily adding an acyl side chain. It may be necessary to introduce lysine residue into the sequence solely for the purpose of providing a convenient site at which to add an acyl side chain. Alternatively the acyl side chain may be added to the lysine residue in advance of the synthesis of the peptide, whereupon its incorporation at the relevant synthetic step will result directly in acylation. This methodology is advantageous if the peptide sequence contains more than one lysine residue as it avoids the necessity of using selective conditions that acylate only the particular lysine of interest. Preferably, the peptide derivatives have three, more preferably two, and most preferably one acyl side chain substituent. Examples of acyl (and other lipophilic substituents), approaches and specific synthetic methods of attaching such to peptides (with and without the use of spacers) are described in U.S. Patent No. 6,268,343; and U.S. Patent Number 6,458,924. Further examples of saturated fatty acids suitable for acyl derivatisation of compounds of the invention are butyric (butanoic acid): $CH_3(CH_2)_2COOH$; caproic (hexanoic acid): $CH_3(CH_2)_4COOH$; caprylic (octanoic acid): $CH_3(CH_2)_6COOH$; capric (decanoic acid): $CH_3(CH_2)_8COOH$; lauric (dodecanoic acid): $CH_3(CH_2)_{10}COOH$; myristic (tetradecanoic acid): $CH_3(CH_2)_{12}COOH$; palmitic (hexadecanoic acid): $CH_3(CH_2)_{14}COOH$; stearic (octadecanoic acid): $CH_3(CH_2)_{16}COOH$; arachidic (eicosanoic acid): $CH_3(CH_2)_{18}COOH$; behenic (docosanoic acid): $CH_3(CH_2)_{20}COOH$.

According to certain preferred embodiments, acyl side chains may be added at position 30 and/or position 33 and/or positions 38 to 46 of the peptide back bone.

Pharmaceutically acceptable amides and carbonates of the compounds of Formula (I) may comprise a C_{1-6} alkyl-, C_{5-10} aryl-, C_{5-10} ar-C_{1-6} alkyl-, or amino acid-ester or -amide, or -carbamate attached at an appropriate site, for example at an amino group.

Methods for lipidization of sulfhydryl-containing compounds with fatty acid derivatives are disclosed in U.S. Patent No. 5,936,092; U.S. Patent No. 6,093,692; and U.S. Patent No. 6,225,445. Fatty acid derivatives of a compound of the invention comprising a compound of the invention linked to fatty acid via a disulfide linkage may be used for delivery of a compound of the invention to neuronal cells and tissues. Lipidisation markedly increases the absorption of the compounds relative to the rate of absorption of the corresponding unlipidised compounds, as well as prolonging blood and tissue retention of the compounds.

Moreover, the disulfide linkage in lipidised derivative is relatively labile in the cells and thus facilitates intracellular release of the molecule from the fatty acid moieties. Suitable lipid-containing moieties are hydrophobic substituents with 4 to 26 carbon atoms, preferably 5 to 19 carbon atoms. Suitable lipid groups include, but are not limited to, the following: palmitoyl ($C_{15}H_{31}$,), oleoyl ($C_{15}H_{29}$), stearoyl ($C_{17}H_{35}$), cholate; and deoxycholate.

It will be appreciated by the skilled artisan that particular amino acid residues may be introduced to the oxm sequence in order to facilitate one or more of the modifications described herein.

Cyclization methods include cyclization through the formation of a disulfide bridge and head-to-tail cyclization using a cyclization resin. Cyclized peptides may have enhanced stability, including increased resistance to enzymatic degradation, as a result of their conformational constraints. Cyclization may in particular be expedient where the uncyclized peptide includes an N-terminal cysteine group. Suitable cyclized peptides include monomeric and dimeric head-to-tail cyclized structures. Cyclized peptides may include one or more additional residues, especially an additional cysteine incorporated for the purpose of formation of a disulfide bond or a side chain incorporated for the purpose of resin-based cyclization.

A compound of the invention may be pegylated. Pegylated compounds of the invention may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). WO 2006/082517 and US 2006/171920, which are incorporated herein by reference, provide examples and associated methods of pegylating peptides and analogues and derivatives thereof.

Chemical moieties for derivitization of a compound of the invention may also be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. A polymer moiety for derivatisation of a compound of the invention may be of any molecular weight, and may be branched or unbranched. For ease in handling and manufacturing, the preferred molecular weight of a polyethylene glycol for derivatisation of a compound of the invention is from about l kDa to about 100 kDa, the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight. Polymers of other molecular weights may be used, depending on the desired therapeutic profile, for example the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known

effects of the polyethylene glycol to a therapeutic protein or analog. For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

Salts and solvates of compounds of the invention that are suitable for use in a medicament are those wherein a counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of the compounds of the invention and their pharmaceutically acceptable salts or solvates.

Suitable salts according to the invention include those formed with organic or inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed with hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycollic, lactic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, and isethionic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutical acceptable salts. Pharmaceutically acceptable salts with bases include ammonium salts, alkali metal salts, for example potassium and sodium salts, alkaline earth metal salts, for example calcium and magnesium salts, and salts with organic bases, for example dicyclohexylamine and N-methyl-D-glucomine.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. Such complexes are known as "solvates". For example, a complex with water is known as a "hydrate". The present invention provides solvates of compounds of the invention.

Peptides of the invention may be made by any suitable technique for making peptides, including but not limited to conventional methodology, for example, synthesis from

individual amino acids, especially step-wise synthesis using an automatic peptide synthesizer; modification of native peptides; or recombinant manufacturing techniques.

Conditions

The invention provides a pharmaceutical composition comprising a peptide according to the invention and one or more pharmaceutically acceptable carriers. The invention also provides a pharmaceutical composition for use in the control of appetite, feeding, food intake, energy expenditure and calorie intake, the composition comprising an effective amount of a compound according to the invention. More particularly, the invention provides a pharmaceutical composition for use in the treatment of obesity, for use in the treatment of eating disorders, or for use in the treatment of diabetes or a symptom of diabetes, or for use in the treatment or prevention of comorbidities associated with obesity or excess weight.

Moreover, the invention provides a method of reducing excess weight, for example cosmetic excess weight, comprising administering to a patient desiring to reduce weight an effective amount of a compound or a pharmaceutical composition according to the invention.

Furthermore, the invention provides a method of of treating or preventing obesity or diabetes or another co-morbitity of obesity in a subject in need thereof comprising administering to the subject an effective amount of a compound or a pharmaceutical composition according to the invention.

The invention also provides a method of reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject in need thereof comprising administering to the subject a peptide or a pharmaceutical composition according to the invention.

The invention also provides a method of causing weight loss or preventing weight gain for cosmetic purposes comprising administering to the subject a peptide or a pharmaceutical composition according to the invention.

The invention also provides a peptide of the invention for use as a medicament. It may for use as a medicament for the treatment of obesity or diabetes or of a co-morbidity of obesity. It may be for use as a medicament for reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject.

The invention also provides use of a compound according to the invention in the manufacture of a medicament for use in the treatment of a condition selected from obesity, eating disorders, diabetes, heart disease, hypertension, lipid disease, and disorders of intestinal and gastric motor activity and other aspects of gut and intestinal function, for example, water absorption and fluid handling, or pancreatic function including the endocrine pancreas, or disorders of hepato-biliary function, or prevention of cancer. In particular, the invention provides the use of a peptide of the invention for the manufacture of a medicament for the treatment of obesity or diabetes or of a co-morbidity of obesity. Further, the invention provides use of a compound according to the invention in the manufacture of a medicament for use in the control of any one or more of appetite, feeding, food intake, energy expenditure and calorie intake. In particular, the invention provides the use of a peptide of the invention for the manufacture of a medicament for reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject.

The subject to whom the compound is administered may be overweight, for example, obese. Alternatively, or in addition, the subject may be diabetic, for example having insulin resistance or glucose intolerance, or both. The subject may have diabetes mellitus, for example, the subject may have Type II diabetes. The subject may be overweight, for example, obese and have diabetes mellitus, for example, Type II diabetes.

In addition, or alternatively, the subject may have, or may be at risk of having, a disorder in which obesity or being overweight is a risk factor. Such disorders include, but are not limited to, cardiovascular disease, for example hypertension, atherosclerosis, congestive heart failure, and dyslipidemia; stroke; gallbladder disease; osteoarthritis; sleep apnea; reproductive disorders for example, polycystic ovarian syndrome; cancers, for example breast, prostate, colon, endometrial, kidney, and esophagus cancer; varicose veins; acanthosis nigricans; eczema; exercise intolerance; insulin resistance; hypertension; hypercholesterolemia; cholithiasis; osteoarthritis; orthopedic injury; insulin resistance, for example, type 2 diabetes and syndrome X; metabolic syndrome; and thromboembolic disease (see Kopelman (2000), Nature 404:635-43; Rissanen et al., British Med. J. 301, 835, 1990).

Other disorders associated with obesity include depression, anxiety, panic attacks, migraine headaches, PMS, chronic pain states, fibromyalgia, insomnia, impulsivity, obsessive-compulsive disorder, irritable bowel syndrome (IBS), and myoclonus. Furthermore, obesity

is a recognized risk factor for increased incidence of complications of general anesthesia. (See e.g., Kopelman, Nature 404:635-43, 2000). In general, obesity reduces life span and carries a serious risk of co-morbidities such as those listed above.

Other diseases or disorders associated with obesity are birth defects, maternal obesity being associated with increased incidence of neural tube defects, carpal tunnel syndrome (CTS); chronic venous insufficiency (CVI); daytime sleepiness; deep vein thrombosis (DVT); end stage renal disease (ESRD); gout; heat disorders; impaired immune response; impaired respiratory function; infertility; liver disease; lower back pain; obstetric and gynecologic complications; pancreatititis; as well as abdominal hernias; acanthosis nigricans; endocrine abnormalities; chronic hypoxia and hypercapnia; dermatological effects; elephantitis; gastroesophageal reflux; heel spurs; lower extremity edema; mammegaly which causes considerable problems such as bra strap pain, skin damage, cervical pain, chronic odors and infections in the skin folds under the breasts, etc.; large anterior abdominal wall masses, for example abdominal panniculitis with frequent panniculitis, impeding walking, causing frequent infections, odors, clothing difficulties, lower back pain; musculoskeletal disease; pseudo tumor cerebri (or benign intracranial hypertension), and sliding hiatil hernia.

Wynne et al (Intenational Journal of Obesity 12: 1729-1736, 2006) described how administering 400 nmoles of pre-prandial oxyntomodulin, three times daily for four days, increased activity-related energy expenditure by 143+/-109 kcal/day or 26.2+/-9.9% (P=0.0221); total energy expenditure by 9.4+/-4.8% (P=0.0454) and physical activity level by 9.5+/-4.6% (P=0.0495). Accordingly, the present invention further provides a method for increasing energy expenditure in a subject. The method includes, for example, peripherally administering a therapeutically effective amount of a compound of the invention to the subject, thereby altering energy expenditure. Energy is burned in all physiological processes. The body can alter the rate of energy expenditure directly, by modulating the efficiency of those processes, or changing the number and nature of processes that are occurring. For example, during digestion the body expends energy moving food through the bowel, and digesting food, and within cells, the efficiency of cellular metabolism can be altered to produce more or less heat.

In one aspect the method of the invention involves manipulation of the arcuate circuitry that alter food intake coordinately, and reciprocally alter energy expenditure. Energy expenditure is a result of cellular metabolism, protein synthesis, metabolic rate, and calorie utilization. Thus, in this aspect of the invention, administration of a compound of the invention may result in increased energy expenditure, and decreased efficiency of calorie utilization.

The invention also provides a method for improving a lipid profile in a subject. The invention also provides a method for alleviating a condition or disorder that can be alleviated by reducing nutrient availability.

Appetite can be measured by any means known to one of skill in the art. For example, decreased appetite can be assessed by a psychological assessment. For example, administration of a compound of the invention results in a change in perceived hunger, satiety, and/or fullness. Hunger can be assessed by any means known to one of skill in the art. For example, hunger is assessed using psychological assays, such as by an assessment of hunger feelings and sensory perception using a questionnaire, such as, but not limited to, a Visual Analog Score (VAS) questionnaire. In one specific, non-limiting example, hunger is assessed by answering questions relating to desire for food, drink, prospective food consumption, nausea, and perceptions relating to smell or taste.

A compound of the invention may be used for weight control and treatment, for example reduction or prevention of obesity, in particular any one or more of the following: preventing and reducing weight gain; inducing and promoting weight loss; and reducing obesity as measured by the Body Mass Index. A compound of the invention may be used in the control of any one or more of appetite, satiety and hunger, in particular any one or more of the following: reducing, suppressing and inhibiting appetite; inducing, increasing, enhancing and promoting satiety and sensations of satiety; and reducing, inhibiting and suppressing hunger and sensations of hunger. A compound of the invention may be used in maintaining any one or more of a desired body weight, a desired Body Mass Index, a desired appearance and good health.

A subject may be a subject who desires weight loss, for example female and male subjects who desire a change in their appearance. A subject may desire decreased feelings of hunger, for example the subject may be a person involved in a lengthy task that requires a high level of concentration, for example soldiers on active duty, air traffic controllers, or truck drivers on long distance routes, etc.

The present invention may also be used in treating, prevention, ameliorating or alleviating conditions or disorders caused by, complicated by, or aggravated by a relatively high nutrient availability. The term "condition or disorder which can be alleviated by reducing caloric (or nutrient) availability" is used herein to denote any condition or disorder in a subject that is either caused by, complicated by, or aggravated by a relatively high nutrient availability, or

that can be alleviated by reducing nutrient availability, for example by decreasing food intake. Subjects who are insulin resistant, glucose intolerant, or have any form of diabetes mellitus, for example, type 1, 2 or gestational diabetes, can also benefit from methods in accordance with the present invention.

Conditions or disorders associated with increased caloric intake include, but are not limited to, insulin resistance, glucose intolerance, obesity, diabetes, including type 2 diabetes; eating disorders, insulin-resistance syndromes, and Alzheimer's disease.

According to the present invention, a compound of the invention is preferably used in the treatment of a human. However, while the compounds of the invention will typically be used to treat human subjects they may also be used to treat similar or identical conditions in other vertebrates for example other primates; farm animals for example swine, cattle and poultry; sport animals for example horses; companion animals for example dogs and cats.

In summary, the invention also provides a peptide of the invention for use as a medicament for the prevention or treatment of obesity. There is also provided a peptide of the invention for use as a medicament for the prevention or treatment of diabetes or of a co-morbidity of obesity. Further, there is provided a peptide of the invention for use as a medicament for reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject.

The invention also provides a method of treating or preventing obesity in a subject in need thereof comprising administering to the subject a peptide according to the invention. There is also provided a method of treating or preventing diabetes or of a co-morbidity of obesity in a subject in need thereof comprising administering to the subject a peptide according to the invention. Further, there is provided a method of reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject in need thereof comprising administering to the subject a peptide according to the invention or a pharmaceutical composition according to the invention.

Compositions

While it is possible for the active ingredient to be administered alone, it is preferable for it to be present in a pharmaceutical formulation or composition. Accordingly, the invention provides a pharmaceutical formulation comprising a compound of the invention, or a variant

or derivative thereof, or a salt or solvate thereof, as defined above, and a pharmaceutically acceptable excipient. Pharmaceutical compositions of the invention may take the form of a pharmaceutical formulation as described below.

The pharmaceutical formulations according to the invention include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered doses, pressurized aerosols, nebulizers or insufflators, and including intranasally or via the lungs), rectal and topical (including dermal, transdermal, transmucosal, buccal, sublingual, and intraocular) administration, although the most suitable route may depend upon, for example, the condition and disorder of the recipient.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with a pharmaceutical carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Various 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., Journal of Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S, 1988.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The present compounds can, for example, be administered in a form suitable for immediate

release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The compounds can be formulated, for administration orally, with delivery agents or carriers that facilitate the transport of therapeutic macromolecules and highly charged compounds across cell membranes, especially in the small intestine. Such delivery agents or carriers may in addition inhibit enzymatic degradation of peptides during passage through the gastrointestinal (GI) tract and/or the formulation may include additional agents that protect against such degradation. The present compounds can also be administered liposomally.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of the invention can also be delivered through the oral cavity by sublingual and/or buccal administration. Moulded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from

sterile powders, granules and tablets of the kind previously described. Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor. An aqueous carrier may be, for example, an isotonic buffer solution at a pH of from about 3.0 to about 8.0, preferably at a pH of from about 3.5 to about 7.4, for example from 3.5 to 6.0, for example from 3.5 to about 5.0. Useful buffers include sodium citrate-citric acid and sodium phosphate-phosphoric acid, and sodium acetate/acetic acid buffers. The composition preferably does not include oxidizing agents and other compounds that are known to be deleterious to oxm and oxm agonists.

Excipients that can be included are, for instance, other proteins, such as human serum albumin or plasma preparations. If desired, the pharmaceutical composition may also contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art. Conveniently in compositions for nasal aerosol or inhalation administration the compound of the invention is delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoro-methane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator can be formulated to contain a powder mix of the compound and a suitable powder base, for example lactose or starch. In one specific, non-limiting example, a compound of the invention is administered as an aerosol from a metered dose valve, through an aerosol adapter also known as an actuator. Optionally, a stabilizer is also included, and/or porous particles for deep lung delivery are included (e.g., see U.S. Patent No. 6,447,743). Intranasal formulations may include delivery agents for reversibly opening the nasal tight junction, thereby increasing drug permeability (e.g., see US Patent Application 10/322,266).

Formulations for rectal administration may be presented as a retention enema or a suppository with the usual carriers such as cocoa butter, synthetic glyceride esters or polyethylene glycol. Such carriers are typically solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerine or sucrose and acacia. Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of the invention are also suitably administered as sustained-release systems. Suitable examples of sustained-release systems of the invention include suitable polymeric materials, for example semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules; suitable hydrophobic materials, for example as an emulsion in an acceptable oil; or ion exchange resins; and sparingly soluble derivatives of the compound of the invention, for example, a sparingly soluble salt. Sustained-release systems may be administered orally; rectally; parenterally; intracistemally; intravaginally; intraperitoneally; topically, for example as a powder, ointment, gel, drop or transdermal patch; bucally; or as an oral or nasal spray.

Preparations for administration can be suitably formulated to give controlled release of compounds of the invention. For example, the pharmaceutical compositions may be in the form of particles comprising one or more of biodegradable polymers, polysaccharide jellifying and/or bioadhesive polymers, amphiphilic polymers, agents capable of modifying the interface properties of the particles of the compound of the invention. These compositions exhibit certain biocompatibility features which allow a controlled release of the active substance. See U.S. Patent No. 5,700,486.

A compound of the invention may be delivered by way of a pump (see Langer, Science 249:1527-1533, 1990; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201, 1987; Buchwald et al., Surgery 88:507, 1980; Saudek et al., N. Engl. J. Med. 321:574, 1989) or by a continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The key factor in selecting an appropriate dose is the result obtained, as measured by decreases in total body weight or ratio of fat to lean mass, or by other criteria for measuring control or prevention of obesity or prevention of obesity-related conditions, as are deemed appropriate by the practitioner. Other controlled release systems are discussed in the review by Langer, supra. In another aspect of the disclosure, compounds of the invention are delivered by way of an implanted pump, described, for example, in U.S. Patent No. 6,436,091; U.S. Patent No. 5,939,380; U.S. Patent No. 5,993,414.

Implantable drug infusion devices are used to provide patients with a constant and long term dosage or infusion of a drug or any other therapeutic agent. Essentially such device may be categorized as either active or passive. A compound of the present invention may be formulated as a depot preparation. Such a long acting depot formulation can be administered by implantation, for example subcutaneously or intramuscularly; or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials, for example as an emulsion in an acceptable oil; or ion exchange resins; or as a sparingly soluble derivatives, for example, as a sparingly soluble salt.

A therapeutically effective amount of a compound of the invention may be administered as a single pulse dose, as a bolus dose, or as pulse doses administered over time. Thus, in pulse doses, a bolus administration of a compound of the invention is provided, followed by a time period wherein a compound of the invention is administered to the subject, followed by a second bolus administration. In specific, non-limiting examples, pulse doses of a compound of the invention are administered during the course of a day, during the course of a week, or during the course of a month.

In one embodiment, a therapeutically effective amount of a compound of the invention is administered with a therapeutically effective amount of another agent, for example an additional appetite suppressant, a food-intake-reducing, dipetidyl peptidase-IV (DPP-IV) inhibiting, plasma glucose-lowering or plasma lipid-altering agent. Specific, non-limiting examples of an additional appetite suppressant include amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine, fenfluramine, dexfenfluramine, sibutramine, rimonabant, and fluoxetine. Specific, non-limiting examples of DPP-IV inhibitors include Januvia (sitagliptin phosphate), and Galvus (vildagliptin). The compound

of the invention can be administered simultaneously with the additional agent, or it may be administered sequentially. Thus, in one embodiment, the compound of the invention is formulated and administered with an additional agent as a single dose.

In another embodiment, a therapeutically effective amount of a compound of the invention is administered in combination with a therapeutically effective amount of another agent, for the treatment of diseases other than obesity, for example diabetes, in which specific non limiting examples of an additional therapeutic agent are GLP-1 or an analogue thereof, exenatide, and pramlintide.

A compound of the invention may be administered whenever the effect, e.g., appetite suppression, decreased food intake, or decreased caloric intake, is desired, or slightly before to whenever the effect is desired, such as, but not limited to about 10 minutes, about 15 minutes, about 30 minutes, about 60 minutes, about 90 minutes, about 120 minutes, about 4 hours, about 8 hours, or about 12 hours, before the time the effect is desired.

A compound of the invention may be administered in combination with whenever the effect, e.g., appetite suppression, decreased food intake, or decreased caloric intake, is desired, or slightly before to whenever the effect is desired, such as, but not limited to about 10 minutes, about 15 minutes, about 30 minutes, about 60 minutes, about 90 minutes, about 120 minutes, about 4 hours, about 8 hours, or about 12 hours, before the time the effect is desired.

Dosages

The therapeutically effective amount of a compound of the invention will be dependent on the molecule utilized, the subject being treated, the severity and type of the affliction, and the manner and route of administration. For example, a therapeutically effective amount of a compound of the invention may vary from about 0.01 μg per kilogram (kg) body weight to about 1 g per kg body weight, for example about .0.1 μg to about 5 mg per kg body weight, or about 1 μg to about 1 mg per kg body weight per day. A compound of the invention may be administered to a subject at 0.5 to 200 picomole (pmol) per kg body weight, or about 20 pmol per kg body weight. For especially active compounds or compounds administered by an especially efficient route, in one specific, non-limiting example, a compound of the invention is administered in a dose of about 1 nmol or more, 2 nmol or more, 5 nmol or more, or 10 nmol or more and the dose of the compound of the invention is generally not more than 100 nmol, for example, the dose is 90 nmols or less, 80 nmols or less, 70 nmols or less, 60 nmols or less, 50 nmols or less, 40 nmols or less, 30 nmols or less, 20 nmols or less, or 10 nmols or less. For a less active compound or a compound administered by a less efficient route, in

another specific, non-limiting example, a compound of the invention is administered in a dose of about 100 nmol or more, 200 nmol or more, 300 nmol or more, 400 nmol or more, 500 nmol or more, 600 nmol or more, 700 nmol or more, 800 nmol or more, 900 nmol or more, or 1 μmol or more and the dose of the compound of the invention is generally not more than 10 μmols, for example, the dose is 9 μmols or less, 8 μmols or less, 7 μmols or less, 6 μmols or less, 5 μmols or less, 4 μmols or less, 3 μmols or less, 2 μmols or less, 1 μmol or less. For example, a dosage range may comprise any combination of any of the specified lower dose limits with any of the specified upper dose limits. Thus, examples of non-limiting dose ranges of compounds of the invention are within the range of from 1 nmol to 1 μmol, from 1 to 900 nmols, or from 1 to 800 nmols. For especially active compounds or compounds administered by an especially efficient route, the dose may be from 1 nmol to 100 nmol, from 2 to 80 nmols, or from 5 to 60 nmols. For a less active compound or a compound administered by a less efficient route, the dose may be from 100 nmol to 10 μmol, from 200 nmol to 5 μmols, or from 500 nmols to 2 μmols.

In one specific, non-limiting example, from about 0.5 to about 50 nmol of a compound of the invention is administered, for example about 1 to about 20 nmol, for example, about 2 nmol is administered as a subcutaneous injection. The exact dose is readily determined by one of skill in the art based on the potency of the specific compound utilized, the age, weight, sex and physiological condition of the subject.

In another specific non-limiting example, a compound of the invention is administered to a subject in a dose of about 1 μg to about 2 mg per dose, about once, about twice, about three times, or about four times per day., A therapeutically effective amount of a compound of the invention may vary from about 0.01 μg per kilogram (kg) body weight to about 1 g per kg body weight, for example about 0.1 μg to about 5 mg per kg body weight, or about 5 μg to about 1 mg per kg body weight per day. Bearing in mind that a typical oxyntomudilin analogue of the invention has a molecular weight of around 4500, a compound of the invention may be administered to a subject at 2.25 to 900 ng per kg body weight, or about 90 ng per kg body weight. For especially active compounds or compounds administered by an especially efficient route, in one specific, non-limiting example, a compound of the invention is administered in a dose of about 4.5 μg or more, 9 μg or more, 22.5 μg or more, or 45 μg or more and the dose of the compound of the invention is generally not more than 450 μg, for example, the dose is 405 μg or less, 360 μg or less, 315 μg or less, 270 μg or less, 225 μg or less, 180 μg or less, 135 μg or less, 90 μg or less, or 45 μg or less. For a less active compound or a compound administered by a less efficient route, in another specific, non-

limiting example, a compound of the invention is administered in a dose of about 450 μg or more, 900 μg or more, 1350 μg or more, 1800 μg or more, 2250 μg or more, 2700 μg or more, 3150 μg or more, 3600 μg or more, 4050 μg or more, or 4500 μg or more and the dose of the compound of the invention is generally not more than 45000 μg , for example, the dose is 40500 μg or less, 36000 μg or less, 31500 μg or less, 27000 μg or less, 22500 μg or less, 18000 μg or less, 13500 μg or less, 9000 μg or less, 45000 μg or less. For example, a dosage range may comprise any combination of any of the specified lower dose limits with any of the specified upper dose limits. Thus, examples of non-limiting dose ranges of compounds of the invention are within the range of from 4.5 μg to 4500 μg, from 4.5 to 4050 μg , or from 4.5 to 3600 μg. For especially active compounds or compounds administered by an especially efficient route, the dose may be from 4.5 μg to 450 μg, from 9 to 360 μg, or from 22.5 to 270 μg. For a less active compound or a compound administered by a less efficient route, the dose may be from 450 μg to 45000 μg, from 900 μg to 22500 μg, or from 2250 to 9000 μg.

Suitable doses of compounds of the invention also include those that result in a reduction in calorie intake, food intake, or appetite, or increase in energy expenditure that is equivalent to the reduction in calorie intake, food intake, or appetite, or to increase the energy expenditure, caused by levels of oxm that have been observed in man. Examples of doses include, but are not limited to doses that produce the effect demonstrated when the serum levels of oxm are from about 800 pM to about 1300 pM, or from about 900 pM to about 1000 pM, or about 950 pM.

Suitable doses of compounds of the invention also include those that are equivalent to levels of oxm seen in subjects experiencing conditions associated with reduced appetite, for example jejunoileal bypass (Sarson *et al., Int J Obes*, 1981, 5:471–480; Holst *et al., Scand J Gastroenterol*, 1979, 14:205–207).

In a study of the effects of oxyntomodulin on appetite suppression and food intake reduction in humans (Cohen *et al., J. Clin. Endocrinol. Metab.*, 2003, 88(10), 4696-4701) it was found that an infusion of oxyntomodulin to human volunteers at 3.0 pmol/kg.min for 90 minutes led to a significantly reduced *ad libitum* energy intake (19.3 +/- 5.6%; P<0.01). The total oxyntomodulin infused was 270 pmol/kg body weight. The observed oxyntomodulin-like immunoreactivity in the blood of the subjects rose to around 800 pmol/L during the infusion.

In a study of the effects of oxyntomodulin on weight loss in humans (Wynne *et al., Diabetes.*, 2005, 54(Aug), 2390-2395) it was found that subcutaneous injections of oxyntomodulin to humans volunteers resulted in a significant reduction of body weight. Over the study period of 28 days, body weight of the treatment group was reduced by 2.3 ± 0.4 kg in the treatment group compared with 0.5 ± 0.5 kg in the control group (P = 0.0106). 1.8 mg (approximately 400 nmol) of oxyntomodulin was administered three times daily 30 mins before meals. On average, the treatment group had an additional 0.45kg weight loss per week. Energy intake by the treatment group was significantly reduced by 170 ± 37 kcal (25 ± 5%) at the initial study meal within the 28 day study period (P = 0.0007) and by 250 ± 63 kcal (35 ± 9%) at the final study meal during the 28 day study period (P = 0.0023), with no change in subjective food palatability. Oxyntomodulin treatment resulted in weight loss and a change in the levels of adipose hormones consistent with a loss of adipose tissue. The anorectic effect was maintained over the 4-week period.

The compounds of the invention have been found to be more active and/or longer-lasting than native oxyntomodulin as used in human studies to date (Cohen *et al.* (2003) and Wynne *et al.* (2005) *Diabetes* 54(Aug), 2390-2395). The dosage required for a compound of the invention may be somewhat lower than that required for native oxyntomodulin. The dosages of peptides of the invention required to observe an effect in humans can be expected to be a lower, for example 2.5 times, 200 times, 400 times, and 1-4000 times lower than the dose of native oxyntomodulin. The magnitude of the potency of the peptides of the invention in comparison to the native oxyntomodulin peptide may also allow the frequency of administration a compound of the invention to be lower than that required for native oxyntomodulin.

The disclosure is illustrated by the following non-limiting Examples.

EXAMPLES

Materials and Methods

Animals: All animal procedures were approved by the British Home Office Animals (Scientific Procedures) Act 1986 (Project License number 70/5516). Male C57BL/6 mice and male Wistar rats were maintained in individual cages under controlled temperature (21-23 °C) with *ad libitum* access to standard chow (RM1 diet, SDS Ltd, Witham, Essex, UK) and to water. The light cycle was 12 hours light and 12 hours dark with 'dawn' at 07:00, lights full on at 07:30, 'dusk' at 19:00 with lights off at 19:30. These times were fixed in the animal facility. All animals were handled almost daily for on average nine days prior to the first

study. During the acclimatization period, mice received two saline injections at least two days apart in order to further acclimatize to the procedure on the study days. It was found in rats that minimising the number of injections provided an optimal response, and so acclimatization injections were not used.

Intra-peritoneal (IP) injections: IP injections were administered to mice via a 0.5 ml syringe with a 29-gauge needle (maximum injection volume 0.1 ml). The maximum volume administered IP was 0.1 ml.

Subcutaneous (SC) injections: SC injections were administered to rats via a 0.5 ml syringe with a 29-gauge needle (maximum injection volume 0.2 ml), in a volume of 0.1 ml if administered to the thigh skin, or 0.2 ml if administered to the neck scruff.

Study protocol: C57BL/6 mice (20-35 g) were injected with the peptide under investigation following a 20-hour fast. Wistar rats were injected following a 24-hour fast. Typically 6 to 10 rodents were used per experimental group. Injections were typically administered at 9:00. A pre-weighed quantity of chow was presented immediately after injection. The remaining food was measured at regular time intervals (e.g. 1, 2, 3,4, 6, 8, 24, 32 and 48 hours following injection) and food intake calculated.

Peptides Synthesis

Synthesis of peptides

Peptides were produced by solid phase step-wise synthesis (SPSS) using the Fmoc N-terminal protection strategy. Chain assembly was performed on Applied Biosystems 431, 433 or Pioneer automated synthesisers. Solid phase resins were used with factory pre-loaded C terminal amino acid or with an amide linker as appropriate. The following side-chain protecting groups were used: Asn(Trt), Gln(Trt), Cys(Trt), His(Trt), Asp(tBu), Glu(tBu), Ser(tBu), Thr(tBu), Tyr(tBu), Arg(Pbf), Lys(Boc), Trp(Boc). In some cases, where synthesis difficulty was anticipated, pre-formed oxazolidine dipeptides were used in place of respective monomers. All chemicals (from various suppliers including Applied Biosystems, Merck Biosciences and AGCT) were synthesis grade. Feedback monitoring to optimise syntheses was employed on all instruments.

Recovery of peptides

After synthesis, peptides were cleaved from the solid phase resin support and fully side chain deprotected. This was achieved by treatment for 2 hours with trifluoroacetic acid (TFA) containing 4% water and 2.5% tri-isopropylsilane to scavenge side-chain protecting groups. Peptide-TFA solutions were filtered from the resins and the peptides precipitated with methyl tertiary butyl ether (MTBE). Peptides were isolated by centrifugation, washed in MTBE and dried under vacuum.

Analysis and purification of peptides

Peptides were dissolved in de-ionized water, with addition of acetic acid where necessary. Peptide solutions were clarified by centrifugation or filtration (Whatman GD/X syringe filter) prior to analysis and purification.

All peptide products were analysed by reverse phase HPLC on an Applied Biosystems BioCad instrument using an analytical Brownlee Aquapore RP300 C8 or Phenomenex Synergi Hydro C18 column. Purification was performed by reverse phase HPLC using preparative columns of the above types. Acetonitrile-water gradients (with TFA as counter–ion) were used for elution of products. Capillary Zone Electrophoresis (CZE) was performed on crude and purified peptides using a Hewlett Packard 3DCE instrument. Molecular weight determination was performed on a Micromass MALDI –R mass spectrometer.

Purified peptides were freeze-dried in pharmaceutical grade glass vials (Adelphi Vials) and closed under vacuum.

Derivatised side chains

Peptides having side chains derivatised with an acyl or alkyl group were prepared by standard methods.

Solubility of derivatised peptides

Derivatised polypeptides should be fully dissolved before administration. In order to achieve solubility it may be necessary to dissolve the polypeptides in a small amount of dilute alkali (for example, 50 µl 0.01 NaOH) and then dilute the dissolved peptide in saline.

Inhibition of food intake experiments.

Example 1 (comparative example).

The feeding effect of native oxyntomodulin (human) was investigated by intraperitoneal injection of 1400 nmoles/kg to groups of fasted mice. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figure 2. Due to the relatively low activity of native oxyntomodulin, a high dose was given. Less significant results are observed with lower doses.

Example 2 (comparative example).

The feeding effect of native oxyntomodulin (human) was investigated by subcutaneous injection of 1400 nmoles/kg to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 6 hours is shown in comparison to saline in Figure 3. It can be seen that even at a high dose of 1400 nmol/kg, native oxyntomodulin is not capable of reducing food intake in fasted rats under these conditions. At lower doses, the same lack of effectiveness is observed.

Example 3.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 178 [SEQ.ID NO:178]; PEPTIDE NO: 82 [SEQ ID NO:82]; PEPTIDE NO: 58 [SEQ ID NO:58]; and PEPTIDE NO: 52 [SEQ ID NO:52]. The analogues were administered at a dose of 10 (PEPTIDE NO: 178 [SEQ ID NO:178]) and 10 (PEPTIDE NO: 82 [SEQ ID NO:82]; PEPTIDE NO: 58 [SEQ ID NO:58]; and PEPTIDE NO: 52 [SEQ ID NO:52]) nmoles/kg by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figures 4 to 7. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 4.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 164 [SEQ ID NO:164]; and PEPTIDE NO: 167 [SEQ ID NO:167]. The analogues were administered at a dose of 4 and 5 nmoles/kg respectively, by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 48 hours (PEPTIDE NO: 164 [SEQ ID NO:164]) and 32 hours (PEPTIDE NO:167 [SEQ ID NO:167]) is shown in comparison to saline in Figures 8 and 9. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the

whole 48 (PEPTIDE NO: 164 [SEQ ID NO:164]) and 32 (PEPTIDE NO: 167 [SEQ ID NO:167]) hour period; that is to say that the food intake over the first 24 hour period is lower than in the saline control and continues to remain below it in the following 24 hours (PEPTIDE NO: 164 [SEQ ID NO:164]) or 8 hours (PEPTIDE NO:167 [SEQ ID NO:167]). It is also lower than in the control group treated with native oxyntomodulin.

Example 5.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 100 [SEQ ID NO:100]; and PEPTIDE NO: 148 [SEQ ID NO:148]. The analogues were administered at a dose of 20 and 10 nmoles/kg respectively, by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figures 10 and 11. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 6.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 60 [SEQ ID NO:60]; and PEPTIDE NO: 94 [SEQ ID NO:94]. The analogues were administered at a dose of 100 and 5 nmoles/kg respectively, by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figures 12 and 13. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 7.

The feeding effects of the following analogue of oxyntomodulin was investigated: PEPTIDE NO: 155 [SEQ ID NO:155]. The analogue was administered at a dose of 4 nmoles/kg by subcutaneous injection to a group of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 32 hours is shown in comparison to saline in Figure 14. The analogue demonstrates a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 32 hour period; that is to say that the food intake over the first 24 hour period is lower

than in the saline control and continues to remain below it in the following 8 hours. It is also lower than in the control group treated with native oxyntomodulin.

Example 8.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 142 [SEQ ID NO:142]; PEPTIDE NO: 184 [SEQ ID NO:184]; and PEPTIDE NO: 172 [SEQ ID NO:172]. The analogues were administered at a dose of 3 nmoles/kg by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figures 15 to 17. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 9.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 4 [SEQ ID NO:4]; PEPTIDE NO: 195 [SEQ ID NO:195]; PEPTIDE NO: 136 [SEQ ID NO:136]; and PEPTIDE NO: 108 [SEQ ID NO:108]. The analogues were administered at doses of 5, 800, 5 and 100 nmoles/kg respectively, by intraperitoneal injection to groups of fasted mice. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figures 18 to 21. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 10.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 142 [SEQ ID NO:142]; PEPTIDE NO: 22 [SEQ ID NO:22]; PEPTIDE NO: 153 [SEQ ID NO:153]; and PEPTIDE NO: 199 [SEQ ID NO:199]. The analogues were administered at a dose of 3 nmoles/kg, 200 nmoles/kg (PEPTIDE NO: 153 [SEQ ID NO:153]), and 500 nmoles/kg (PEPTIDE NO: 199 [SEQ ID NO:199]) by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figures 22 to 25. The analogues demonstrate a potent and long acting suppression of food

intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 11.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 210 [SEQ ID NO:210]; PEPTIDE NO: 211 [SEQ ID NO:211]; PEPTIDE NO: 213 [SEQ ID NO:213]; and PEPTIDE NO: 214 [SEQ ID NO:214]. The analogues were administered at a dose of 20, 200, 400 and 400 nmoles/kg respectively by intraperitoneal injection to groups of fasted mice. A further group was administered saline (control). Mean cumulative food intake over the course of 48 hours is shown in comparison to saline in Figures 26 to 29. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 48 hour period; that is to say that the food intake over the first 24 hour period is lower than in the saline control and continues to remain below it in the following 24 hours. It is also lower than in the control group treated with native oxyntomodulin.

Example 12.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 201 [SEQ ID NO:201]; and PEPTIDE NO: 202 [SEQ ID NO:202]. The analogues were administered at a dose of 5 nmoles/kg by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 48 hours is shown in comparison to saline in Figures 30 and 31. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 48 hour period; that is to say that the food intake over the first 24 hour period is lower than in the saline control and continues to remain below it in the following 24 hours. It is also lower than in the control group treated with native oxyntomodulin.

Example 13.

The feeding effect of the following analogue of oxyntomodulin was investigated: PEPTIDE NO: 203 [SEQ ID NO:203]. The analogue was administered at a dose of 100 nmoles/kg by subcutaneous injection to a group of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figure 32. The analogue demonstrates a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the

whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 14.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 204 [SEQ ID NO:204]; and PEPTIDE NO: 205 [SEQ ID NO:205]. The analogues were administered at a dose of 5 nmoles/kg by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 32 hours is shown in comparison to saline in Figures 33 and 34. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 32 hour period; that is to say that the food intake over the first 24 hour period is lower than in the saline control and continues to remain below it in the following 8 hours. It is also lower than in the control group treated with native oxyntomodulin.

Example 15.

The feeding effects of the following analogues of oxyntomodulin were investigated: PEPTIDE NO: 206 [SEQ ID NO:206]; PEPTIDE NO: 207 [SEQ ID NO:207]and PEPTIDE NO: 209 [SEQ ID NO:209]. The analogues were administered at a dose of 80 nmoles/kg by subcutaneous injection to groups of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 48 hours is shown in comparison to saline in Figures 35 to 37. The analogues demonstrate a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 48 hour period; that is to say that the food intake over the first 24 hour period is lower than in the saline control and continues to remain below it in the following 24 hours. It is also lower than in the control group treated with native oxyntomodulin.

Example 16.

The feeding effect of the following analogue of oxyntomodulin was investigated: PEPTIDE NO: 215 [SEQ ID NO:215]. The analogue was administered at a dose of 5 nmoles/kg by subcutaneous injection to a group of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figure 38. The analogue demonstrates a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than

in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 17.

The feeding effect of the following analogue of oxyntomodulin was investigated: PEPTIDE NO: 216 [SEQ ID NO:216]. The analogue was administered at a dose of 10 nmoles/kg by subcutaneous injection to a group of fasted rats. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figure 39. The analogue demonstrates a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 18.

The feeding effect of the following analogue of oxyntomodulin was investigated: PEPTIDE NO: 355 [SEQ ID NO:355]. The analogue was administered at a dose of 5 nmoles/kg by subcutaneous injection to a group of fasted mice. A further group was administered saline (control). Mean cumulative food intake over the course of 4 hours is shown in comparison to saline in Figure 40. The analogue demonstrates a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 4 hour period; that is to say that the food intake over the 4 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

Example 19.

The feeding effect of the following analogue of oxyntomodulin was investigated: PEPTIDE NO: 130 [SEQ ID NO:130]. The analogue was administered at a dose of 20 nmoles/kg by subcutaneous injection to a group of fasted mice. A further group was administered saline (control). Mean cumulative food intake over the course of 24 hours is shown in comparison to saline in Figure 41. The analogue demonstrates a potent and long acting suppression of food intake in comparison to the saline control. The food intake suppression continues for the whole 24 hour period; that is to say that the food intake over the 24 hour period is lower than in the saline control. It is also lower than in the control group treated with native oxyntomodulin.

It will be appreciated that throughout the above examples, compounds of the invention are capable of inhibiting food intake at doses markedly lower than that of the native peptide used in the comparator experiments.

Claims

1. A peptide comprising the amino acid sequence:

Xaa1 Xaa2 Xaa3 Gly4 Thr5 Phe6 Thr7 Ser8 Asp9 Tyr10 Ser11 Lys12 Tyr13 Leu14

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 Trp25 Leu26

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 Lys33 Asn34 Asn35 Ile36 Ala37;

wherein:

Xaa1 is His1 or D-His1,
Xaa2 is Ser2 or Ala2,
Xaa3 is Gln3 or Asp3;

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is:

Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
or Asp15 Ser16 Arg17 Arg18 Ala19 Gln20 Asp21 Phe22 Val23 Gln24;

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is:

Met27 Asn28 Thr29 Lys30 Arg31 Asn32,
Lys27 Asn28 Ala29 Gly30 Pro31 Ser32,
or Lys27 Asn28 Gly29 Gly30 Pro31 Ser32

or a peptide as set out above in which residue Asn34 is replaced with Asp34;

or a peptide as set out above in which Xaa3 is Glu3;

with the proviso that if
Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is
Asp15 Ser16 Arg17 Arg18 Ala19 Gln20 Asp21 Phe22 Val23 Gln24,

then Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is not
Met27 Asn28 Thr29 Lys30 Arg31 Asn32

(SEQ ID NO: 356).

2. A peptide as claimed in claim 1, wherein

Xaa15 Xaa16 Xaa17 Xaa18 Xaa19 Xaa20 Xaa21 Xaa22 Xaa23 Xaa24 is:

Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Glu16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
Glu15 Gln16 Glu17 Leu18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Glu24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Leu23 Gln24,
Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Glu24,
or Glu15 Gln16 Glu17 Ile18 Val19 Lys20 Tyr21 Phe22 Ile23 Gln24

(SEQ ID NO: 359).

3. A peptide as claimed in any of claims 1 to 2, wherein

Xaa1 Xaa2 Xaa3 is

His1 Ser2 Gln3, or.
D-His1 Ser2 Gln3, or
D-His1 Ala2 Gln3, or
D-His1 Ala2 Asp3

(SEQ ID NO: 360).

4. A peptide as claimed in any of claims 1 to 3, wherein

Xaa27 Xaa28 Xaa29 Xaa30 Xaa31 Xaa32 is:

Lys27 Asn28 Ala29 Gly30 Pro31 Ser32,
or Lys27 Asn28 Gly29 Gly30 Pro31 Ser32

(SEQ ID NO: 361).

5. A peptide as claimed in claim 1 having an amino acid sequence selected from the group consisting of:

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 1)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 2)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 3)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 4)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 5)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 6)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 7)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 8)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 9

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 10)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 11)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 12)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 13)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 14)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 15)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 16)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 17)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 18)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 19)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 20)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 21)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 22)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 23)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 24)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 25)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 26)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 27)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 28)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 29)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 30)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 31)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 32)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 33)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 34)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 35)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 36)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 37)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 38)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 39)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 40)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 41)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 42)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 43)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 44)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 45)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 46)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 47)

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 48)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 49)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 50)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 51)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 52)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 53)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 54)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 55)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 56)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 57)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 58)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 59

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 60

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 61

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 62)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 63)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 64)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 65)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 66)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 67)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 68)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 69)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 70)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 71)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 72)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 73)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 74)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 75)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 76)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 77)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 78)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 79)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 80)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 81)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 82)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 83)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 84)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 85)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 86)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 87)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 88)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 89)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 90)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 91)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 92)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 93)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 94)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 95)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 96)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 97)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 98)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 99)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 100)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 101)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 102)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 103)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 104)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 105)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 106)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 107)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 108)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 109)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 110)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 111)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 112)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 113)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 114)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 115)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 116)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 117)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 118)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 119)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 120)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 121)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 122)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 123)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 124)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 125)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 126)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 127)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 128)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 129)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 130)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 131)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 132)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 133)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 134)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 135)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 136)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 137)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 138)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 139)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 140)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 141)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 142)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 143)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 144)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 145)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 146)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 147)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 148)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 149)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 150)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 151)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 152)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 153)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 154)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 155)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 156)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 157)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 158)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 159)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 160)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 161)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 162)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 163)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 164)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 165)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 166)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 167)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 168)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 169)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 170)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 171)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 172)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 173)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 174)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 175)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 176)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 177)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 178)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 179)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 180)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 181)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 182)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 183)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 184)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 185)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 186)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 187)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 188)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 189)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 190)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 191)

D-HisAla Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 192)

6. A peptide as claimed in any one of claims 1 to 5, wherein the peptide has an additional extension moiety of sequence -A-B-C, wherein:

A is absent or 1, 2, 3 or 4 Ala residues or 1, 2, 3 or 4 Glu residues

B is absent or 1, 2, 3 or 4 Ala residues or 1, 2, 3 or 4 Glu residues

provided that A and B do not both comprise Ala residues, and that A and B do not both comprise Glu residues; and

C is Lys, or Lys with an acid selected from capric acid, lauric acid, myristic acid, palmitic acid, stearic acid and arachidic acid, attached via its –COOH group to the $-NH_2$ group of the Lys side chain by means of a peptide bond.

7. A peptide as claimed in claim 6, wherein A or B or both A and B are absent.

8. A peptide as claimed in claim 6, wherein A is one Glu residue, and B is one Ala residue.

9. A peptide as claimed in any of claims 6 to 8, wherein C is a Lys residue.

10. A peptide as claimed in any of claims 6 to 8, wherein:

- C is a Lys residue with lauric acid attached via its –COOH group to the -NH2 group of the Lys side chain by means of a peptide bond.
- C is a Lys residue with myristic acid attached via its –COOH group to the -NH2 group of the Lys side chain by means of a peptide bond.
- C is a Lys residue with palmitic acid attached via its –COOH group to the -NH2 group of the Lys side chain by means of a peptide bond.
-C is a Lys residue with stearic acid attached via its –COOH group to the -NH2 group of the Lys side chain by means of a peptide bond.
- C is a Lys residue with arachidic acid attached via its –COOH group to the -NH2 group of the Lys side chain by means of a peptide bond.
- C is a Lys residue with capric acid attached via its –COOH group to the -NH2 group of the Lys side chain by means of a peptide bond.

11. A peptide according to claim 6 having a structure sequence selected from the group consisting of:

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 201)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 202)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala Lys (SEQ ID NO: 203)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 204)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 205)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-myristoyl (SEQ ID NO: 206)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-palmitoyl (SEQ ID NO: 207)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-stearoyl (SEQ ID NO: 208)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-arachidoyl (SEQ ID NO: 209)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys (SEQ ID NO: 210)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 211)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 212)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-palmitoyl (SEQ ID NO: 213)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-arachidoyl (SEQ ID NO: 214)

12. A peptide according to claim 1 having a structure sequence selected from the group consisting of:

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 215)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 216)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 217)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 218)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 219)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 220)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 221)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala (SEQ ID NO: 222)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 223)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 224)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 225)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala (SEQ ID NO: 226)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 227)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 228)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 229)

D-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 230)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 231)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala (SEQ ID NO: 232)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 233)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 234)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 235)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 236)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 237)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 238)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 239)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 240)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 241)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 242)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala Lys (SEQ ID NO: 243)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 244)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 245)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-myristoyl (SEQ ID NO: 246)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-palmitoyl (SEQ ID NO: 247)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-stearoyl (SEQ ID NO: 248)

D-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-arachidoyl (SEQ ID NO: 249)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys (SEQ ID NO: 250)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 251)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys-palmitoyl (SEQ ID NO: 252)

D-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys-arachidoyl (SEQ ID NO: 253)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 254)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 255)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 256)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 257)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 258)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 259)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 260)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala (SEQ ID NO: 261)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 262)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 263)

L-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 264)

L-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala (SEQ ID NO: 265)

L-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 266)

L-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 267)

L-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 268)

L-His Ala Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 269)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 270)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Glu Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala (SEQ ID NO: 271)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 272)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 273)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 274)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 275)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 276)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 277)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 278)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala (SEQ ID NO: 279)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 280)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 281)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asp Asn Ile Ala Lys (SEQ ID NO: 282)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 283)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Lys (SEQ ID NO: 284)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-myristoyl (SEQ ID NO: 285)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-palmitoyl (SEQ ID NO: 286)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-stearoyl (SEQ ID NO: 287)

L-His Ala Asp Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asp Asn Ile Ala Ala Ala Lys-arachidoyl (SEQ ID NO: 288)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys (SEQ ID NO: 289)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 290)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys-palmitoyl (SEQ ID NO: 291)

L-His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asp Asn Ile Ala Glu Ala Lys-arachidoyl (SEQ ID NO: 292)

13. A peptide according to claim 1 having a structure sequence selected from the group comprising:

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 293)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 294)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 295)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 296)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 297)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 298)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 299)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 300)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 301)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 302)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 303)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 304)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 305)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 306)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 307)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 308)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 309)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 310)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 311)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 312)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala Lys (SEQ ID NO: 313)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 314)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 315)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-myristoyl (SEQ ID NO: 316)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-palmitoyl (SEQ ID NO: 317)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-stearoyl (SEQ ID NO: 318)

D-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-arachidoyl (SEQ ID NO: 319)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys (SEQ ID NO: 320)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 321)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-palmitoyl (SEQ ID NO: 322)

D-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-arachidoyl (SEQ ID NO: 323)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 324)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 325)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Glu Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 326)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 327)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 328)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 329)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 330)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 331)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 332)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala (SEQ ID NO: 333)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 334)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 335)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 336)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 337)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 338)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 339)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 340)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala (SEQ ID NO: 341)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 342)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 343)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Ile Val Lys Tyr Phe Ile Gln Trp Leu Met Asn Thr Lys Arg Asn Lys Asn Asn Ile Ala Lys (SEQ ID NO: 344)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 345)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Gln Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Lys (SEQ ID NO: 346)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-myristoyl (SEQ ID NO: 347)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-palmitoyl (SEQ ID NO: 348)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-stearoyl (SEQ ID NO: 349)

L-His Ala Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Ile Gln Trp Leu Lys Asn Gly Gly Pro Ser Lys Asn Asn Ile Ala Ala Ala Lys-arachidoyl (SEQ ID NO: 350)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys (SEQ ID NO: 351)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-myristoyl (SEQ ID NO: 352)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-palmitoyl (SEQ ID NO: 353)

L-His Ser Glu Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Glu Glu Glu Leu Val Lys Tyr Phe Leu Gln Trp Leu Lys Asn Ala Gly Pro Ser Lys Asn Asn Ile Ala Glu Ala Lys-arachidoyl (SEQ ID NO: 354)

14. A pharmaceutical composition comprising a peptide as claimed in any one of claims 1 to 13 and one or more pharmaceutically acceptable carriers.

15. A pharmaceutical composition as claimed in claim 14 which is for peripheral administration.

16. A pharmaceutical composition as claimed in claim 14 or 15 which is for administration subcutaneously, intravenously, intramuscularly, intranasally, transdermally, transmucosally, orally, bucally, sublingually or via the lungs.

17. Use of a peptide as claimed in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or treatment of obesity.

18. Use of a peptide as claimed in any one of claims 1 to 13 for the manufacture of a medicament for the prevention or treatment of diabetes or of a co-morbidity of obesity.

19. Use of a peptide as claimed in any of claims 1 to 13 for the manufacture of a medicament for reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject.

20. The use as claimed in claim any one of claims 17 to 19, wherein the peptide is administered peripherally.

21. The use as claimed in claim any one of claims 17 to 20, wherein the peptide is administered subcutaneously, intravenously, intramuscularly, intranasally, transdermally, transmucosally, orally, bucally, sublingually or via the lungs.

22. A peptide as claimed in any of claims 1 to 13 for use as a medicament.

23. A peptide as claimed in any of claims 1 to 13 for use as a medicament for the prevention or treatment of obesity.

24. A peptide as claimed in any of claims 1 to 13 for use as a medicament for the prevention or treatment of diabetes or of a co-morbidity of obesity.

25. A peptide as claimed in any of claims 1 to 13 for use as a medicament for reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject.

26. A peptide as claimed in any one of claims 22 to 25, wherein the peptide composition is administered peripherally.

27. A peptide as claimed in any one of claims 22 to 26, wherein the peptide is administered subcutaneously, intravenously, intramuscularly, intranasally, transdermally, transmucosally, orally, bucally, sublingually or via the lungs.

28. A method of treating or preventing obesity in a subject in need thereof comprising administering to the subject a peptide according to any of claims 1 to 13 or a pharmaceutical composition according to any of claims 14 to 16.

29. A method of treating or preventing diabetes or of a co-morbidity of obesity in a subject in need thereof comprising administering to the subject a peptide according to any of claims 1 to 13 or a pharmaceutical composition according to any of claims 14 to 16.

30. A method of reducing appetite in a subject, reducing food intake in a subject or reducing calorie intake in a subject, reducing body weight in a subject, reducing body weight gain in a subject or increasing energy expenditure in a subject in need thereof comprising administering to the subject a peptide according to any of claims 1 to 13 or a pharmaceutical composition according to any of claims 14 to 16.

31. A method of causing weight loss or preventing weight gain for cosmetic purposes comprising administering to the subject a peptide according to any of claims 1 to 13 or a pharmaceutical composition according to claim 14 to 16.

32. A method as claimed in any of claims 28 to 31, wherein the subject is overweight.

33. A method as claimed in any of claims 28 to 32, wherein the subject is obese.

34. A method as claimed in any of claims 28 to 33, wherein the subject is diabetic.

35. The method of any of claims 28 to 34, wherein the peptide or pharmaceutical composition is administered peripherally.

36. The method of any of claims 28 to 35, wherein the peptide or pharmaceutical composition is administered subcutaneously, intravenously, intramuscularly, intranasally, transdermally, transmucosally, orally, bucally, sublingually or via the lungs.