MODIFICATION OF FEEDING BEHAVIOR

PRIORITY CLAIM

This application claims the benefit of U.S. Provisional Application No. 60/324,406, filed September 24, 2001, and U.S. Provisional Application No. 60/392,109, filed June 28, 2002, and UK Application No. GB0200507.2 Filed January 10, 2002, which are all incorporated by reference in their entirety herein.

STATEMENT OF GOVERNMENT SUPPORT

This disclosure was made with United States government support pursuant to grants RR00163, DK51730 and DK55819, from the National Institutes of Health. The United States government has certain rights in the disclosure.

FIELD

This application relates to the use of agents to control appetite, feeding, food intake, energy expenditure and calorie intake, particularly in the field of obesity.

BACKGROUND

According to the National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994), between one third and one half of men and women in the United States are overweight. In the United States, sixty percent of men and fifty-one percent of women, of the age of 20 or older, are either overweight or obese. In addition, a large percentage of children in the United States are overweight or obese.

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 persons reduces important disease risk factors. Even a small weight loss, such as 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, overweight and obese individuals often cannot sufficiently control these factors to effectively lose weight. Pharmacotherapy is available; several weight loss drugs have been approved by the 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. 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. 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. Thus, a need remains for agents that can be used to effect weight loss in overweight and obese subjects.

SUMMARY

According to a first aspect of the present invention, there is provided a use of PYY or an agonist thereof for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of

weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject

a) in the case of PYY, in an amount effective to achieve physiological levels of PYY_{3-36} observed postprandially, or

b) in the case of a PYY agonist, in an amount effective to mimic physiological levels of PYY_{3-36} observed postprandially.

According to a second aspect of the present invention, there is provided a use of PYY or an agonist thereof for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject

a) in the case of PYY, in an amount effective to achieve physiological levels of PYY_{3-36}, or

b) in the case of PYY agonist, in an amount effective to mimic physiological levels of PYY_{3-36}.

According to a third aspect of the present invention, there is provided a use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject in an amount effective to achieve physiological levels of PYY_{3-36} observed postprandially.

According to a fourth aspect of the present invention, there is provided a use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject at a dose of from about 0.5 to about 135 pmol per kilogram body weight of the subject.

According to a fifth aspect of the present invention, there is provided a use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which

medicament is in a form suitable for peripheral administration to the subject at a dose of not more than 100 nmoles.

According to a sixth aspect of the present invention, there is provided a use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject at a dose of not more than 405μg.

Disclosed herein are findings that peripheral administration of PYY, or an agonist thereof, to a subject can result in decreased food intake, caloric intake, and appetite, and an alternation in energy metabolism. The subject can be any subject,

including, but not limited to, a human subject. In several embodiments, the subject desires to lose weight, is obese, overweight, or suffers from a weight-related disorder. PYY_{3-36} can preferably be administered to the subject.

In one embodiment, a method is disclosed for decreasing calorie intake in a subject. The method includes peripherally administering a therapeutically effective amount of PYY or an agonist thereof to the subject, thereby decreasing the calorie intake of the subject.

In another embodiment, a method is disclosed for decreasing appetite in a subject. The method includes peripherally administering a therapeutically effective amount of PYY or an agonist thereof to the subject, thereby decreasing the appetite of the subject.

In a further embodiment, a method is disclosed for decreasing food intake in a subject. The method includes peripherally administering a therapeutically effective amount of PYY or an agonist thereof to the subject, thereby decreasing the food intake of the subject.

In yet another embodiment, a method is disclosed herein for increasing energy expenditure in a subject. The method includes peripherally administering a therapeutically effective amount of PYY or an agonist thereof to the subject, thereby increasing energy expenditure in the subject.

A method is also disclosed for decreasing calorie intake, food intake, or appetite in a human subject. The method includes peripherally injecting a therapeutically effective amount of PYY or an agonist thereof in a pharmaceutically acceptable carrier to the subject in a pulse dose, thereby decreasing the calorie intake, food intake, or appetite of the subject.

Disclosed herein are findings that peripheral administration of an antagonist of PYY to a subject results in increased food intake, caloric intake, and appetite, and an alteration in energy metabolism. The subject can be any subject, including, but not limited to, a human subject. In several embodiments, the subject desires to gain weight, is anorexic or cachexic.

The foregoing and other features and advantages will become more apparent from the following detailed description of several embodiments, which proceeds with reference to the accompanying figures.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a set of diagrams and digital images showing the generation of transgenic mice expressing EGFP in ARC POMC neurons. Fig. 1a is a schematic diagram of the structure of the POMC-EGFP transgene. Fig. 1b is a digital image showing the identification of a single POMC neuron (arrowhead on recording electrode tip) by EGFP fluorescence (upper) and IR-DIC microscopy (lower) in a living ARC slice prior to electrophysiological recordings. Fig. 1c is a set of digital images showing the co-localization (bright, on right) of EGFP (left) and ß-endorphin immunoreactivity (middle) in ARC POMC neurons. Scale bars: b & c, 50 μm. Fig. 1d is a set of diagrams showing the distribution of EGFP-positive neuronal soma throughout the ARC nucleus. o = 5 cells, • = 10 cells.

Fig. 2 is a tracing and graphs showing activation of MOP-Rs hyperpolarizes the EGFP-labeled POMC neurons by opening G protein-coupled inwardly-rectifying potassium channels. Fig. 2a is a tracing showing met-enkephalin hyperpolarizes POMC neurons and inhibits all action potentials. The horizontal bar indicates the time when 30 μM Met-Enk was bath-applied to the slice. Fig. 2b is a graph showing met-enkephalin current and reversal potential is shifted by extracellular K^+ concentration. Fig. 2c is a graph showing met-enkephalin activates MOP-Rs on POMC neurons. A Met-Enk (30 μM) current was observed and the MOP-R specific antagonist CTAP (1 μM) was applied for 1 minute. Following CTAP Met-Enk elicited no current. The figure is representative of three experiments.

Fig. 3 are tracings and graphs demonstrating that leptin depolarizes POMC neurons via a non-specific cation channel, and decreases GABAergic tone onto POMC cells. Fig. 3a is a tracing demonstrating that leptin depolarizes POMC

neurons and increases the frequency of action potentials within 1 to 10 minutes of addition. The figure is a representative example of recordings made from 77 POMC neurons. Fig. 3b is a graph showing that leptin causes a concentration dependent depolarization of POMC cells. The depolarization caused by leptin was determined at 0.1, 1, 10, 50, and 100 nM (EC_{50} =5.9 nM) in (8, 7, 9, 3, 45) cells respectively. Fig. 3c is a graph showing that leptin depolarizes POMC cells by activating a nonspecific cation current. The figure is representative of the response in 10 cells. Fig. 3d is a graph showing that leptin decreases the frequency of IPSCs in POMC cells. The figure is an example of 5 cells in which leptin (100 nM) decreased the frequency of IPSCs. Fig. 3e is a tracing demonstrating that leptin had no effect on 5 adjacent non-fluorescent ARC neurons. Fig. 3f is a tracing showing that leptin hyperpolarized 5 non-fluorescent ARC neurons.

Fig. 4 is a set of images showing that the GABAergic inputs to POMC cells are from NPY neurons that co-express GABA. Fig. 4a is a graph showing that NPY decreases the frequency of mini IPSCs in POMC neurons. Fig. 4b is a graph demonstrating that D-Trp^8-γMSH (7nM), a dose that selectively activates MC3-R, increases the frequency of GABAergic IPSCs in POMC neurons. Fig. 4c is a tracing showing that D-Trp^8-γMSH hyperpolarizes POMC neurons. Figs. 4a, 4b and 4c are representative. Fig. 4d is a set of digital images demonstrating that expression of NPY in nerve terminals adjacent to POMC neurons in the ARC. NPY nerve terminals (black, arrowheads); POMC neuronal soma (grey). Scale bar, 10 μm. Fig. 4e is a digital image showing expression of GABA and NPY in nerve terminals synapsing onto POMC neurons in the ARC. GABA immunoreactivity (10 nm gold particles, arrowheads without tail) and NPY immunoreactivity (25 nm gold particles, arrows with tail) are in separate vesicle populations co-localized within synaptic boutons that make direct contact with the soma of POMC neurons (DAB contrasted with uranyl acetate and lead citrate, diffuse black in cytoplasm). Scale bar, 1 μm. Fig. 4f is a diagram of the model of NPY/GABA and POMC neurons in the ARC.

Fig. 5 is a set of graphs relating to the feeding response to PYY_{3-36} in rats. Fig. 5a is a bar graph of dark-phase feeding tabulating food intake after

intraperitoneal injection of PYY_{3-36}. Freely feeding rats were injected with PYY_{3-36} at the doses indicated (μg/100g), or saline, just prior to 'lights off' and 4-hour cumulative food intake was measured. Results are the mean ± s.e.m. (n = 8 per group), * = $p < 0.05$, ** = $p < 0.01$, *** = < 0.001 compared to saline. Fig. 5b is a bar graph of food intake after intraperitoneal injection of PYY_{3-36}. Fasted rats were injected with PYY_{3-36} at the doses indicated (μg/100g), or saline, and 4-hour cumulative food intake was measured. Results are shown as the mean ± s.e.m. (n = 8 per group), * = $p < 0.05$, ** = $p < 0.01$, *** = < 0.001 compared to saline. Fig. 5c is a bar graph of cumulative food intake after intraperitoneal injection of saline or PYY_{3-36}. Fasted rats were injected with either saline (closed bars) or PYY_{3-36} 5μg/100g (open bars) and cumulative food intake measured at the time points indicated. Results are expressed as mean ± s.e.m. (n = 12 per group), ** = $p < 0.01$ compared to saline. Fig. 5d is a line graph of body weight gain during chronic treatment with PYY_{3-36}. Rats were injected intraperitoneally with PYY_{3-36} 5μg/100g (open squares) or saline (filled inverted triangles) twice daily for 7 days. Body weight gain was calculated each day. Results are expressed as mean ± s.e.m. (n = 12 per group) ** = $p < 0.01$ compared to saline.

Fig. 6 is a set of digital images of c-fos expression in *Pomc-EGFP* mice. Figs. 6a and 6b are digital images of representative sections (bregma –1.4 mm[22]) of c-fos expression in the arcuate nucleus of *Pomc-EGFP* mice response to intraperitoneal saline (Fig. 6a) or PYY_{3-36} (5μg/100g) (Fig. 6b). Scale bar 100 μm. 3V, third ventricle; Arc, arcuate nucleus. Figs. 6c and 6d are digital images of representative sections showing POMC-EGFP neurons (Fig. 6c) and c-fos immunoreactivity (Fig. 6d) either co-localizing (bright arrows) or alone (single darker arrow). Scale bar 25 μm.

Fig. 7 is a set of bar graphs relating to intra-arcuate PYY_{3-36} in rats and feeding effects of IP PYY_{3-36} in *Y2r*- null mice. Fig. 7a is a bar graph of food intake following intra-arcuate PYY_{3-36} injection. Fasted rats were injected with saline or PYY_{3-36} into the arcuate nucleus at the doses indicated. Post-injection 2-hour food intake was measured, ** = $p < 0.01$ compared to saline. Figs. 7b and 7c are bar graphs of feeding response to PYY_{3-36} in *Y2r*-null mice following IP administration:

wild type littermates mice (Fig. 7b) and *Y2r*-null mice (Fig. 7c), fasted for 24 hours, were injected with PYY_{3-36} at the doses indicated (μg/100g), or saline, and 4-hour cumulative food intake was measured. Results are the mean ± s.e.m. (n = 5 per group), * = $p < 0.05$, ** = $p < 0.01$ compared to saline.

Fig. 8 is a set of images relating to the electrophysiological and neuropeptide responses to PYY_{3-36} and Y2A. Fig. 8a is a tracing showing the effect of PYY_{3-36} (10 nM) on the frequency of action potentials in POMC neurons (whole-cell configuration recordings; n = 22) * $p < 0.05$. PYY_{3-38} was administered at time D for 3 minutes; baseline, -3 to 0 minute; PYY_{3-36}, 2-5 minutes; and wash-out, 8-11 minutes. Inset shows a representative recording of membrane potential and action potential frequency. Fig. 8b is a graph of the effect if PYY_{3-38} (10nM) on the frequency of action potentials in loose cell-attached patch recordings (n=8). Data from individual cells were normalized to the firing rate for the 200s before PYY_{3-38} addition. Fig. 8c is a tracing and a graph of the effect of PYY_{3-36} (50nM) on spontaneous IPSCs onto POMC neurons (n=13). Inset shows a representative recording of IPSCs before and after PYY_{3-36} (50nM), respectively. Results in Fig. 8a-8c are expressed as mean ± s.e.m. Fig. 8d and 8e are bar graphs showing NPY (Fig. 8d) and ∝-MSH (Fig. 8e) released from hypothalamic explants in response to Y2A. Hypothalamic slices were incubated with artificial CSF (aCSF), with or without 50nM Y2A, for 45 minutes. Results are expressed as mean ± s.e.m. (n=40); ** = $p<0.01$; *** = $p<0.001$ compared to saline.

Fig. 9 is a set of graphs showing the effect of PYY_{3-36} infusion on appetite and food intake in human subjects. Fig. 9a is a graph of the calorie intake from a "free-choice" buffet meal 2 hours after infusion with saline or PYY_{3-36}. The thin lines indicate individual changes in calorie intake for each subject between saline and PYY_{3-36} administration. The thick line represents mean change between the two infusions (n = 12). Fig. 9b is a graph of the 24-hour calorie intake following infusion with saline or PYY_{3-36}. Total calorie intake, as assessed by food diaries, is shown for the 24-hour period following either saline or PYY_{3-36} infusion. Data is given as mean ± s.e.m. (n = 12), *** = $p < 0.0001$ compared to saline. Fig. 9c is a graph of the appetite score (relative scale). Visual analogue scores (Raben et al., *Br.*

J. Nutr. 73, 517-30, 1995) show perceived hunger during and after infusions. The results are presented as change from baseline scores and are the mean ± s.e.m. for all 12 subjects.

SEQUENCE LISTING

The nucleic and amino acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases, and three letter code for amino acids, as defined in 37 C.F.R. 1.822. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included by any reference to the displayed strand.

DETAILED DESCRIPTION

I. Abbreviations

α-MSH: alpha melanocortin stimulating hormone

Arc: arcuate nucleus

EPSP: excitatory postsynaptic potential

GABA: γaminobutyric acid

GFP, EGFP: green fluorescent protein

IPSC: inhibitory postsynaptic current

kb: kilobase

kg: kilogram

MOP-R: μ-opiod receptor

MV: millivolts

NPY: neuropeptide Y

pmol: picomole

POMC: proopiomelanocortin

RIA: radioimmunoassay

RPA: RNase protection assay

s.e.m: standard error of the mean

TH: tyrosine hydroxylase

μM: micromolar

V: volts

Y2A: N-acetyl (Leu ^{28}, Leu ^{31}) NPY (24-36)

II. Terms

Unless otherwise noted, technical terms are used according to conventional usage. Definitions of common terms in molecular biology may be found in Benjamin Lewin, *Genes V*, published by Oxford University Press, 1994 (ISBN 0-19-854287-9); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); and Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive Desk Reference*, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8).

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

Action potential: A rapidly propagated electrical message that speeds along an axon of a neuron and over the surface membrane of many muscle and glandular cells. In axons they are brief, travel at constant velocity, and maintain a constant amplitude. Like all electrical messages of the central nervous system, the action potential is a membrane potential change caused by the flow of ions through ion channels in the membrane. In one embodiment, an action potential is a regenerative wave of sodium permeability.

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 veterinary subjects.

Anorexia: A lack or loss of the appetite for food. In one embodiment, anorexia is a result of "anorexia nervosa." This is an eating disorder primarily affecting females, usually with onset in adolescence, characterized by refusal to maintain a normal minimal body weight, intense fear of gaining weight or becoming obese, and a disturbance of body image resulting in a feeling of being fat or having fat in certain areas even when extremely emaciated, undue reliance on body weight

or shape for self-evaluation, and amenorrhea. Associated features often include denial of the illness and resistance to psychotherapy, depressive symptoms, markedly decreased libido, and obsessions or peculiar behavior regarding food, such as hoarding. The disorder is divided into two subtypes, a restricting type, in which weight loss is achieved primarily through diet or exercise, and a binge-eating/purging type, in which binge eating or purging behavior also occur regularly.

Antagonist: A substance that tends to nullify the action of another, as an agent that binds to a cell receptor without eliciting a biological response, blocking binding of substances that could elicit such responses.

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, and fluoxetine.

Binding: A specific interaction between two molecules, such that the two molecules interact. Binding can be specific and selective, so that one molecule is bound preferentially when compared to another molecule. In one embodiment, specific binding is identified by a disassociation constant (K_d).

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 current standards for both men and women accepted as "normal" are a BMI of 20-24.9 kg/m^2. In one embodiment, a BMI of greater than 25 kg/m^2 can be used to identify an obese subject. Grade I obesity corresponds to a BMI of 25-29.9 kg/m^2. Grade II obesity corresponds to a BMI of 30-40 kg/m^2; and Grade III obesity corresponds to a BMI greater than 40 kg/m^2 (Jequier, *Am. J Clin. Nutr.* 45:1035-47, 1987). Ideal body weight will vary among species and individuals based on height, body build, bone structure, and sex.

c-fos: The cellular homologue of the viral v-fos oncogene found in FBJ (Finkel-Biskis-Jinkins) and FBR murine osteosarcoma viruses (MSV). The human

fos gene maps to chromosome 14q21-q31. Human fos has been identified as TIS-28.

C-fos is thought to have an important role in signal transduction, cell proliferation, and differentiation. It is a nuclear protein which, in combination with other transcription factors (for example, jun) acts as a trans-activating regulator of gene expression. C-fos is an immediate early response gene, which are believed to play a key role in the early response of cells to growth factors. C-fos is involved also in the control of cell growth and differentiation of embryonic hematopoietic cells and neuronal cells. The human c-fos coding amino acid and nucleic sequences are known (e.g., see Verma et al., *Cold Spring Harb. Symp. Quant. Biol.* 51, 949, 1986; GenBank Accession Nos. K00650 and M16287, and is available on the internet).

Cachexia: General physical wasting and malnutrition that is often associated with a chronic disease process. Cahexia is frequently seen in patients with cancer, AIDS, or other diseases. Cachexia includes, but is not limited to 1) cancerous cachexia, seen in cases of malignant tumor; 2) cardiac cachexia, an emaciation due to heart disease, usually caused by a combination of increased caloric expenditure and decreased caloric intake or utilization; 3) fluoric cachexia, seen in fluorosis; 4) hypophysial cachexia; 5) cachexia hypophysiopriva, a cluster of symptoms resulting from total deprivation of function of the pituitary gland, including phthisis, loss of sexual function, atrophy of the pituitary target glands, bradycardia, hypothermia, apathy, and coma; 6) malarial cachexia, a group of physical signs of a chronic nature that result from antecedent attacks of severe malaria; 7) cachexia mercurialis, seen in chronic mercury poisioning; 8) pituitary cachexia; 9) saturnine cachexia, seen in chronic lead poisioning; 10) cachexia suprarenalis, associated with Addison's disease; and 11) uremic cachexia, associated with other systemic symptoms of advanced renal failure.

Caloric intake or calorie intake: The number of calories (energy) consumed by an individual.

Calorie: A unit of measurement in food. A standard calorie is defined as 4.184 absolute joules, or the amount of energy it takes to raise the temperature of one gram of water from 15 to 16° C (or1/100th the amount of energy needed to raise

the temperature of one gram of water at one atmosphere pressure from 0° C to 100° C), food calories are actually equal to 1,000 standard calories (1 food calorie = 1 kilocalorie).

Conservative variation: The replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acid, or glutamine for asparagine, and the like. The term "conservative variation" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid provided that antibodies raised to the substituted polypeptide also immunoreact with the unsubstituted polypeptide.

Non-limiting examples of conservative amino acid substitutions include those listed below:

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

Depolarization: An increase in the membrane potential of a cell. Certain stimuli reduce the charge across the plasma membrane. These can be electrical stimuli (which open voltage-gated channels), mechanical stimuli (which activate

mechanically-gated channels) or certain neurotransmitters (which open ligand-gated channels). In each case, the facilitated diffusion of sodium into the cell increases the resting potential at that spot on the cell creating an excitatory postsynaptic potential (EPSP). Depolarizations can also be generated by decreasing the frequency of inhibitory postsynaptic currents (IPSCs), these are due to inhibitory neurotransmitters facilitating the influx of chloride ions into the cell, creating an IPSC. If the potential is increased to the threshold voltage (about -50 mV in mammalian neurons), an action potential is generated in the cell.

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 characterized 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 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. Food intake can be measured by volume or by weight. In one embodiment, food intake is the total amount of food consumed by an individual. In another embodiment, food intake is the amount of proteins, fat, carbohydrates, cholesterol, vitamins, minerals, or any other food component, of the individual. "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 proteins, fat, carbohydrates, cholesterol, vitamins, or minerals consumed by an individual.

Hyperpolarization: A decrease in the membrane potential of a cell. Inhibitory neurotransmitters inhibit the transmission of nerve impulses via hyperpolarization. This hyperpolarization is called an inhibitory postsynaptic potential (IPSP). Although the threshold voltage of the cell is unchanged, a hyperpolarized cell requires a stronger excitatory stimulus to reach threshold.

Inhibitory Postsynaptic Current: A current that inhibits an electrophysiological parameter of a postsynaptic cell. The potential of a postsynaptic cell can be analyzed to determine an effect on a presynaptic cell. In one embodiment, the postsynaptic cell is held in voltage clamp mode, and postsynaptic currents are recorded. If necessary, antagonists of other classes of current can be added. In one specific, non-limiting example, to record GABAergic IPSCs, blockers of excitatory channels or receptors can be added. The instantaneous frequency over time is then determined.

In one embodiment, IPSCs give a measure of the frequency of GABA release from an NPY neuron. Thus, as NPY neurons release GABA onto POMC neurons, measurement of IPSC frequency is a gauge of the inhibitory tone that POMC neurons are receiving, and can be used to assess the effect of an agonist of PYY.

Membrane potential: The electrical potential of the interior of the cell with respect to the environment, such as an external bath solution. One of skill in the art can readily assess the membrane potential of a cell, such as by using conventional whole cell techniques. Activation of a cell is associated with less negative membrane potentials (for example shifts from about –50 mV to about –40 mV). These changes in potential increase the likelihood of action potentials, and thus lead to an increase in the rate of action potentials.

The rate of action potentials can be assessed using many approaches, such as using conventional whole cell access, or using, for example, perforated-patch whole-cell and cell-attached configurations. In each event the absolute voltage or current is not assessed, rather the frequency of rapid deflections characteristic of action potentials is assessed, as a function of time (therefore this frequency is an instantaneous frequency, reported in "bins"). This time component can be related to the time at which a compound, such as a PYY agonist, is applied to the bath to

analyze the effect of the compound, such as the PYY agonist, on action potential firing rate.

Neuropeptide Y (NPY): A 36-amino acid peptide that is a neuropeptide identified in the mammalian brain. NPY is believed to be an important regulator in both the central and peripheral nervous systems and influences a diverse range of physiological parameters, including effects on psychomotor activity, food intake, central endocrine secretion, and vasoactivity in the cardiovascular system. High concentrations of NPY are found in the sympathetic nerves supplying the coronary, cerebral, and renal vasculature and have contributed to vasoconstriction. NPY binding sites have been identified in a variety of tissues, including spleen, intestinal membranes, brain, aortic smooth muscle, kidney, testis, and placenta. In addition, binding sites have been reported in a number of rat and human cell lines.

Neuropeptide Y (NPY) receptor has structure/activity relationships within the pancreatic polypeptide family. This family includes NPY, which is synthesized primarily in neurons; peptide YY (PYY), which is synthesized primarily by endocrine cells in the gut; and pancreatic polypeptide (PP), which is synthesized primarily by endocrine cells in the pancreas. These 36 amino acid peptides have a compact helical structure involving an amino acid structure, termed a "PP-fold" in the middle of the peptide.

NPY binds to several receptors, including the Y1, Y2, Y3, Y4 (PP), Y5, Y6, and Y7 receptors. These receptors are recognized based on binding affinities, pharmacology, and sequence (if known). Most, if not all of these receptors are G protein coupled receptors. The Y1 receptor is generally considered to be postsynaptic and mediates many of the known actions of neuropeptide Y in the periphery. Originally, this receptor was described as having poor affinity for C-terminal fragments of neuropeptide Y, such as the 13-36 fragment, but interacts with the full length neuropeptide Y and peptide YY with equal affinity (e.g., see PCT publication WO 93/09227).

Pharmacologically, the Y2 receptor is distinguished from Y1 by exhibiting affinity for C-terminal fragments of neuropeptide Y. The Y2 receptor is most often differentiated by the affinity of neuropeptide Y(13-36), although the 3-36 fragment of neuropeptide Y and peptide YY provides improved affinity and selectivity (see

Dumont et al., *Society for Neuroscience Abstracts* 19:726, 1993). Signal transmission through both the Y1 and the Y2 receptors are coupled to the inhibition of adenylate cyclase. Binding to the Y-2 receptor was also found to reduce the intracellular levels of calcium in the synapse by selective inhibition of N-type calcium channels. In addition, the Y-2 receptor, like the Y1 receptors, exhibits differential coupling to second messengers (see U.S. Patent No. 6,355,478). Y2 receptors are found in a variety of brain regions, including the hippocampus, substantia nigra-lateralis, thalamus, hypothalamus, and brainstem. The human, murine, monkey and rat Y2 receptors have been cloned (e.g., see U.S. Patent No. 6,420,352 and U.S. Patent No. 6,355,478).

A Y2 receptor agonist is a peptide, small molecule, or chemical compound that preferentially binds to the Y2 receptor and stimulates intracellular signaling. In one embodiment, an agonist for the Y2 receptor binds to the receptor with an equal or greater affinity than NPY. In another embodiment, an agonist selectively binds the Y2 receptor, as compared to binding to another receptor.

One of skill in the art can readily determine the dissociation constant (K_d) value of a given compound. This value is dependent on the selectivity of the compound tested. For example, a compound with a K_d which is less than 10 nM is generally considered an excellent drug candidate. However, a compound that has a lower affinity, but is selective for the particular receptor, can also be a good drug candidate. In one specific, non-limiting example, an assay, such as a competition assay, is used to determine if a compound of interest is a Y2 receptor agonist. Assays useful for evaluating neuropeptide Y receptor antagonists are also well known in the art (see U.S. Patent No. 5,284,839, which is herein incorporated by reference, and Walker et al., *Journal of Neurosciences* 8:2438-2446, 1988).

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. In one embodiment, the Body Mass Index (BMI) is used to assess obesity. In one embodiment, a BMI of 25.0 kg/m^2 to 29.9 kg/m^2 is overweight, while a BMI of 30 kg/m^2 is obese.

In another embodiment, waist circumference is used to assess obesity. In this embodiment, in men a waist circumference of 102 cm or more is considered obese, while in women a waist circumference of 89 cm or more is considered obese. Strong evidence shows that obesity affects both the morbidity and mortality of individuals. For example, an 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. In one embodiment, an overweight individual is any individual who desires to decrease their weight. In another embodiment, an overweight individual is an individual with a BMI of 25.0 kg/m^2 to 29.9 kg/m^2

Pancreatic Polypeptide: A 36 amino acid peptide produced by the pancreas that is has homology to PYY and NPY.

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 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. The terms "polypeptide" or "protein" as used herein are intended to encompass any amino acid sequence and include modified sequences such as glycoproteins. The term "polypeptide" is specifically intended to cover 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 has been fused to another peptide that does not decrease its desired activity.

PYY: A peptide YY polypeptide obtained or derived from any species. Thus, PYY includes the human full length polypeptide (as set forth in SEQ ID NO: 1) and species variations of PYY, including e.g. murine, hamster, chicken, bovine, rat, and dog PYY (SEQ ID NOS: 5-12). In one embodiment, PYY agonists do not include NPY. PYY also includes PYY_{3-36}. A "PYY agonist" is any compound which binds to a receptor that specifically binds PYY, and elicits an effect of PYY. In one embodiment, a PYY agonist is a compound that affects food intake, caloric intake, or appetite, and/or which binds specifically in a Y receptor assay or competes for binding with PYY, such as in a competitive binding assay with labeled PYY. PYY agonists include, but are not limited to, compounds that bind to the Y2 receptor.

Substantially purified: A polypeptide which is substantially free of other proteins, lipids, carbohydrates or other materials with which it is naturally associated. For example, the polypeptide may be at least 50%, 80% or 90% free of other proteins, lipids, carbohydrates or other materials with which it is naturally associated.

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 effect of PYY or an agonist thereof 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.

Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. It is further to be understood that all base sizes or amino acid sizes, and all molecular weight or molecular mass values, given for nucleic acids or polypeptides are approximate, and are provided for description. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The term "comprises" means "includes." All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including explanations of terms, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Methods for Altering Food Intake, Appetite, Caloric Intake and Energy Expenditure

A method is disclosed herein for reducing food intake by peripherally administering to a subject a therapeutically effective amount of PYY or an agonist of PYY. In one embodiment, administration of PYY, or an agonist of PYY, results in a decrease in the amount, either the total weight or the total volume of food. In other embodiment, administration of PYY, or an agonist thereof, results in a decrease of the intake of a food component, such as a decrease in the ingestion of lipids, carbohydrates, cholesterol, or proteins. In the any of the methods disclosed herein, a preferred compound, PYY $_{3-36}$ can be administered. This disclosure includes the corresponding uses of PYY or an agonist thereof for the manufacture of a medicament for the purposes set herein, and includes the use of PYY_{3-36}.

A method is also disclosed herein for reducing caloric intake by peripherally administering to a subject a therapeutically effective amount of PYY or an agonist of PYY. In one embodiment, total caloric intake is reduced by peripheral administration of a therapeutically effective amount of PYY. In other embodiments, the caloric intake from the ingestion of a specific food component, such as, but not limited to, the ingestion of lipids, carbohydrates, cholesterol, or proteins, is reduced.

In an additional embodiment, a method is disclosed herein for reducing appetite by administering a therapeutically effective amount of PYY or an agonist thereof. 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. In this embodiment, administration of PYY 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. In one embodiment, 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 (see the Examples section). 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.

In a further embodiment, a method is disclosed herein for altering energy metabolism in a subject. The method includes peripherally administering a

therapeutically effective amount of PYY or an agonist thereof 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 a further embodiment a method is disclosed herein for any and all manipulations of the arcuate circuitry described in this application, 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 embodiment, peripheral administration of PYY results in increased energy expenditure, and decreased efficiency of calorie utilization. In one embodiment, a therapeutically effective amount of PYY or an agonist thereof is administered to a subject, thereby increasing energy expenditure.

In several embodiments, PYY (e.g., PYY_{3-36}) or an agonist thereof is used for weight control and treatment, 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. The disclosure further relates to the use of PYY or an agonist thereof in 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. The disclosure further relates to the use of PYY an agonist thereof in maintaining any one or more of a desired body weight, a desired Body Mass Index, a desired appearance and good health.

The subject can be any subject, including both human and veterinary mammalian subjects. Thus, the subject can be a human, or can be a non-human primate, a farm animal such as swine, cattle, and poultry, a sport animal or pet such as dogs, cats, horses, hamsters, rodents, or a zoo animal such as lions, tigers, or bears.

Obesity is currently a poorly treatable, chronic, essentially intractable metabolic disorder. A therapeutic drug useful in weight reduction of obese persons could have a profound beneficial effect on their health. Thus, the subject can be, but is not limited to, a subject who is overweight or obese. In one embodiment, the subject has, or is at risk of having, a disorder wherein obesity or being overweight is a risk factor for the disorder. Disorders of interest include, but are not limited to, cardiovascular disease, (including, but not limited to, hypertension, atherosclerosis, congestive heart failure, and dyslipidemia), stroke, gallbladder disease, osteoarthritis, sleep apnea, reproductive disorders such as, but not limited to, polycystic ovarian syndrome, cancers (e.g., breast, prostate, colon, endometrial, kidney, and esophagus cancer), varicose veins, acnthosis nigricans, eczema, exercise intolerance, insulin resistance, hypertension hypercholesterolemia, cholithiasis, osteoarthritis, orthopedic injury, insulin resistance (such as, but not limited to, type 2 diabetes and syndrome X) and tromboembolic disease (see Kopelman, *Nature* 404:635-43; Rissanen et al., *British Med. J.* 301, 835, 1990).

Other associated disorders also include depression, anxiety, panic attacks, migraine headaches, PMS, chronic pain states, fibromyalgia, insomnia, impulsivity, obsessive compulsive disorder, and myoclonus. Obesity is a recognized risk factor for increased incidence of complications of general anesthesia. (See e. g., Kopelman, *Nature* 404:635-43, 2000). It reduces life span and carries a serious risk of co-morbidities listed above.

Other diseases or disorders associated with obesity are birth defects (maternal obesity 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 (causing 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 (abdominal

panniculitis with frequent panniculitis, impeding walking, causing frequent infections, odors, clothing difficulties, low back pain), musculoskeletal disease, pseudo tumor cerebri (or benign intracranial hypertension), and sliding hiatil hernia.

The present disclosure relates to treating, prevention, ameliorating or alleviating conditions or disorders caused by, complicated by, or aggravated by a relatively high nutrient availability. By "condition or disorder which can be alleviated by reducing caloric (or nutrient) availability," it is meant 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 (e.g., type 1, 2 or gestational diabetes) can also benefit from this disclosure.

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

In another embodiment, the subject is a subject who desires weight loss, such as female and male subject who desire a change in their appearance. In yet a further embodiment, the subject is a subject who desires decreased feelings of hunger, such as, but not limited to, a person involved in a lengthy task that requires a high level of concentration (e.g., soldiers on active duty, air traffic controllers, or truck drivers on long distance routes, etc.).

The present invention also relates the use of PYY or an antagonist thereof in the control of food intake in a mammal, in particular to increase, promote or stimulate food intake. The disclosure also relates to the use of PYY or an antagonist thereof in weight control and treatment or prevention of wasting or anorexia, in particular any one or more of the following: inducing, promoting and increasing weight gain; reducing, inhibiting and preventing weight loss; and increasing body mass as measured by the Body Mass Index. The invention further relates to the use of an antagonist of PYY or PYY_{3-36} in control of any one or more of appetite, satiety and hunger, in particular any one or more of the following: increasing, inducing and

promoting appetite; reducing, inhibiting or preventing satiety and sensations of satiety; and increasing, promoting and enhancing hunger and sensations of hunger.

Increased weight gain may be desirable for commercial reasons in animal husbandry. Thus, an antagonist of PYY can be used in humans, companion animals and other objectively or subjectively valuable animals, for example, horses. PYY antagonists can be used to stimulate appetite and increase weight gain when appetite is poor and weight is lost or may be lost. Specific, non-limiting examples include during illness, after accidental or surgical trauma (for example, burns, and especially severe burns), during convalescence, in the elderly, and in anorexia and bulimia, and in other wasting conditions. Appetite stimulation and increase in weight may be particularly desirable in specific conditions, for example, during cachexia (wasting) in AIDS, and in cancer patients.

A suitable administration format may be best determined by the subject or by a medical practitioner. In one embodiment, the pharmaceutical compositions that include PYY, or an agonist thereof, or an antagonist thereof, will preferably be formulated in unit dosage form, suitable for individual administration of precise dosages. An effective amount of PYY or an agonist thereof can be administered in a single dose, or in multiple doses, for example daily, during a course of treatment. In one embodiment, PYY is administered whenever the effect (e.g., appetite suppression, decreased food intake, or decreased caloric intake) is desired. In another embodiment, PYY or an analog thereof is administered slightly prior 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, or about 120 minutes, prior to the time the effect is desired. In another embodiment, a time release formulation is utilized.

In one embodiment, a therapeutically effective amount of PYY or an agonist thereof is 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 PYY is provided, followed by a time period wherein no PYY is administered to the subject, followed by a second bolus administration. In specific, non-limiting examples, pulse doses of PYY are administered during the course of a day, during the course of a week, or during the course of a month.

The therapeutically effective amount of PYY or an agonist thereof will be dependent on the molecule utilized, the subject being treated, the severity and type of the affliction, and the manner of administration. For example, a therapeutically effective amount of PYY or an agonist thereof can vary from about 0.01 μg per kilogram (kg) body weight to about 1 g per kg body weight, such as about 1 μg to about 5 mg per kg body weight, or about 5μg to about 1 mg per kg body weight. In another embodiment, PYY or an agonist thereof is administered to a subject at 0.5 to 135 picomole (pmol) per kg body weight, or about 72 pmol per kg body weight. In one specific, non-limiting example about 5 to about 50 nmol is administered as a subcutaneous injection, such as about 2 to about 20 nmol, or about 10 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 (such as the PYY polypeptide, or agonist) utilized, the age, weight, sex and physiological condition of the subject. The dose of an agonist can be a molar equivalent of the therapeutically effective dose of PYY or PYY_{3-36}.

The compositions or pharmaceutical compositions can be administered by any route, including intravenous, intraperitoneal, subcutaneous, sublingual, transdermal, intramuscular, oral, topical, transmucosal, or by pulmonary inhalation. Compositions useful in the disclosure may conveniently be provided in the form of formulations suitable for parenteral (including intravenous, intramuscular and subcutaneous), nasal or oral administration. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion. PYY, including PYY_{3-36}, an agonist of PYY, or an antagonist of PYY, can be administered subcutaneously. It is well known in the art that subcutaneous injections can be easily self-administered.

In some cases, it will be convenient to provide a PYY or a PYY agonist and another food-intake-reducing, plasma glucose-lowering or plasma lipid-altering agent, in a single composition or solution for administration together. In other cases, it may be more advantageous to administer the additional agent separately from said PYY or PYY agonist.

A suitable administration format may best be determined by a medical

practitioner for each patient individually. 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.

PYY, PYY agonists, and PYY antagonists useful in the methods of this disclosure can be provided as parenteral compositions, e.g., for injection or infusion. Preferably, they are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 3.0 to about 8.0, preferably at a pH of about 3.5 to about 7.4, 3.5 to 6.0, or 3.5 to about 5.0. Useful buffers include sodium citrate-citric acid and sodium phosphate-phosphoric acid, and sodium acetate/acetic acid buffers. A form of repository or "depot" slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following transdermal injection or delivery.

Since the PYY and agonists are amphoteric, they may be utilized as free bases, as acid addition salts or as metal salts. The salts must, of course, be pharmaceutically acceptable, and these will include metal salts, particularly alkali and alkaline earth metal salts, e.g., potassium or sodium salts. A wide variety of pharmaceutically acceptable acid addition salts are available. Such products are readily prepared by procedures well known to those skilled in the art.

For use by the physician, the compositions can be provided in dosage unit form containing an amount of a PYY or a PYY agonist with or without another active ingredient, e.g., a food intake-reducing, plasma glucose-lowering or plasma lipid-altering agent. Administration may begin whenever the suppression of nutrient availability, food intake, weight, blood glucose or plasma lipid lowering is desired, for example, at the first sign of symptoms of a weight-related disorder or shortly after diagnosis of obesity, diabetes mellitus, or insulin resistance syndrome.

Therapeutically effective amounts of a PYY or a PYY agonist for use in reducing nutrient availability are those that suppress appetite at a desired level. As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the potency of the particular compound, age and weight of the patient, the patient's physical condition, the blood sugar level, the

weight level to be obtained, and other factors. Similarly, therapeutically effective amounts of a PYY antagonist for use in increasing nutrient availability are those that increase appetite at a desired level. As will be recognized by those in the field, an effective amount of this therapeutic agent will also vary with many factors including the potency of the particular compound, age and weight of the patient, the patient's physical condition, the blood sugar level, the weight level to be obtained, and other factors. Administration may begin whenever the increased of nutrient availability, food intake, weight, blood glucose or plasma lipid lowering is desired, such as, but not limited to, at the first sign of symptoms of a anorexia or at the onset of weight loss due to AIDS.

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

As a pharmaceutical medicament the PYY, PYY agonists, and PYY antagonists of the present disclosure may be administered directly by any suitable technique, including parenterally, intranasally, orally, or by absorption through the skin. The specific route of administration of each agent will depend, e.g., on the medical history of the animal.

For parenteral administration, in one embodiment, PYY, PYY agonists, and PYY antagonists can be formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to PYY and PYY agonists.

Generally, the formulations are prepared by contacting the PYY, PYY agonist, or PYY antagonist, uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

PPY, PYY antagonists, and PYY agonists are also suitably administered by sustained-release systems. Suitable examples of sustained-release PYY and PYY agonists include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt). Sustained-release PPY, PYY antagonist and PYY agonist compositions may be administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray.

Sustained release matrices include polylactides (U.S. Patent No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers 22*:547-556, 1983, poly(2-hydroxyethyl methacrylate)); (Langer et al., *J. Biomed. Mater. Res.*15:167-277, 1981; Langer, *Chem. Tech.* 12:98-105, 1982, ethylene vinyl acetate (Langer et al., *Id.*) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release PPY, PYY antagonists and PYY agonists include liposomally PPY and PYY agonists (see generally, Langer, *Science* 249:1527-1533, 1990; Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317-327 and 353-365, 1989). Liposomes containing PPY peptide and peptide analogs are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. U.S.A.* 82:3688-3692, 1985; Hwang et al., *Proc. Natl. Acad. Sci. U.S.A.* 77:4030-4034, 1980; EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Patent

Application No. 83-118008; U.S. Patent No. 4,485,045, U.S. Patent No. 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mole percent cholesterol, the selected proportion being adjusted for the optimal performance.

Preparations for administration can be suitably formulated to give controlled release of PYY, PYY antagonists and PYY agonists. For example, the pharmaceutical compositions may be in the form of particles comprising a biodegradable polymer and/or a polysaccharide jellifying and/or bioadhesive polymer, an amphiphilic polymer, an agent modifying the interface properties of the particles and a pharmacologically active substance. These compositions exhibit certain biocompatibility features which allow a controlled release of the active substance. See U.S. Patent No. 5,700,486.

In yet an additional embodiment, PPY, PYY antagonists, and PYY agonists are delivered by way of a pump (see Langer, *supra*; 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 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 (*Science* 249:1527-1533, 1990).

In another aspect of the disclosure, PPY, PYY antagonists, and PYY agonists 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.

Active drug or programmable infusion devices feature a pump or a metering system to deliver the drug into the patient's system. An example of such an active drug infusion device currently available is the Medtronic SynchroMed™

programmable pump. Such pumps typically include a drug reservoir, a peristaltic pump to pump out the drug from the reservoir, and a catheter port to transport the pumped out drug from the reservoir via the pump to a patient's anatomy. Such devices also typically include a battery to power the pump as well as an electronic module to control the flow rate of the pump. The Medtronic SynchroMed™ pump further includes an antenna to permit the remote programming of the pump. Passive drug infusion devices, in contrast, do not feature a pump, but rather rely upon a pressurized drug reservoir to deliver the drug. Thus such devices tend to be both smaller as well as cheaper as compared to active devices. An example of such a device includes the Medtronic IsoMed™. This device delivers the drug into the patient through the force provided by a pressurized reservoir applied across a flow control unit.

The implanted pump can be completely implanted under the skin of a patient, thereby negating the need for a percutaneous catheter. These implanted pumps can provide the patient with PYY, PYY antagonist, or a PYY agonist at a constant or a programmed delivery rate, e.g., to give pulsed doses at or around meal time. Constant rate or programmable rate pumps are based on either phase-change or peristaltic technology. When a constant, unchanging delivery rate is required, a constant-rate pump is well suited for long-term implanted drug delivery. If changes to the infusion rate are expected, a programmable pump may be used in place of the constant rate pump system. Osmotic pumps may be much smaller than other constant rate or programmable pumps, because their infusion rate can be very low. An example of such a pump is described listed in U.S. Patent No. 5,728,396.

For oral administration, the pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions,

or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

For administration by inhalation, the compounds for use according to the present disclosure are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, 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 containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations 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 sparingly soluble derivatives, for example, as a sparingly soluble salt.

Pharmaceutical compositions that comprise a PYY, or an agonist thereof, or a PYY antagonist, as described herein as an active ingredient will normally be formulated with an appropriate solid or liquid carrier, depending upon the particular mode of administration chosen. The pharmaceutically acceptable carriers and excipients useful in this disclosure are conventional. For instance, parenteral

formulations usually comprise injectable fluids that are pharmaceutically and physiologically acceptable fluid vehicles such as water, physiological saline, other balanced salt solutions, aqueous dextrose, glycerol or the like. Excipients that can be included are, for instance, other proteins, such as human serum albumin or plasma preparations. If desired, the pharmaceutical composition to be administered 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. Other medicinal and pharmaceutical agents, for instance other appetite suppressants, or protease inhibitors, also may be included. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art.

The dosage form of the pharmaceutical composition will be determined by the mode of administration chosen. For instance, in addition to injectable fluids, inhalation, suppository, and oral formulations can be employed. The pharmaceutical compositions can be produced of conventional mixing, granulating, confectioning, dissolving or lyophilizing processes.

Oral formulations may be liquid (e.g., syrups, solutions or suspensions), or solid (e.g., powders, pills, tablets, or capsules). For example, pharmaceutical compositions for oral use can be obtained by combining the active ingredient with one or more solid carriers, optionally granulating a resulting mixture, and, if desired, processing the mixture or granules, if appropriate with the addition of additional excipients, to form tablets or dragee cores.

Suitable carriers include fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyffolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients include flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts

thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

For parenteral administration compositions include suitable aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, or aqueous injection suspensions that contain viscosity-altering substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers. The active ingredient, optionally together with excipients, can also be in the form of a lyophilisate and can be made into a solution prior to parenteral administration by the addition of suitable solvents. Solutions such as those that are used, for example, for parenteral administration can also be used as infusion solutions.

For inhalation, PYY or an agonist thereof, or a PYY antagonist, is administered as an aerosol or a dispersion in a carrier. In one specific, non-limiting example, PYY or an agonist thereof is administered as an aerosol from a conventional valve, such as, but not limited to, a metered dose valve, through an aerosol adapter also known as an actuator. A suitable fluid carrier can be also included in the formulation, such as, but not limited to, air, a hydrocarbon, such as n-butane, propane, isopentane, amongst others, or a propellant, such as, but not limited to a fluorocarbon. 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).

Compounds with poor solubility in aqueous systems require formulation by using solubilizing agents such as ionic surfactants, cholates, polyethylene glycol (PEG), ethanol, or other agents which may have undesirable effects when used for inhalation. In addition, a treatment requiring successful delivery into alveoli of the lower pulmonary region may preclude from the formulation the use of certain irritants such as chlorofluorocarbons and should involve a minimum number of required doses. Alternatively, to avoid such limitations, liposomes or hydrophobic particles can be used. In one embodiment, an inhalation formulation for a sustained release includes using aerosol droplet particles approximately 1-2.1 μm in size, or of less than 1 μm in size. Small particle aerosol liposomes and liposome-drug combinations for medical use have been previously described (e.g., see EP 87309854.5).

In one embodiment, a therapeutically effective amount of PYY or an agonist thereof is administered with a therapeutically effective amount of another agent, such as, but not limited to, an additional appetite suppressant. Specific, non-limiting example of an additional appetite suppressant include amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine, fenfluramine, dexfenfluramine, and fluoxetine. PYY and/or a PYY agonist can be administered simultaneously with the additional appetite suppressant, or they may be administered sequentially. Thus, in one embodiment, PYY is formulated and administered with an appetite suppressant as a single dose.

Additionally, a method of treating obesity is disclosed herein. The method includes administering to an obese subject a therapeutically effective amount of PYY or a PYY agonist. The PYY agonist can have potency in at least one of food intake or gastric emptying greater than NPY. PYY and/or the PYY agonist can be administered peripherally, such as in a single or divided dose. Suitable single or divided doses include, but are not limited to, 1 μg to about 5 mg or about 0.01 μg/kg to about 500 μg/kg per dose. The subject can be insulin resistant or glucose intolerant, or both. In addition to being obese, the subject can have diabetes mellitus.

A method of reducing food intake is also disclosed herein. The method includes administering to an obese subject a therapeutically effective amount of PYY or a PYY agonist. The PYY agonist can have potency in at least one of food intake or gastric emptying greater than NPY. PYY and/or the PYY agonist can be administered peripherally, such as in a single or divided dose. Suitable single or divided doses include, but are not limited to, 1 μg to about 5 mg or about 0.01 μg/kg to about 500 μg/kg per dose. The subject can have Type II diabetes, and/or can be overweight.

A method is disclosed herein for improving lipid profile in a subject. The method includes administering to the subject an effective amount of PYY or a PYY agonist. An improvement in lipid profile includes, but is not limited to, at least one of reducing cholesterol levels, reducing triglyceride levels and increasing HDL cholesterol levels. PYY and/or the PYY agonist can be administered peripherally, such as in a single or divided dose. PYY and/or the PYY agonist can be

administered peripherally, such as in a single or divided dose. Suitable single or divided doses include, but are not limited to, 1 μg to about 5 mg or about 0.01 μg/kg to about 500 μg/kg per dose. The PYY agonist can have potency in at least one of food intake or gastric emptying greater than NPY.

In another embodiment, a method is disclosed herein for alleviating a condition or disorder which can be alleviated by reducing nutrient availability. The method includes administering to a subject a therapeutically effective amount of PYY or a PYY agonist. Suitable disorders include any of the disorders mentioned above. PYY and/or the PYY agonist can be administered peripherally, such as in a single or divided dose. Suitable single or divided doses include, but are not limited to, 1 μg to about 5 mg or about 0.01 μg/kg to about 500 μg/kg per dose. The PYY agonist can have potency in at least one of food intake or gastric emptying greater than NPY. Suitable doses also include those that raise the concentration of PYY and/or the agonist thereof significantly above the basal concentration of PYY, such as, but not limited to, a dose that that mimic postparandial serum concentrations of PYY (or the agonist). Thus, in one embodiment, PYY or an agonist thereof is administered to achieve the level of to effect a reduction in calorie intake, food intake, or appetite equivalent to the reduction in calorie intake, food intake, or appetite, or to increase the energy expenditure, caused by the postprandial level of PYY3-36. Specific, non-limiting examples of doses include, but are not limited doses that produce the effect demonstrated when the serum levels of PYY are from about 40 pM to about 50 pM, or from about 40 pM to about 45 pM, or to about 43 pM.

For all methods disclosed herein, the dose of PYY or PYY_{3-36} can be based on the physiological levels observed post-prandially. The normal circulating levels of PYY_{3-36} are about 8 pmol/litre, typically rising to about 40 to 60 pmol/litre after a meal. Agonists of PYY can be used at analogous doses. A single dose may be administered per day, or divided doses can be used (see above). As PYY_{3-36} has been shown to be effective for up to 12 and even for up to 24 hours after administration, it is possible to administer only two or even just one doe per day.

In one embodiment, when administered peripherally, PYY, including PYY_{3-36} has its effects at physiological levels. Other gut hormones (e.g., GLP) only

exert an effect at supraphysiological levels when administered peripherally, and side-effects are observed. No side effects are observed when PYY $_{3-36}$ is used. Without being bound by theory, PYY_{3-36} does not affect Y2 receptors throughout the brain, which could cause side effects. It should be noted, without being limiting, that a further advantage of PYY_{3-36} is that PYY_{3-36} does not increase blood pressure. The effects of PYY_{3-36} are as long lasting as 24 hours. Recipients claim a decrease in appetite over that period, and a reduction of food intake of about one third has been reported.

In one specific, non-limiting example, PYY_{3-36} is administered in a dose of about 1 nmol or more, 2 nmol or more, or 5 nmol or more. In this example, the dose of PYY_{3-36} 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, 10 nmols. 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, exemplar non-limiting dose ranges include a dose of PYY_{3-36} may be within the range of form 1 to 100 n mols, from 1 to 90 mols, from 1 to 80 nmols. Exemplary, non-limiting dose ranges include, from 2 to 100 nmols, from 2 to 90 n mols, for example, from 2 to 80 nmols etc., from 5 nmols to 100 mols, from 5 nmols to 90 nmols, from 5 nmols to 80 nmols etc. By way of example, a dose of from about 5 to about 50 nmol may be administered such as, but not limited to, from about 2 to about 20 nmol, for example, about 10 nmol. The selected dose may be administered for example, by injection, for example, as a subcutaneous injection. In one embodiment, a dose of PYY or PYY_{3-36} at 0.143 n moles ($1/7^{th}$ of a mole) is administered per kilogram, to achieve a dose that is similar to the postparandial level of PYY.

If PYY or an agonist thereof is used, the dose is preferably a molar equivalent of a PYY_{3-36} dose, as described above. The doses can be calculated on the basis of a subject, such as a subject weighing from 70 to 75 kg. The exact dose is readily determined by one of skill in the art based on the potency of the specific compound (such as the PYY polypeptide, or agonist) utilized, and the age, weight, sex and physiological condition of the subject.

As disclosed herein, a naturally occurring peptide, PYY or PYY_{3-36} can be used to achieve a physiological effect. This results in minimal side effects and enables long term use, if necessary. The dose of PYY or PYY_{3-36} can be based on the physiological levels observed post-prandially. The normal circulating levels of PYY_{3-36} are about 8 pmol/litre, typically rising to about 40 to 60 pmol/litre after a meal. PYY (e.g., PYY_{3-36}) and agonists can be used at analogous doses. Thus

The various uses of PYY, or an agonist or antagonist thereof, as set out above may be in a method of treatment of a mammalian subject in need of such treatment, or may be in the manufacture of a medicament for such treatment. PYY (e.g., PYY_{3-36}) or an agonist or antagonist thereof should be administered in an amount effective to achieve the stated object. Some of the treatments described above are medical treatments, for example, the treatment of obesity. Others, however, do not relate to medical treatment, and are part of the maintenance of a healthy lifestyle, or are for cosmetic purposes.

PYY Agonists

A PYY agonist, of use in the methods of the present disclosure, is a molecule that binds to a receptor that specifically binds PYY, and elicits an effect of PYY. Assays for binding to PYY receptors, and eliciting a response in a cell with a PYY receptor, are known in the art. A specific assay for detecting a PYY agonist is also disclosed herein. Thus, in one embodiment, a PYY agonist binds to a NPY neuron in the arcuate nucleus, which results in an electrophysiological effect on an NPY neuron. As disclosed herein, NPY neurons synapse with POMC neurons. Thus, the electrophysiological effect on the NYP neuron can result in a further electrophysiological effect on a POMC neuron. In one specific, non-limiting example, an administration of PYY agonist results in hyperpolization of the membrane potential of a POMC neuron. In another specific, non-limiting example, administration of a PYY agonist results in an increase in IPSCs in a POMC neuron.

In another embodiment, PYY agonists do not include NPY. Suitable PYY agonists include molecules that bind NPY neurons, but do not cross the blood/brain barrier. The arcuate nucleus neurons upon which PYY exerts its effects are not protected by the blood/brain barrier, and thus are readily accessible to peripherally

available molecules. In addition, other brain sites that express the Y2 receptor are protected by the blood/brain barrier. Without being bound by theory, agents able to bind to the arcuate Y2R, but that do not cross the blood/brain barrier following peripheral administration, are likely to be of use.

In one embodiment, a PYY agonist is a compound that affects food intake, caloric intake, or appetite, and/or which binds specifically in a Y receptor assay or competes for binding with PYY, such as in a competitive binding assay with labeled PYY. PYY agonists include, but are not limited to, compounds that bind to the Y2 receptor.

PYY and agonists useful in the methods disclosed herein include, but are not limited to, polypeptides comprising, or alternatively consisting of, the amino acid sequence for PPY and agonists thereof, e.g., mutants, fragments and/or variants thereof. Variants include deletions, insertions, inversions, repeats and substitutions (e.g., conservative substitutions and non-conservative substitutions; see, e.g., Tables 1 and 2, *infra*). More than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) can be deleted or inserted or substituted with another amino acid. Typically conservative substitutions are the replacements, one for 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 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. Guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., *Science* 247:1306-1310, 1990.

As another example, polypeptide fragments may contain a continuous series of deleted residues from the amino (N)- or the carboxyl (C)- terminus, or both (see, e.g., Tables 1 and 2, *infra*). Any number of amino acids, ranging from 1 to 24, can be deleted from the N-terminus, the C-terminus or both.

Furthermore, the agonist polypeptides may also include, but are not limited to, polypeptides comprising, or alternatively consisting of, internal deletions of the amino acid sequences for PPY and/or agonist thereof (see, e.g., Table 2, *infra*). Such deletions may comprise one or more amino acid residue deletions (e.g., one,

two, three, four, five, six, seven, eight, nine, ten, etc.) and may begin at any amino acid position (e.g., two, three, four, five, six, seven, eight, nine, ten, etc.). In addition, the polypeptides of this disclosure may contain one or more such internal deletions. Such deletions are contemplated in PPY, NPY and PP.

Also contemplated are agonist peptides that are PPY, NPY and/or PP chimeras having high affinity and/or selectivity for the Y2 receptor. These chimeras may comprise amino acid substitutions of one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) from PPY, NPY and/or PP, variants, mutants and/or deletions thereof, with one or more amino acids (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.) from a second PPY, NPY, or PP, variants, mutations and/or deletions thereof. These substitutions may begin at any amino acid position (e.g., two, three, four, five, six, seven, eight, nine, ten, etc.).

Preferably, the peptide is selective for the Y2 receptor. That is, it binds with higher affinity to Y2 compared to other receptors, such as Y1, Y2, Y3, Y4, Y5 and Y6. In another embodiment, the peptide is selective for the Y2 and Y5 receptors over the Y1, Y3, Y4 and Y6 receptors.

Other polypeptide fragments are fragments comprising structural or functional domain of the polypeptides of this disclosure. Such fragments include amino acid residues that comprise a polyproline-type II helix (residues 1-8), beta-turn (residues 9-14), amphipathic alpha-helix (residues 15-32) and/or a C-terminal turn structure (residues 33-36). See, Kirby et al., *J Med Chem* 36:385-393, 1993.

In addition, this disclosure includes the use of a polypeptide or agonist comprising, or alternatively consisting of, the amino acid sequence for PPY, NPY and PP species variants (see Table 1, *infra*) and/or mutants, and fragments thereof.

Also contemplated are fusion proteins, whereby a PYY or PYY agonist will be 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. Any known peptide or protein can be used as the fusion partner (e.g., serum albumin, carbonic anhydrase, glutathione-S-transferase or thioredoxin, etc.). Preferred fusion partners will not have an adverse biological activity *in vivo*. Such fusion proteins may be designed linking the carboxy-terminus of the fusion partner to the amino-terminus of the PYY or agonist

peptide, or vice versa. Optionally, a cleavable linker region may be used linking the PYY or PYY agonist to the fusion partner, and may be cleaved *in vivo* thereby resulting in the release of an active form of PYY or a PYY agonist. Examples of such cleavage regions include, but are not limited to, the linker regions D-D-D-D-Y (SEQ ID NO: 330), G-P-R (SEQ ID NO: 331), A-G-G (SEQ ID NO: 332) and H-P-F-H-L (SEQ ID NO 333), which can be cleaved by enterokinase, thrombin, ubiquitin cleaving enzyme and renin, respectfully. See, e.g., U.S. Patent No. 6,410,707.

Also contemplated as useful PYY agonists are Y2 specific NPY peptide agonists as described in U.S. Patent No. 5,026,685; U.S. Patent No. 5,574,010; U.S. Patent No. 5,604,203; U.S. Patent No. 5,696,093; U.S. Patent No. 6,046,167. See below:

Preferred PPY agonists are described herein as follows.

TABLE 1 - PYY: Variation Among Species

PEPTIDE YY	AA SEQUENCE
Human	YPIKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 1)
Rat	YPAKPEAPGEDASPEELSRYYASLRHYLNLVTRQRY (SEQ ID NO: 5)
Pig	YPAKPEAPGEDASPEELSRYYASLRHYLNLVTRQRY (SEQ ID NO: 6)
Guinea pig	YPSKPEAPGSDASPEELARYYASLRHYLNLVTRQRY (SEQ ID NO: 7)
Frog	YPPKPENPGEDASPEEMTKYLTALRHYINLVTRQRY (SEQ ID NO: 8)
Raja	YPPKPENPGDDAAPEELAKYYSALRHYINLITRQRY (SEQ ID NO: 9)
Dogfish	YPPKPENPGEDAPPEELAKYYSALRHYINLITRQRY (SEQ ID NO: 10)
Lampetra	FPPKPDNPGDNASPEQMARYKAAVRHYINLITRQRY (SEQ ID NO: 11)
Petromyzon	MPPKPDNPSPDASPEELSKYMLAVRNYINLITRQRY (SEQ ID NO: 12)

NEUROPEPTIDE Y	AA SEQUENCE
Human	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 2)
Rat	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 13)
Rabbit	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 14)
Dog	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 15)
Pig	YPSKPDNPGEDAPAEDLARYYSALRHYINLITRQRY (SEQ ID NO: 16)
Cow	YPSKPDNPGEDAPAEDLARYYSALRHYINLITRQRY (SEQ ID NO: 17)
Sheep	YPSKPDNPGDDAPAEDLARYYSALRHYINLITRQRY (SEQ ID NO: 18)

	Guinea pig	YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 19)
	Avian	YPSKPDSPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 20)
	Rana	YPSKPDNPGEDAPAEDMAKYYSALRHYINLITRQRY (SEQ ID NO: 21)
	Goldfish	YPTKPDNPGEGAPAEELAKYYSALRHYINLITRQRY (SEQ ID NO: 22)
5	Dogfish	YPSKPDNPGEGAPAEDLAKYYSALRHYINLITRQRY (SEQ ID NO: 23)
	Lampetra	PPNKPDSPGEDAPAEDLARYLSAVRHYINLITRQRY (SEQ ID NO: 24)

PANCREATIC POLYPEPTIDE	AA SEQUENCE
Human	ASLEPEYPGDNATPEQMAQYAAELRRYINMLTRPRY (SEQ ID NO: 3)
10 Sheep	APLEPVYPGDNATPEQMAQYAADLRRYINMLTRPRY (SEQ ID NO: 25)
Pig	APLEPVYPGDDATPEQMAQYAAELRRYINMLTRPRY (SEQ ID NO: 26)
Dog	APLEPVYPGDDATPEQMAQYAAELRRYINMLTRPRY (SEQ ID NO: 27)
Cat	APLEPVYPGDNATPEQMAQYAAELRRYINMLTRPRY (SEQ ID NO: 28)
Cow	APLEPEYPGDNATPEQMAQYAAELRRYINMLTRPRY (SEQ ID NO: 29)
15 Rat	APLEPMYPGDYATHEQRAQYETQLRRYINTLTRPRY (SEQ ID NO: 30)
Mouse	APLEPMYPGDYATPEQMAQYETQLRRYINTLTRPRY (SEQ ID NO: 31)
Guinea pig	APLEPVYPGDNATPEQQMAQYAAEMRRYINMLTRPRY (SEQ ID NO: 32)
Chicken	GPSQPTYPGDDAPVEDLIRFYNDLQQYLNVVTRHRY (SEQ ID NO: 33)
Alligator	TPLQPKYPGDGAPVEDLIQFYNDLQQYLNVVTRPRF (SEQ ID NO: 34)
20 Bullfrog	APSEPHHPGDQATPDQLAQYYSDLYQYITFITRPRF (SEQ ID NO: 35)

Ref: Beck-Sickinger, A.G., Jung, G., *Biopolymers 37:123-142, 1995.*

TABLE 2 – PEPTIDE AGONIST OF PYY

25

PEPTIDE	SEQUENCE
PPY(3-36)(human)	IKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 334)

Ref: Eberlein et al., *Peptides* 10:797-803, 1989; Grandt et al., *Peptides* 15(5):815-

30 20, 1994.

Variations of PPY(3-36)

N-Terminal Deletions of PYY, including but not limited to: PYY(26-36), PYY(25-36), PYY(24-36), PYY(23-36), PYY(22-36), PYY(21-36), PYY(20-36), PYY(19-

35 36), PYY(18-36), PYY(17-36), PYY(16-36), PYY(15-36), PYY(14-36), PYY(13-36), PYY(12-36), PYY(11-36), PYY(10-36), PYY(9-36), PYY(8-36), PYY(7-36), PYY(6-36), PYY(5-36), PYY(4-36), PYY(3-36).

Ref: See, e.g., Balasubramaniam et al., *Pept Res* 1(1):32-5, Sep-Oct 1998; Liu et al., *J Gastrointest Surg* 5(2):147-52, Mar-Apr 2001.

PEPTIDE SEQUENCE

NPY (human)

YPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 2)

Ref: Tatemoto et al., *Proc Natl Acad Sci* U.S.A. 79:5485-9, 1982.

Variations of NPY

N-Terminal Deletions of NPY, including but not limited to: NPY(26-36), NPY(25-36), NPY(24-36), NPY(23-36), NPY(22-36), NPY(21-36), NPY(20-36), NPY(19-36), NPY(18-36), NPY(17-36), NPY(16-36), NPY(15-36), NPY(14-36), NPY(13-36), NPY(12-36), NPY(11-36), NPY(10-36), NPY(9-36), NPY(8-36), NPY(7-36), NPY(6-36), NPY(5-36), NPY(4-36), NPY(3-36).

Ref: See e.g., Gehlert et al., *Proc Soc Exp Biol Med* 218:7-22, 1998; Sheikh et al., *Am J Physiol* 261:G701-15, Nov. 1991.

Internal Deletions, including but not limited to: (1-4)-Aca-(14-36)pNPY, (1-4)-Aca-(15-36)pNPY, (1-4)-Aca-(16-36)pNPY, (1-4)-Aca-(17-36)pNPY, (1-4)-Aca-(18-36)pNPY, (1-4)-(31-36)pNPY11, (1-4)-Aca-(31-36)pNPY, (4-1)-(31-36)pNPY, (4-1)-Aca-(31-36)pNPY, $(4\text{-}1)_D$-(31-36)pNPY, $(4\text{-}1)_D$-Aca-(31-36)pNPY.

Ref: Fournier et al., *Mol Pharmacol* 45(1):93-101, Jan 1994.

Additional Internal Deletion Mutants, including but not limited to: des-$AA^{10\text{-}17}$-NPY, des-$AA^{10\text{-}17}$, Ac-[D-Lys^9(ε-Ac-Ala)]NPY, des-$AA^{10\text{-}17}$, Ac[D-Lys^9(ε-Ac-Ala)]NPY, des-$AA^{10\text{-}17}$[$Ala^{7,21}$]NPY, des-$AA^{10\text{-}17}$[$Cys^{7,21}$]NPY, des-$AA^{10\text{-}17}$[Glu^7,Lys^{21}]NPY, des-$AA^{11\text{-}17}$[D-Lys^{10}(ε-Ac), $Cys^{7,21}$]NPY, des-$AA^{10\text{-}17}$[D-Cys^7, D-Lys(ε-Ac), Cys^{21}]NPY,des-$AA^{10\text{-}17}$[D-Cys^7, Lys^9(ε-Ac), Cys^{21}]NPY, des-$AA^{10\text{-}17}$[$Cys^{7,21}$, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[Asp^7, Dpr^{21}, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[Glu^7, Lys^{21}, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[$Cys^{7,21}$, Leu^{31}, Pro^{34}]NPY, des-$AA^{10\text{-}20}$[$Cys^{7,21}$, Pro^{34}]NPY, des-$AA^{10\text{-}17}$[$Cys^{2,27}$]NPY, des-$AA^{10\text{-}17}$[Cys^2, D-Cys^{27}]NPY.

Ref: Kirby et al., *J Med Chem* 38:4579-86, 1995.

Cyclic agonist of NPY, including but not limited to: [Lys 25-Glu 29]NPY(Ac-25-36), [Glu 25-Lys 29]NPY(Ac-25-36), [Lys 26-Glu31]NPY(Ac-25-36), [Glu 27-Lys 31]NPY(Ac-25-36), [Lys28-Glu 32]NPY(Ac-25-36), [Lys27-Glu34]NPY(Ac-25-36).

Ref: Rist et al., *Eur J Biochem* 247:1019-1028, 1997.

D-amino acid substitutions: [D-Tyr^{1}]NPY, [D-Pro^{2}]NPY, [D-Ser^{3}]NPY, [D-Lys^{4}]NPY, [D-Pro^{5}]NPY, [D-Asp^{6}]NPY, [D-Asn^{7}]NPY, [D-Pro^{8}]NPY, [D-Ala^{9}]NPY, [D-Glu^{10}]NPY, [D-Asp^{11}]NPY, [D-Ala^{12}]NPY, [D-Pro^{13}]NPY, [D-Ala^{14}]NPY, [D-Glu^{15}]NPY, [D-Asp^{16}]NPY, [D-Leu^{17}]NPY, [D-Ala^{18}]NPY, [D-Arg^{19}]NPY, [D-Tyr^{20}]NPY, [D-Tyr^{21}]NPY, [D-Ser^{22}]NPY, [D-Ala^{23}]NPY, [D-Leu^{24}]NPY, [D-Arg^{25}]NPY, [D-His^{26}]NPY, [D-Tyr^{27}]NPY, [D-Ile^{28}]NPY, [D-Asn^{29}]NPY, [D-Leu^{30}]NPY, [D-Ile^{31}]NPY, [D-Thr^{32}]NPY, [D-Arg^{33}]NPY, [D-Gln^{34}]NPY, [D-Arg^{35}]NPY, [D-Tyr^{36}]NPY, [D-Tyr^{1}, D-Pro^{2}]NPY, [D-Ser^{3}, D-Lys^{4}]NPY, [D-Pro^{5}, D-Asp^{6}]NPY, [D-Asn^{7}, D-Pro^{8}]NPY, [D-Glu^{10}, D-Asp^{11}]NPY, [D-Asp^{11}, D-Ala^{12}]NPY, [D-Pro^{13}, D-Ala^{14}]NPY, [D-Glu^{15}, D-Asp^{16}]NPY, [D-Met^{17}, D-Ala^{18}]NPY, [D-Arg^{19}, D-Tyr^{20}]NPY, [D-Tyr^{21}, D-Ser^{22}]NPY, [D-Ala^{23}, D-Leu^{24}]NPY, [D-Arg^{25}, D-His^{26}]NPY, [D-Tyr^{27}, D-Ile^{28}]NPY, [D-Asn^{29}, D-Leu^{30}]NPY, [D-Ile^{31}, D-Thr^{32}]NPY, [D-Arg^{33}, D-Gln^{34}]NPY, [D-Arg^{35}, D-Tyr^{36}]NPY.

Ref: Kirby et al., *J Med Chem* 36:3802-08, 1993; Grundemar et al., *Regulatory Peptides* 62:131-136, 1996.

Other NPY Agonist and Analogs

PEPTIDE	SEQUENCE
NPY(3-36)	SKPDNPGEDAPAEDMARYYSALRHYINLITRQRY (SEQ ID NO: 335)

Ref: Grandt et al., *Regulatory Peptides* 67(1):33-7, 1996.

PEPTIDE	SEQUENCE
N-Acetyl NPY(24-36)	LRHYINLITRQRY (SEQ ID NO: 213)

Ref: Potter et al., *Eur J Pharmacol* 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

N-Acetyl [Leu^{28}, Leu^{31}] NPY(24-36)

LRHYLNLLTRQRY (SEQ ID NO: 214)

Ref: Potter et al., *Eur J Pharmacol* 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

[Leu^{28}, Leu^{31}] NPY(24-36)

LRHYLNLLTRQRY (SEQ ID NO: 215)

Ref: Potter et al., *Eur J Pharmacol* 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

[Leu^{17}, Gln^{19}, Ala^{21}, Ala^{22}, Glu^{23}, Leu^{28}, Leu^{31}] NPY(13-36)

PAEDLAQYAAELRHYLNLLTRQRY (SEQ ID NO: 216)

Ref: Potter et al., Eur J Pharmacol 267(3):253-262, May 17, 1994.

PEPTIDE SEQUENCE

Cyclo S-S [Cys^{20},Cys^{24}]pNPY

SKPDNPGEDAPAEDMARCYSACRHYINLITRQRY (SEQ ID NO: 315)

Ref: Soll et al., *Eur J Biochem* 268(10):2828-37, May 2001.

PEPTIDE SEQUENCE

Cyclo-(28/32)-Ac-[Lys^{28}-Glu^{32}]-(25-36)-pNPY

RHYLNLIGRQRY (SEQ ID NO: 316)

Ref: Cabrele et al., *J Pept Sci* 6(3):97-122, Mar 2000.

PEPTIDE SEQUENCE

Cyclo-(27/31)-Ac-[Glu^{27}-Lys^{31}]-(25-36)-pNPY

RHGLNLLGRQRY (SEQ ID NO: 317)

Ref: Cabrele et al., *J Pept Sci* 6(3):97-122, Mar 2000.

PEPTIDE SEQUENCE

[Tyr^{32}, Leu^{34}]NPY(27-36)

YINLIYRLRY (SEQ ID NO: 318)

Ref: Leban et al., *J Med Chem* 38:1150-57, 1995.

PEPTIDE SEQUENCE

[Tyr^{32}, Leu^{34}]NPY(26-36)

HYINLIYRLRY (SEQ ID NO: 319)

Ref: Leban et al., *J Med Chem* 38:1150-57, 1995.

PEPTIDE SEQUENCE

[Tyr^{32}, Leu^{34}]NPY(25-36)

RHYINLIYRLRY (SED ID NO: 320)

Ref: Leban et al., *J Med Chem* 38:1150-57, 1995.

[Leu^{31}]NPY(27-36)

YINLLYRQRY (SEQ ID NO: 321)

Ref: Leban et al., *J Med Chem* 38:1150-57, 1995.

PEPTIDE SEQUENCE

[Tyr^{32}, Leu^{34}] (1-4)-Ahr-(27-36)NPY

YPSL-Aha-YINLIYRLRY (SED ID NO: 322)

Ref: Leban et al., *J Med Chem* 38:1150-57, 1995.

PEPTIDE SEQUENCE

[Tyr^{32}, Leu^{34}]NPY(28-36)

INLIYRLRY (SEQ ID NO: 323)

Ref: Leban et al., *J Med Chem* 38:1150-57, 1995.

PEPTIDE SEQUENCE

PP (human)

ASLEPEYPGDNATPEQMAQYAAELRRYINMLTRPRY (SEQ ID NO: 3)

Ref: Kimmel et al., *Endocrinology* 83:1323-30, 1968.

Variations of PP

N-Terminal Deletions including but not limited to: PP(26-36), PP(25-36), PP(24-36), PP(23-36), PP(22-36), PP(21-36), PP(20-36), PP(19-36), PP(18-36), PP(17-36), PP(16-36), PP(15-36), PP(14-36), PP(13-36), PP(12-36), PP(11-36), PP(10-36), PP(9-36), PP(8-36), PP(7-36), PP(6-36), PP(5-36), PP(4-36), PP(3-36).

TABLE 3 – EXAMPLES OF CONSERVATIVE AMINO ACID SUBSTITUTIONS OF PYY

Single point mutations of PYY(25-36)

PEPTIDE	SEQUENCE
[Lys^{25}]PPY(25-36)	KHYLNLVTRQRY (SEQ ID NO: 36)
[Thr^{27}]PPY(25-36)	RHTLNLVTRQRY (SEQ ID NO: 37)
[Phe^{27}]PPY(25-36)	RHFLNLVTRQRY (SEQ ID NO: 38)
[Ile^{28}]PYY (25-36)	RHYINLVTRQRY (SEQ ID NO: 39)
[Val^{28}]PYY (25-36)	RHYVNLVTRQRY (SEQ ID NO: 40)
[Gln^{29}]PYY (25-36)	RHYLQLVTRQRY (SEQ ID NO: 41)
[Ile^{30}]PYY (25-36)	RHYLNIVTRQRY (SEQ ID NO: 42)
[Val^{30}]PYY (25-36)	RHYLNVVTRQRY (SEQ ID NO: 43)
[Ile^{31}]PYY (25-36)	RHYLNLITRQRY (SEQ ID NO: 44)
[Leu^{31}]PYY (25-36)	RHYLNLLTRQRY (SEQ ID NO: 45)
[Ser^{32}]PYY (25-36)	RHYLNLVSRQRY (SEQ ID NO: 46)
[Lys^{33}]PYY (25-36)	RHYLNLVTKQRY (SEQ ID NO: 47)
[Asn^{34}]PYY (25-36)	RHYLNLVTRNRY (SEQ ID NO: 48)
[Lys^{35}]PYY (25-36)	RHYLNLVTRQKY (SEQ ID NO: 49)
[Thr^{36}]PYY (25-36)	RHYLNLVTRQRT (SEQ ID NO: 50)
[Phe^{36}]PYY (25-36)	RHYLNLVTRQRF (SEQ ID NO: 51)

Double point mutations

PEPTIDE	SEQUENCE
[Lys^{25}, Thr^{27}]PPY(25-36)	KHTLNLVTRQRY (SEQ ID NO: 52)
[Lys^{25}, Phe^{27}]PPY(25-36)	KHFLNLVTRQRY (SEQ ID NO: 53)
[Lys^{25}, Ile^{28}]PPY(25-36)	KHYINLVTRQRY (SEQ ID NO: 54)
[Lys^{25}, Val^{28}]PPY(25-36)	KHYVNLVTRQRY (SEQ ID NO: 55)
[Lys^{25}, Gln^{29}]PPY(25-36)	KHYLQLVTRQRY (SEQ ID NO: 56)
[Lys^{25}, Ile^{30}]PPY(25-36)	KHYLNIVTRQRY (SEQ ID NO: 57)
[Lys^{25}, Val^{30}]PPY(25-36)	KHYLNVVTRQRY (SEQ ID NO: 58)
[Lys^{25}, Ile^{31}]PPY(25-36)	KHYLNLITRQRY (SEQ ID NO: 59)
[Lys^{25}, Leu^{31}]PPY(25-36)	KHYLNLLTRQRY (SEQ ID NO: 60)
[Lys ^{25}, Ser ^{32}]PPY(25-36)	KHYLNLVSRQRY (SEQ ID NO: 61)
[Lys^{25}, Lys^{33}]PPY(25-36)	KHYLNLVTKQRY (SEQ ID NO: 62)
[Lys^{25}, Asn^{34}]PPY(25-36)	KHYLNLVTRNRY (SEQ ID NO: 63)

[Lys^{25}, Lys^{35}]PPY(25-36)	KHYLNLVTRQKY (SEQ ID NO: 64)
[Lys^{25}, Thr^{36}]PPY(25-36)	KHYLNLVTRQRT (SEQ ID NO: 65)
[Lys^{25}, Phe^{36}]PPY(25-36)	KHYLNLVTRQRF (SEQ ID NO: 66)
[Thr^{27}, Ile^{28}]PPY(25-36)	RHTINLVTRQRY (SEQ ID NO: 67)
[Thr^{27}, Val^{28}]PPY(25-36)	RHTVNLVTRQRY (SEQ ID NO: 68)
[Thr^{27}, Gln^{29}]PPY(25-36)	RHTLQLVTRQRY (SEQ ID NO: 69)
[Thr^{27}, Ile^{30}]PPY(25-36)	RHTLNIVTRQRY (SEQ ID NO: 70)
[Thr^{27}, Val^{30}]PPY(25-36)	RHTLNVVTRQRY (SEQ ID NO: 71)
[Thr^{27}, Ile^{31}]PPY(25-36)	RHTLNLITRQRY (SEQ ID NO: 72)
[Thr^{27}, Leu^{31}]PPY(25-36)	RHTLNLLTRQRY (SEQ ID NO: 73)
[Thr^{27}, Ser^{32}]PPY(25-36)	RHTLNLVSRQRY (SEQ ID NO: 74)
[Thr^{27}, Lys^{33}]PPY(25-36)	RHTLNLVTKQRY (SEQ ID NO: 75)
[Thr^{27}, Asn^{34}]PPY(25-36)	RHTLNLVTRNRY (SEQ ID NO: 76)
[Thr^{27}, Lys^{35}]PPY(25-36)	RHTLNLVTRQKY (SEQ ID NO: 77)
[Thr^{27}, Thr^{36}]PPY(25-36)	RHTLNLVTRQRT (SEQ ID NO: 78)
[Thr^{27}, Phe^{36}]PPY(25-36)	RHTLNLVTRQRF (SEQ ID NO: 79)
[Phe^{27}, Ile^{28}]PPY(25-36)	RHFINLVTRQRY (SEQ ID NO: 80)
[Phe^{27}, Val^{28}]PPY(25-36)	RHFVNLVTRQRY (SEQ ID NO: 81)
[Phe^{27}, Gln^{29}]PPY(25-36)	RHFLQLVTRQRY (SEQ ID NO: 82)
[Phe^{27}, Ile^{30}]PPY(25-36)	RHFLNIVTRQRY (SEQ ID NO: 83)
[Phe^{27}, Val^{30}]PPY(25-36)	RHFLNVVTRQRY (SEQ ID NO: 84)
[Phe^{27}, Ile^{31}]PPY(25-36)	RHFLNLITRQRY (SEQ ID NO: 85)
[Phe^{27}, Leu^{31}]PPY(25-36)	RHFLNLLTRQRY (SEQ ID NO: 86)
[Phe^{27}, Ser^{32}]PPY(25-36)	RHFLNLVSRQRY (SEQ ID NO: 87)
[Phe^{27}, Lys^{33}]PPY(25-36)	RHFLNLVTKQRY (SEQ ID NO: 88)
[Phe^{27}, Asn^{34}]PPY(25-36)	RHFLNLVTRNRY (SEQ ID NO: 89)
[Phe^{27}, Lys^{35}]PPY(25-36)	RHFLNLVTRQKY (SEQ ID NO: 90)
[Phe^{27}, Thr^{36}]PPY(25-36)	RHFLNLVTRQRT (SEQ ID NO: 91)
[Phe^{27}, Phe^{36}]PPY(25-36)	RHFLNLVTRQRF (SEQ ID NO: 92)
[Gln^{29}, Ile^{30}]PYY (25-36)	RHYLQIVTRQRY (SEQ ID NO: 93)
[Gln^{29}, Val^{30}]PYY (25-36)	RHYLQVVTRQRY (SEQ ID NO: 94)
[Gln^{29}, Ile^{31}]PYY (25-36)	RHYLQLITRQRY (SEQ ID NO: 95)
[Gln^{29}, Leu^{31}]PYY (25-36)	RHYLQLLTRQRY (SEQ ID NO: 96)
[Gln^{29}, Ser^{32}]PYY (25-36)	RHYLQLVSRQRY (SEQ ID NO: 97)
[Gln^{29}, Leu^{33}]PYY (25-36)	RHYLQLVTKQRY (SEQ ID NO: 98)
[Gln^{29}, Asn^{34}]PYY (25-36)	RHYLQLVTRNRY (SEQ ID NO: 99)
[Gln^{29}, Leu^{35}]PYY (25-36)	RHYLQLVTRQKY (SEQ ID NO: 100)
[Gln^{29}, Thr^{36}]PYY (25-36)	RHYLQLVTRQRT (SEQ ID NO: 101)
[Gln^{29}, Phe^{36}]PYY (25-36)	RHYLQLVTRQRF (SEQ ID NO: 102)

[Ile^{30}, Ile^{31}]PYY (25-36)	RHYLNIITRQRY (SEQ ID NO: 103)
[Ile^{30}, Leu^{31}]PYY (25-36)	RHYLNILTRQRY (SEQ ID NO: 104)
[Ile^{30}, Ser^{32}]PYY (25-36)	RHYLNIVSRQRY (SEQ ID NO: 105)
[Ile^{30}, Lys^{33}]PYY (25-36)	RHYLNIVTKQRY (SEQ ID NO: 106)
[Ile^{30}, Asn^{34}]PYY (25-36)	RHYLNIVTRNRY (SEQ ID NO: 107)
[Ile^{30}, Lys^{35}]PYY (25-36)	RHYLNIVTRQKY (SEQ ID NO: 108)
[Ile^{30}, Thr^{36}]PYY (25-36)	RHYLNIVTRQRT (SEQ ID NO: 109)
[Ile^{30}, Phe^{36}]PYY (25-36)	RHYLNIVTRQRF (SEQ ID NO: 110)
[Val^{30}, Ile^{31}]PYY (25-36)	RHYLNVITRQRY (SEQ ID NO: 111)
[Val^{30}, Leu^{31}]PYY (25-36)	RHYLNVLTRQRY (SEQ ID NO: 112)
[Val^{30}, Ser^{32}]PYY (25-36)	RHYLNVVSRQRY (SEQ ID NO: 113)
[Val^{30}, Lys^{33}]PYY (25-36)	RHYLNVVTKQRY (SEQ ID NO: 114)
[Val^{30}, Asn^{34}]PYY (25-36)	RHYLNVVTRNRY (SEQ ID NO: 115)
[Val^{30}, Lys^{35}]PYY (25-36)	RHYLNVVTRQKY (SEQ ID NO: 116)
[Val^{30}, Thr^{36}]PYY (25-36)	RHYLNVVTRQRT (SEQ ID NO: 117)
[Val^{30}, Phe^{36}]PYY (25-36)	RHYLNVVTRQRF (SEQ ID NO: 118)
[Ile^{31}, Ser^{32}]PYY (25-36)	RHYLNLISRQRY (SEQ ID NO: 119)
[Ile^{31}, Lys^{33}]PYY (25-36)	RHYLNLITKQRY (SEQ ID NO: 120)
[Ile^{31}, Asn^{34}]PYY (25-36)	RHYLNLITRNRY (SEQ ID NO: 121)
[Ile^{31}, Lys^{35}]PYY (25-36)	RHYLNLITRQKY (SEQ ID NO: 122)
[Ile^{31}, Thr^{36}]PYY (25-36)	RHYLNLITRQRT (SEQ ID NO: 123)
[Leu^{31}, Phe^{36}]PYY (25-36)	RHYLNLITRQRF (SEQ ID NO: 124)
[Leu^{31}, Ser^{32}]PYY (25-36)	RHYLNLLSRQRY (SEQ ID NO: 125)
[Val^{31}, Lys^{33}]PYY (25-36)	RHYLNLLTKQRY (SEQ ID NO: 126)
[Leu^{31}, Asn^{34}]PYY (25-36)	RHYLNLLTRNRY (SEQ ID NO: 127)
[Leu^{31}, Lys^{35}]PYY (25-36)	RHYLNLLTRQKY (SEQ ID NO: 128)
[Leu^{31}, Thr^{36}]PYY (25-36)	RHYLNLLTRQRT (SEQ ID NO: 129)
[Leu^{31}, Phe^{36}]PYY (25-36)	RHYLNLLTRQRF (SEQ ID NO: 130)
[Ser^{32}, Lys^{33}]PYY (25-36)	RHYLNLVSKQRY (SEQ ID NO: 131)
[Ser^{32}, Asn^{34}]PYY (25-36)	RHYLNLVSRNRY (SEQ ID NO: 132)
[Ser^{32}, Lys^{35}]PYY (25-36)	RHYLNLVSRQKY (SEQ ID NO: 133)
[Ser^{32}, Thr^{36}]PYY (25-36)	RHYLNLVSRQRT (SEQ ID NO: 134)
[Ser^{32}, Phe^{36}]PYY (25-36)	RHYLNLVSRQRY (SEQ ID NO: 135)
[Lys^{33}, Asn^{34}]PYY (25-36)	RHYLNLVTKNRY (SEQ ID NO: 136)
[Lys^{33}, Lys^{35}]PYY (25-36)	RHYLNLVTKQKY (SEQ ID NO: 137)
[Lys^{33}, Thr^{36}]PYY (25-36)	RHYLNLVTKQRT (SEQ ID NO: 138)
[Lys^{33}, Phe^{36}]PYY (25-36)	RHYLNLVTKQRF (SEQ ID NO: 139)
[Asn^{34}, Lys^{35}]PYY (25-36)	RHYLNLVTRNKY (SEQ ID NO: 140)
[Asn^{34}, Thr^{36}]PYY (25-36)	RHYLNLVTRNRT (SEQ ID NO: 141)

[Asn^{34}, Phe^{36}]PYY (25-36)	RHYLNLVTRNRF (SEQ ID NO: 142)
[Lys^{35}, Thr^{36}]PYY (25-36)	RHYLNLVTRQKT (SEQ ID NO: 143)
[Lys^{35}, Phe^{36}]PYY (25-36)	RHYLNLVTRQKF (SEQ ID NO: 144)

Point Mutations of PYY(24-36)

PEPTIDE	SEQUENCE
PYY(24-36)	LRHYLNLVTRQRY (SEQ ID NO: 145)
[Ile^{24}]PYY(24-36)	IRHYLNLVTRQRY (SEQ ID NO: 146)
[Val^{24}]PYY(24-36)	VRHYLNLVTRQRY (SEQ ID NO: 147)

Also included as PYY(24-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these three mutants with any of the above listed mutants for PYY(25-36), e.g., [Lys^{25}]PPY(24-36) (Amino acid sequence=LKHYLNLVTRQRY (SEQ ID NO: 191)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 145.

Point Mutations of PYY(23-36)

PEPTIDE	SEQUENCE
PYY(23-36)	SLRHYLNLVTRQRY (SEQ ID NO: 148)
[Thr^{23}]PYY(23-36)	TLRHYLNLVTRQRY (SEQ ID NO: 149)

Also included as PYY(23-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(24-36), e.g., [Lys^{25}]PPY(23-36) (Amino acid sequence=SLKHYLNLVTRQRY (SEQ ID NO: 192)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 148.

Point Mutations of PYY(22-36)

PEPTIDE	SEQUENCE
PYY(22-36)	ASLRHYLNLVTRQRY (SEQ ID NO: 150)
[Ser^{22})PYY(22-36)	SSLRHYLNLVTRQRY (SEQ ID NO: 151)

Also included as PYY(22-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two

mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(23-36), e.g., [Lys^{25}]PPY(22-36) (Amino acid sequence=ASLKHYLNLVTRQRY (SEQ ID NO: 193)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 150.

Point Mutations of PYY(21-36)

PEPTIDE	SEQUENCE
PYY(21-36)	YASLRHYLNLVTRQRY (SEQ ID NO: 152)
[Thr^{21}]PYY(21-36)	TASLRHYLNLVTRQRY (SEQ ID NO: 153)
[Phe^{21}]PYY(21-36)	FASLRHYLNLVTRQRY (SEQ ID NO: 154)

Also included as PYY(21-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these three mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(22-36), e.g., [Lys^{25}]PPY(21-36) (Amino acid sequence=YASLKHYLNLVTRQRY (SEQ ID NO: 194)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 152.

Point Mutations of PYY(20-36)

PEPTIDE	SEQUENCE
PYY(20-36)	YYASLRHYLNLVTRQRY (SEQ ID NO: 155)
[Thr^{20}]PYY(20-36)	TYASLRHYLNLVTRQRY (SEQ ID NO: 156)
[Phe^{20}]PYY(20-36)	FYASLRHYLNLVTRQRY (SEQ ID NO: 157)

Also included as PYY(20-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these three mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(21-36), e.g., [Lys^{25}]PPY(20-36) (Amino acid sequence=YYASLKHYLNLVTRQRY (SEQ ID NO: 195)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 155.

Point Mutations of PYY(19-36)

PEPTIDE	SEQUENCE
PYY(19-36)	RYYASLRHYLNLVTRQRY (SEQ ID NO: 158)

[Lys[19]]PYY(19-36)	KYYASLRHYLNLVTRQRY (SEQ ID NO: 159)

Also included as PYY(19-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(20-36), e.g., [Lys[25]]PPY(19-36) (Amino acid sequence=RYYASLKHYLNLVTRQRY (SEQ ID NO: 196)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 158.

Point Mutations of PYY(18-36)

PEPTIDE	SEQUENCE
PYY(18-36)	NRYYASLRHYLNLVTRQRY (SEQ ID NO: 160)
[Gln[18]]PYY(18-36)	QRYYASLRHYLNLVTRQRY (SEQ ID NO: 161)

Also included as PYY(18-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(19-36), e.g., [Lys[25]]PPY(18-36) (Amino acid sequence=NRYYASLKHYLNLVTRQRY (SEQ ID NO: 197)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 160.

Point Mutations of PYY(17-36)

PEPTIDE	SEQUENCE
PYY(17-36)	LNRYYASLRHYLNLVTRQRY (SEQ ID NO: 162)
[Ile[17]]PYY(17-36)	INRYYASLRHYLNLVTRQRY (SEQ ID NO: 163)
[Val[17]]PYY(17-36)	VNRYYASLRHYLNLVTRQRY (SEQ ID NO: 164)

Also included as PYY(17-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these three mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(18-36), e.g., [Lys[25]]PPY(17-36) (Amino acid sequence=LNRYYASLKHYLNLVTRQRY (SEQ ID NO: 198)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 162.

Point Mutations of PYY(16-36)

PEPTIDE	SEQUENCE
PYY(16-36)	ELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 165)
[Asp^{16}]PYY(16-36)	DLNRYYASLRHYLNLVTRQRY (SEQ ID NO: 166)

Also included as PYY(16-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(17-36), e.g., [Lys^{25}]PPY(16-36) (Amino acid sequence=ELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 199)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 165.

Point Mutations of PYY(15-36)

PEPTIDE	SEQUENCE
PYY(15-36)	EELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 167)
[Asp^{15}]PYY(15-36)	DELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 168)

Also included as PYY(15-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(16-36), e.g., [Lys^{25}]PPY(15-36) (Amino acid sequence=EELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 200)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 167.

Point Mutations of PYY(14-36)

PEPTIDE	SEQUENCE
PYY(14-36)	PEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 169)

Also included as PYY(14-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of this PYY(14-36) mutant with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(15-36), e.g., [Lys^{25}]PPY(23-36) (Amino acid

sequence=PEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 201) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 169.

Point Mutations of PYY(13-36)

PEPTIDE	SEQUENCE
PYY(13-36)	SPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 170)
[Thr^{13}]PYY(13-36)	TPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 171)

Also included as PYY(13-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(14-36), e.g., [Lys^{25}]PPY(13-36) (Amino acid sequence=SEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 202)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 170.

Point Mutations of PYY(12-36)

PEPTIDE	SEQUENCE
PYY(12-36)	ASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 172)
[Ser^{12}]PYY(12-36)	SSPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 173)

Also included as PYY(12-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(13-36), e.g., [Lys^{25}]PPY(12-36) (Amino acid sequence=ASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 203)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 172.

Point Mutations of PYY(11-36)

PEPTIDE	SEQUENCE
PYY(11-36)	DASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 174)
[Glu^{11}]PYY(11-36)	EASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 175)

Also included as PYY(12-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two

mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(12-36), e.g., [Lys^{25}]PPY(11-36) (Amino acid sequence=DASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 204)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 174.

Point Mutations of PYY(10-36)

PEPTIDE	SEQUENCE
PYY(10-36)	EDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 176)
[Asp^{10}]PYY(10-36)	DDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 177)

Also included as PYY(10-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(11-36), e.g., [Lys^{25}]PPY(10-36) (Amino acid sequence=EDASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 205)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 176.

Point Mutations of PYY(9-36)

PEPTIDE	SEQUENCE
PYY(9-36)	GEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 178)

Also included as PYY(9-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of this PPY(9-36) mutant with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(10-36), e.g., [Lys^{25}]PPY(9-36) (Amino acid sequence=GEDASPEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 206)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 178.

Potin Mutations of PYY(8-36)

PEPTIDE	SEQUENCE
PYY(8-36)	PGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 179)

Also included as PYY(8-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of this PPY(8-36) mutant with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(9-36), e.g., [Lys^{25}]PPY(8-36) (Amino acid sequence= SEQ ID NO: 207)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 179.

Point Mutations of PYY(7-36)

PEPTIDE	SEQUENCE
PYY(7-36)	APGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 180)
[Ser^{9}]PYY(7-36)	SPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 181)

Also included as PYY(7-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(8-36), e.g., [Lys^{25}]PPY(7-36) (Amino acid sequence=APGEDASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 208)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 180.

Point Mutations of PYY(6-36)

PEPTIDE	SEQUENCE
PYY(6-36)	EAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 182)
[Asp^{6}]PYY(6-36)	DAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 183)

Also included as PYY(6-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of either of these two mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(7-36), e.g., [Lys^{25}]PPY(6-36) (Amino acid sequence=EAPGEDASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 209)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 182.

Point Mutations of PYY(5-36)

PEPTIDE	SEQUENCE
PYY(5-36)	PEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 184)

Also included as PYY(5-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of this PPY(5-36) mutant with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(6-36), e.g., [Lys^{25}]PPY(5-36) (Amino acid sequence=PEAPGEDASPEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 210)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 184.

Point Mutations of PYY(4-36)

PEPTIDE	SEQUENCE
PYY(4-26)	KPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 185)
[Arg^4]PYY(4-36)	RPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 186)
[Gln^4]PYY(4-36)	QPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 187)
[Asn^4]PYY(4-36)	NPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 188)

Also included as PYY(4-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these four mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(5-36), e.g., [Lys^{25}]PPY(4-36) (Amino acid sequence=KPEAPGEDASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 211)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 185.

Point Mutations of PYY(3-36)

PEPTIDE	SEQUENCE
PYY(3-36)	IKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 1)
[Leu^3]PYY(3-36)	LKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 189)
[Val^3] PYY(3-36)	VKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY (SEQ ID NO: 190)

Also included as PYY(3-36) mutations are polypeptide variations (amino acid sequence variations) resulting from the combination of any of these three mutants with any of the above listed mutants for PYY(25-36), and/or any of the above listed mutants for PYY(4-36), e.g., [Lys^{25}]PPY(3-36) (Amino acid sequence=IKPEAPGEDASEELNRYYASLKHYLNLVTRQRY (SEQ ID NO: 212)) would result from combining the mutations from SEQ ID NO: 36 with SEQ ID NO: 1.

Also contemplated are PYY agonists (NPY analogs) having the formula:

X-Q-R_{19} -R_{20} -R_{21} -R_{22} -R_{23} -Leu-R_{25} -R_{26} -R_{27} -R_{28} -R_{29} -R_{30} -R_{31} -R_{32} -Arg-R_{34} - Arg-R_{36} -Y

wherein X is H or C^{α} Me or N^{α} Me or desamino or an acyl group having 7 carbon atoms or less; Q is R_{17} -R_{18}, R_{18} or desQ; R_{17} is Met, Arg, Nle, Nva, Leu, Ala or D-Ala; R_{18} is Ala, Ser, Ile, D-Ala, D-Ser or D-Ile; R_{19} is Arg, Lys or Gln; R_{20} is Tyr or Phe; R_{21} is Tyr, Glu, His or Ala; R_{22} is Ser, Ala, Thr, Asn or Asp; R_{23} is Ala, Asp, Glu, Gln, Asn or Ser; R_{25} is Arg or Gln; R_{26} is His, Arg or Gln; R_{27} is Phe or Tyr; R_{28} is Ile, Leu, Val or Arg; R_{29} is Asn or Ile; R_{30} is Leu, Met, Thr or Val; R_{31} is Ile, Val or Leu; R_{32} is Thr or Phe; R_{34} is Gln, Pro or His; R_{36} is Phe or Tyr; and Y is NH_2 or OH; provided that when Q is R_{18}, then at least one of R_{27} and R_{36} is Phe. Analogs of NPY have the following applications: potent postsynaptic treatment of hypertension and cardiogenic shock, the treatment of acute cardiovascular circulatory failure, and the elevation of intracellular calcium. See U.S. Patent No. 5,026,685.

Certain preferred NPY analogs have the formula: X-R_{18}-Arg-Tyr-Tyr-R_{22}-R_{23}-Leu-Arg-His-Tyr-R_{28}-Asn-Leu-R_{31}-Thr-Arg-Gln-Arg-Tyr-NH_2, wherein X is H or C^{α} Me or N^{α} Me or desamino or an acyl group having 7 carbon atoms or less; R_{18} is Ala or Ser; R_{22} is Ser or Ala; R_{23} is Ala or Ser; R_{27} is Phe or Tyr; R_{28} is Ile or Leu; R_{31} is Ile or Val; and R_{36} is Phe or Tyr; provided that at least one of R_{27} and R_{36} is Phe. See U.S. Patent No. 5,026,685.

Other contemplated NPY analogs have the formula:

X-R_{17} -R_{18} -Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-R_{27}-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-R_{36}-NH_2,

wherein R_{17} is Arg or Leu and R_{18} is Ser or Ala or Ile; and wherein X, R_{27} and R_{36} are as previously indicated.

Still other preferred NPY analogs have the formula:

X-R_{18}-Arg-Tyr-Tyr-Ala-Ser-Leu-R_{25}-His-R_{27}-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-R_{36}-NH_2,

wherein X is desamino or C^a Me or N^a Me and wherein R_{18}, R_{25}, R_{27} and R_{36} are as previously indicated.

Examples of such NPY agonists include:

pNPY (17-36) having the formula:
H-Leu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 217)

The peptide hNPY (17-36) having the formula:
H-Met-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 218)

The peptide [Phe^{27}]-NPY (18-36) having the formula:
H-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 219)

The peptide [Ac-D-Ala^{17}]-NPY (17-36) having the formula:

Ac-D-Ala-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 220)

The peptide NPY (19-36) having the formula:
H-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 221)

The peptide [Nle^{17}]-NPY (17-36) having the formula:
H-Nle-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 222)

The peptide [D-Ser^{18}]-NPY (18-36) having the formula:
H-D-Ser-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 223)

The peptide [Ala^{17}, His^{21}]-NPY (17-36) having the formula:
H-Ala-Ala-Arg-Tyr-His-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 224)

The peptide [D-Ile^{18}]-NPY (18-36) having the formula:
D-Ile-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 225)

The peptide [Ac-Arg^{17}]-NPY (17-36) having the formula:
Ac-Arg-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 226)

The peptide [Gln^{19}]-NPY (19-36) having the formula:
H-Gln-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 227)

The peptide [Phe^{20}]-NpY (18-36) having the formula:

H-Ala-Arg-Phe-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 228)

The peptide [C^a MeLeu^{17}]-pNPY (17-36) having the formula:
H-C^a MeLeu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 229)

The peptide [N^a MeLeu^{17}]-pNPY (17-36) having the formula:
H-N^a MeLeu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln- Arg-Tyr-NH_2 (SEQ ID NO: 230)

The peptide [desamino Ala^{18}]-NpY (18-36) having the formula:
desamino-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr- NH_2 (SEQ ID NO: 231)

The peptide [For-Ala^{18}, Glu^{23}, Arg^{26}]-NPY (18-36) having the formula:
For-Ala-Arg-Tyr-Tyr-Ser-Glu-Leu-Arg-Arg-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 232)

The peptide [Nva^{17}, Ala^{21}, Leu^{28}]-NPY (17-36) having the formula:
H-Nva-Ala-Arg-Tyr-Ala-Ser-Ala-Leu-Arg-His-Tyr-Leu-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 233)

The peptide [Thr^{22}, Gln^{23}]-NPY (18-36) having the formula:
H-Ala-Arg-Tyr-Tyr-Thr-Gln-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 234)

The peptide [desamino Leu^{17}, Asn^{23}, Val^{30}]-NPY (17-36) having the formula:
H-desamino Leu-Ala-Arg-Tyr-Tyr-Ser-Asn-Leu-Arg-His-Tyr-Ile-Asn-Val-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 235)

The peptide [Asp^{22}, Ser^{23}, Thr^{30}]-NPY (18-36) having the formula: H-Ala-Arg-Tyr-Tyr-Asp-Ser-Leu-Arg-His-Tyr-Ile-Asn-Thr-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 236)

The peptide [Gln^{25}, Leu^{31}, Pro^{34}]-NPY (18-36) having the formula: H-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Gln-His-Tyr-Ile-Asn-Leu-Leu-Thr-Arg-Pro-Arg-Tyr-NH_2 (SEQ ID NO: 237)

The peptide [Gln^2 Phe^{36}]-NPY (17-36) having the formula: H-Leu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-Gln-Tyr-Arg-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 238)

The peptide [Phe^{36}]-pPYY (19-36) having the formula: H-Arg-Tyr-Tyr-Ala-Ser-Leu-Arg-His-Tyr-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 239)

The peptide pPYY (18-36) having the formula: H-Ser-Arg-Tyr-Tyr-Ala-Ser-Leu-Arg-His-Tyr-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 240)

The peptide [Ac-Ser^{18}, Phe^{27}]-pPYY (I8-36) having the formula: Ac-Ser-Arg-Tyr-Tyr-Ala-Ser-Leu-Arg-His-Phe-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 241)

The peptide [Nle^{17}, Asn^{22}, Phe^{27}]-NPY (17-36) having the formula: H-Nle-Ala-Arg-Tyr-Tyr-Asn-Ala-Leu-Arg-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 242)

The peptide [D-Ala^{18}, Glu^{21}, His^{34}]-NPY (18-36) having the formula: H-D-Ala-Arg-Tyr-Glu-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-His-Arg-Tyr-NH_2 (SEQ ID NO: 243)

The peptide [Bz-Leu^{17}, Pro^{34}, Phe^{36}]-pNPY (17-36) having the formula: Bz-Leu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Pro-Arg-Phe-NH_2 (SEQ ID NO: 244)

The peptide [Lys^{19}, Phe^{27}, Val^{28}]-NpY (18-36) having the formula: H-Ala-Lys-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Val-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 245)

The peptide [D-Ala^{17}, Val^{28}, Phe^{32}]-NPY (17-36) having the formula: D-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Val-Asn-Leu-Ile-Phe-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 246)

The peptide [C^{a} MeSer^{18}, Met^{30}, Phe^{36}]-NPY (18-36) having the formula: H-C^{a} MeSer-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Met-Ile-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 247)

The peptide [Arg^{17}, Ile^{18}, Phe^{27,36}]-NPY (17-36) having the formula: H-Arg-Ile-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 248)

The peptide [Ser^{18}, Phe^{27}]-pNPY (17-36) having the formula: H-Leu-Ser-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 249)

The peptide [N^{a} MeIle^{18}, Gln^{25}, Phe^{27}]-NPY (18-36) having the formula: N^{a} MeIle-Arg-Tyr-Tyr-Ser-Ala-Leu-Gln-His-Phe-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 250)

The peptide [D-Ser^{18}, Phe^{36}]-NPY (18-36) having the formula: H-D-Ser-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Phe-NH_2 (SEQ ID NO: 251)

The peptide [Asp^{23}, Arg^{26}]hNPY (17-36) having the formula: H-Met-Ala-Arg-Tyr-Tyr-Ser-Asp-Leu-Arg-Arg-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 252)

The peptide [Glu^{23}, Ile^{29}]-NPY (18-36) having the formula: H-Ala-Arg-Tyr-Tyr-Ser-Glu-Leu-Arg-His-Tyr-Ile-Ile-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 253)

The peptide [D-Ala^{17}]-NPY(17-36)-OH having the formula: D-Ala-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-OH (SEQ ID NO: 254).

Other peptide YY agonists have the formula:

$$R_2\text{-}X\text{-}A^{22}\text{-}A^{23}\text{-}A^{24}\text{-}A^{25}\text{-}A^{26}\text{-}A^{27}\text{-}A^{28}\text{-}A^{29}\text{-}A^{30}\text{-}A^{31}\text{-}A^{32}\text{-}Y\text{-}R_4$$

(R_1 bonded to A^{22}; R_3 bonded to A^{32})

wherein:

X is a chain of 0-5 amino acids, inclusive, the N-terminal one of which is bonded to R_1 and R_2

Y is a chain of 0-4 amino acids, inclusive, the C-terminal one of which is bonded to R_3 and R_4

R_1 is H, C_1 -C_2 alkyl (e.g., methyl), C_6 -C_{18} aryl (e.g., phenyl, napthaleneacetyl), C_1 --C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7 -C_{18} aralkyl (e.g., benzyl), or C_7 -C_{18} alkaryl (e.g., p-methylphenyl);

R_2 is H, C_1 -C_{12} alkyl (e.g., methyl), C_6 -C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1 -C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7 -C_{18} aralkyl (e.g., benzyl), or C_7 -C_{18} alkaryl (e.g., p-methylphenyl);

A^{22} is an aromatic amino acid, Ala, Aib, Anb, N-Me-Ala, or is deleted;

A^{23} is Ser, Thr, Ala, N-Me-Ser, N-Me-Thr, N-Me-Ala, or is deleted;

A^{24} is Leu, lie, Vat, Trp, Gly, Aib, Anb, N-Me-Leu, or is deleted;

A^{25} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1 -C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{26} is His, Thr, 3-Me-His, 1-Me-His, β-pyrozolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1 -C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{27} is an aromatic amino acid other than Tyr;

A^{28} is Leu, Ile, Vat, Trp, Aib, Aib, Anb, or N-Me-Leu;

A^{29} is Asn, Ala, Gln, Gly, Trp, or N-Me-Asn;

A^{30} is Leu, Ile, Val, Trp, Aib, Anb, or N-Me-Leu;

A^{31} is Vat, Ile, Trp, Aib, Anb, or N-Me-Val;

A^{32} is Thr, Ser, N-Me-Set, or N-Me-Thr;

R_3 is H, C_1 -C_{12} alkyl (e.g., methyl), C_6 -C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1 -C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7 -C_{18} aralkyl (e.g., benzyl), or C_7 -C_{18} alkaryl (e.g., p-methylphenyl);

R_4 is H, C_1 -C_{12} alkyl (e.g., methyl), C_6 -C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1 -C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7 -C_{18} aralkyl (e.g., benzyl), or C_7 -C_{18} alkaryl (e.g., p-methylphenyl), or a pharmaceutically acceptable salt thereof. See U.S. Patent No. 5,574,010.

Particularly preferred agonists of this formula to be used in the method of the disclosure include:

N-α-Ala-Ser-Leu-Arg-His-Trp-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ ID NO: 255).

Other peptide YY agonists have the formula:

$$R_2\text{-}A^{25}\text{-}A^{26}\text{-}A^{27}\text{-}A^{28}\text{-}A^{29}\text{-}A^{30}\text{-}A^{31}\text{-}A^{32}\text{-}Y\text{-}R_4$$

(R_1 and R_3 attach to the N-terminal amino acid)

wherein:

the N-terminal amino acid bonds to R_1 and R_2;

Y is a chain of 0-4 amino acids, inclusive the C-terminal one of which bonds to R3 and R4;

R_1 is H, C_1 -C_{12} alkyl, C_6 -C_{18} aryl, C_1 -C_{12} acyl, C_7 -C_{18} aralkyl, or C_7 -C_{18} alkaryl;

R_2 is H, C_1 -C_{12} alkyl, C_6 -C_{18} aryl, C_1 -C_{12} acyl, C_7 -C_{18} aralkyl, or C_7 -C_{18} alkaryl;

A^{25} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1 -C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{26} is Ala, His, Thr, 3-Me-His, 1-Me-His, β-pyrozolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1 -C_{10} alkyl group, or an aryl group), Orn or is deleted;

A^{27} is an aromatic amino acid;

A^{28} is Leu, Ile, Val, Trp, Aib, Anb, or N-Me-Leu;

A^{29} is Asn, Ala, Gln, Gly, Trp, or N-Me-Asn;

A^{30} is Leu, Ile, Val, Trp, Aib, Anb, or N-Me-Leu;

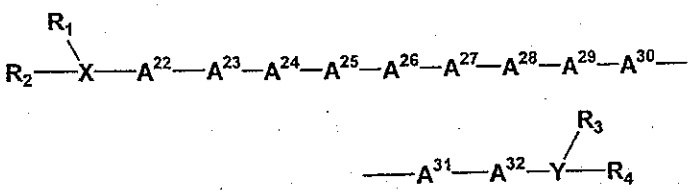
A^{31} is Val, Ile, Trp, Aib, Anb, or N-Me-Val;

A^{32} is Thr, Set, N-Me-Set, or N-Me-Thr or D-Trp;

R_3 is H, C_1-C_{12} alkyl, C_6 -C_{18} aryl, C_1 -C_{12} acyl, C_7 -C_{18} aralkyl, or C_7 -C_{18} alkaryl; and

R_4 is H, C_1 -C_{12} alkyl, C_6 -C_{18} aryl, C_1 -C_{12} acyl, C_7 -C_{18} aralkyl, or C_7 -C_{18} alkaryl, or a pharmaceutically acceptable salt thereof. Note that, unless indicated otherwise, for all peptide YY agonists described herein, each amino acid residue, e.g., Leu and A^1, represents the structure of NH--C(R)H--CO--, in which R is the side chain. Lines between amino acid residues represent peptide bonds which join the amino acids. Also, where the amino acid residue is optically active, it is the L-form configuration that is intended unless D-form is expressly designated.

Other PYY agonists have the formula:



wherein:

X is a chain of 0-5 amino acids, inclusive, the N-terminal one of which is bonded to R_1 and R_2;

Y is a chain of 0-4 amino acids, inclusive, the C-terminal one of which is bonded to R_3 and R_4;

R_1 is H, C_1-C_{12} alkyl (e.g. methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

R_2 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

A^{22} is an aromatic amino acid, Ala, Aib, Anb, N-Me-Ala, or is deleted;

A^{23} is Ser, Thr, Ala, Aib, N-Me-Ser, N-Me-Thr, N Me-Ala, or is deleted;

A^{24} is leu, Ile, Val, Trp, Gly, Nle, Nva, Aib, Anb, N-Me-Leu, or is deleted;

A^{25} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lye-e-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{26} is Ala, His, Thr, 3-Me-His, 1-Me-His, β-pyrozolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl groups or an aryl group), Orn, or is deleted;

A^{27} is an aromatic amino acid other than Tyr;

A^{28} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{29} is Asn, Ala, Gin, Gly, Trp, or N-Me-Asn;

A^{30} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{31} is Val, Leu, Ile, Trp, Nle, Nva, Aib, Anb, or N-Me-Val;

A^{32} is Thr, Ser, N-Me-Ser, N-Me-Thr, or D-Trp;

R_3 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl); and

R_4 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl), or a pharmaceutically acceptable salt thereof.

In preferred embodiments, A^{27} is Phe, Nal, Bip, Pcp, Tic, Trp, Bth, Thi, or Dip.

In preferred embodiments X is A^{17}-A^{18}-A^{19}-A^{20}-A^{21} wherein

A^{17} is Cys, Leu, Ile, Val, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{18} is Cys, Ser, Thr, N-Me-Ser, or N-Me-Thr;

A^{19} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or C_6-C_{18} aryl group), Cys, or Orn;

A^{20} is an aromatic amino acid, or Cys; and

A^{21} is an aromatic amino acid, Cys, or a pharmaceutically acceptable salt thereof. In yet other preferred embodiments, Y is A^{33}-A^{34}-A^{35}-A^{36} wherein

A^{33} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or an aryl group), Cys, or Orn;

A^{34} is Cys, Gln, Asn, Ala, Gly, N-Me-Cln, Aib, or Anb;

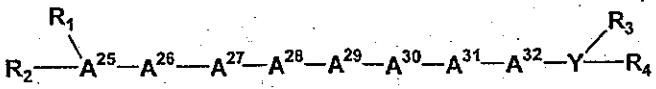
A^{35} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or C_6-C_{18} aryl group), Cys, or Orn; and

A^{36} is an aromatic amino acid, Cys or a pharmaceutically acceptable salt thereof. See U.S. Patent No. 5,604,203.

Particular embodiments include compounds has the formula: N-α-Ac-Ala-Ser-Leu-Arg-His-Phe-Leu-Asn-Leu-Val-Thr-Arg-Gin-Arg-Tyr-NH_2 (SEQ. ID. NO: 325), H-Ala-Ser-Leu-Arg-His-Phe-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ. ID. NO: 326), N-α-Ac-Ala-Ser-Leu-Arg-Thr-Arg-Gin-Arg-Tyr-NH_2 (SEQ. ID. NO: 327), N-α-Ac-Ala-Ser-Leu-Arg-His-Thi-Leu-Asn-Leu-Val-Thr-Arg-Gin-Arg-Tyr-NH_2 (SEQ. ID. NO: 328), N-α-Ac-Tyr-Ser-Leu-Arg-His-Phe-Leu-Asn-Leu-Val-Thr-Arg-Gin-Arg-Tyr-NH_2 (SEQ. ID. NO: 329) or a pharmaceutically acceptable salt thereof.

Other PYY agonists have the formula:

(Formula II)



wherein the N-terminal amino acid is bounded to R_1 and R_2; Y is a chain of 0-4 amino acids, inclusive the C-terminal one of which is bonded to R_3 and R_4;

R_1 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

R_2 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl);

A^{25} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or an aryl group), Orn, or is deleted;

A^{26} is Ala, His, Thr, 3-Me-His, 1-Me-His, β-pyrozolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl groups or an aryl group), Orn, or is deleted;

A^{27} is an aromatic amino acid;

A^{28} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{29} is Asn, Ala, Gin, Gly, Trp, or N-Me-Asn;

A^{30} is Leu, Ile, Val, Trp, Nle, Nva, Aib, Anb, or N-Me-Leu;

A^{31} is Val, Ile, Trp, Nle, Nva, Aib, Anb, or N-Me-Val;

A^{32} is Thr, Ser, N-Me-Ser, N-Me-Thr, or D-Trp;

R_3 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl); and

R_4 is H, C_1-C_{12} alkyl (e.g., methyl), C_6-C_{18} aryl (e.g., phenyl, naphthaleneacetyl), C_1-C_{12} acyl (e.g., formyl, acetyl, and myristoyl), C_7-C_{18} aralkyl (e.g., benzyl), or C_7-C_{18} alkaryl (e.g., p-methylphenyl), or a pharmaceutically acceptable salt thereof. See U.S. Patent No. 5,604,203.

In particular embodiments, A^{27} is Phe, Nal, Bip, Pcp, Tic, Trp, Bth, Thi, or Dip.

In particular embodiments X is A^{33}-A^{34}-A^{35}-A^{36} wherein

A^{33} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or C_6-C_{18} aryl group), Cys, or Orn;

A^{34} is Gln, Asn, Ala, Gly, N-Me-Gin, Aib, Cys, or Anb;

A^{35} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R (where R is H, a branched or straight chain C_1-C_{10} alkyl group, or C_6-C_{18} aryl group), Cys, or Orn; and

A^{36} is an aromatic amino acid, Cys, or a pharmaceutically acceptable salt thereof.

Preferably, the compound has the formula: N-α-Ac-Arg-His-Phe-Leu-Asn-Leu-Val-Thr-Arg-Gln-Arg-Tyr-NH_2 (SEQ. ID. NO: 324).

Examplary PYY agonists include:

YPAKEAPGEDASPEELSTYYASLR [im-DNP-His^{26}] YLNLVTRZRY-NH_2	(SEQ ID NO: 256)
PYY(22-36) ASLRHYLNLVTRQRY-NH_2	(SEQ ID NO: 257)
[Ala^{32}]PYY ASLRHYLNLV[Ala]RQRY-NH_2	(SEQ ID NO: 258)
[$Ala^{23,32}$]PYY A[Ala]LRHYLNLV[Ala]RQRY-NN_2	(SEQ ID NO: 259)
[Glu^{28}]PYY(22-36) ASLRHY[Glu]NLVTRQRY-NH_2	(SEQ ID NO: 260)
N-α-Ac-PYY(22-36) N-α-Ac-ASLRHYLNLVTRORY-NH_2	(SEQ ID NO: 261)
N-α-Ac[p.CL.Phe^{26}]PYY N-α-Ac-ASLR[p.CL.Phe^{26}]YLNLVTRQRY-NH_2	(SEQ ID NO: 262)
N-α-Ac[Glu^{28}]PYY N-α-Ac-ASLRHY[Glu]NLVTRQRY-NH_2	(SEQ ID NO: 263)
N-α-Ac[Phe^{27}]PYY N-α-Ac-ASLRH[Phe]ENLVTRQR[N-Me-Tyr]-NH_2	(SEQ ID NO: 264)
N-α-Ac]8N-Me-Tyr^{36}]PYY N-α-Ac-ASLRHYENLVTR0R[N-Me-Tyr]-NH_2	(SEQ ID NO: 265)
N-α-myristoyl-PYY(2214 36) N-α-myristoyl-ASLRHYLNLVTRQRY-NH_2	(SEQ ID NO: 266)
N-α-naphthateneacetyl-PYY(22-36) N-α- naphthateneacetyl-ASLRHYLNLVTRQRY-NH_2	(SEQ ID NO: 267)
N-α-Ac[Phe^{27}]PYY N-α-Ac-ASLRH[Phe]ENLVTR0R[N-Me-Tyr]-NH_2	(SEQ ID NO: 268)
N-α-Ac-PYY (22-36) N-α-Ac-ASLRHYLNLVTRQRY-NH_2	(SEQ ID NO: 269)
N-α-Ac-[Bth^{27}]PYY (22-36) N-α-Ac-ASLRH[Bth]LNLVTRQRY-NH_2	(SEQ ID NO: 270)
N-α-Ac-[Bip^{27}]PYY (22-36) N-α-Ac-ASLRH[Bth]LNLVTRQRY-NH_2	(SEQ ID NO: 271)
N-α-Ac-[Nal^{27}]PYY (22-36)	(SEQ ID NO: 272)

N-α-Ac-ASLRH[Bth]LNLVTRQRY-NH_2	(SEQ ID NO: 273)
N-α-Ac-[Trp^{27}]PYY (22-36)	(SEQ ID NO: 274)
N-α-Ac-ASLRH[Trp]LNLVTRQRY-NH_2	(SEQ ID NO: 275)
N-α-Ac-[Thi^{27}]PYY (22-36)	
N-α-Ac-ASLRN[Thi]LNLVTRQRY-NH_2	(SEQ ID NO: 276)
N-α-Ac-[Tic^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Tic]LNLVTRQRY-NH_2	(SEQ ID NO: 277)
N-α-Ac-[Phe^{27}]PYY (25-36)	
N-α-Ac-H[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 279)
N-α-Ac-[Phe^{27},Thi^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLVTRQR[Thi]-NH_2	(SEQ ID NO: 280)
N-α-Ac-[Thz^{26},Phe^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Thz][Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 281)
N-α-Ac-[Phe^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Thz][Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 282)
N-α-Ac-[Phe^{27}]PYY (22-36)	
N-α-Ac-[Phe]SLRN[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 289)
N-α-Ac-[Tyr^{22},Phe^{27}]PYY (22-36)	
N-α-Ac-[Tyr]SLRH[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 290)
N-α-Ac-[Trp^{28}]PYY (22-36)	
N-α-Ac-ASLRHY[Trp]NLVTRQRY-NH_2	(SEQ ID NO: 291)
N-α-Ac-[Trp^{28}]PYY (22-36)	
N-α-Ac-ASLRHYLN[Trp]VTRQRY-NH_2	(SEQ ID NO: 292)
N-α-Ac-[Ala^{26},Phe^{27}]PYY (22-36)	
N-α-Ac-ASLR[Ala][Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 293)
N-α-Ac-[Bth^{27}]PYY (22-36)	
N-α-Ac-ASLR[Bth]LNLVTRQRY-NH_2	(SEQ ID NO: 294)
N-α-Ac-[Phe^{27}]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLVTRQRY-NH_2	(SEQ ID NO: 295)
N-α-Ac-[$Phe^{27,36}$]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLVTRQR[Phe]-NH_2	(SEQ ID NO: 296)
N-α-Ac-[Phe^{27}, D-Trp^{32}]PYY (22-36)	
N-α-Ac-ASLRH[Phe]LNLV[D-Trp]RQRY-NH_2	(SEQ ID NO: 297)

Other PYY agonists include neurophilic Y Y2 receptor specific peptides having the formula:

$X1(-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13-X14)_n-X15$

wherein

X1 is NH, CH_3CO or one or two naturally occurring amino acids.

X2 is Leu, Ile or Val.

X3 is Arg, Lys or His.

X4 is His, Lys or Arg.

X5 is Tyr or Phe.

X6 is Leu, Ile or Val.

X7 is Asn or Gln.

X8 is Leu, Ile or Val.

X9 is Leu, Ile or Val.

X10 is Thr or Ser.

X11 is Arg, His or Lys.

X12 is Gln or Asn.

X13 is Arg, His or Lys.

X14 is Tyr or Phe.

X15 is COOH, NH_2 or one or two naturally occurring amino acids with the terminal amino acid being in the normal or carboxamide form; and

n is 1 to 5. See U.S. Patent No. 5,696,093.

Examplary agonists include:

CH_3CO-L-R-H-Y-L-N-L-L-T-R-Q-R-Y-NH_2 (SEQ ID NO: 298)

CH_3CO-L-R-H-Y-I-N-L-I-T-R-Q-R-Y-NH_2 (SEQ ID NO: 299)

NH_2-L-R-H-Y-L-N-L-L-T-R-Q-R-Y-NH_2 (SEQ ID NO: 300)

NH_2-L-R-H-Y-I-N-L-I-T-R-Q-R-Y-NH_2 (SEQ ID NO: 301)

Other PYY agonists have the formula:

N-α-R^1 -[$Nle^{24,28,30}$, Trp^{27}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2,

N-α-R^1 -[$Nle^{24,28}$, $Trp^{27,30}$, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2,

N-α-R^1 -[$Nle^{24,28,30}$, Phe^{27}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2,

N-α-R^1 -[$Nle^{24,28}$, Phe^{27}, Trp^{30}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2,

N-α-R^1 -[Trp^{30}, $\psi^{35/36}$]PYY(25-36)-NH_2,

N-α-R^1 -[Trp^{30}]PYY(25-36)-NH_2,

N-α-R^1 -[$Nle^{24,28}$, Trp^{30}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2 and

N-α-R^1 -[Nle^{28}, Trp^{30}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2 or a pharmaceutically-acceptable salt thereof,

wherein R^1 is H, (C_1 -C_{12})alkyl or (C_1 -C_{12})acyl; and

ψ is a pseudopeptide bond selected from the group consisting of --CH_2 --NH--, --CH_2 --S--, --CH_2 --CH_2 --, --CH_2 --O-- and --CH_2 --CO--. See U.S. Patent No. 6,046,162.

Particular compounds of the immediately foregoing group of compounds are where R^1 is acetyl and ψ is --CH_2 --NH--.

A particular group of compounds is selected from a group consisting of

N-α-Ac-[$Nle^{24,28,30}$, Trp^{27}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 302)

N-α-Ac-[$Nle^{24,28}$, $Trp^{27,30}$, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 303)

N-α-Ac-[$Nle^{24,28,30}$, Phe^{27}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 304)

N-α-Ac-[$Nle^{24,28}$, Phe^{27}, Trp^{30}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 305)

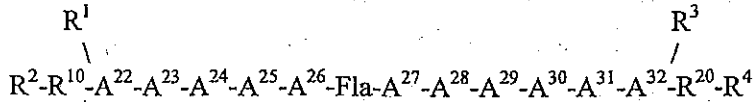
N-α-Ac-[Trp^{30}, $\psi^{35/36}$]PYY(25-36)-NH_2, (SEQ ID NO: 306)

N-α-Ac-[Trp^{30}]PYY(25-36)-NH_2 (SEQ ID NO: 307) and

N-α-Ac-[Nle^{28}, Trp^{30}, Nva^{31}, $\psi^{35/36}$]PYY(22-36)-NH_2, (SEQ ID NO: 308) or a pharmaceutically acceptable salt thereof.

Another particular compound has the formula N-α-Ac-[$Nle^{24,28}$, Trp^{30}, Nva.sup.31, $\psi^{35/36}$]PYY(22-36)-NH_2 (SEQ. ID. NO: 309) or a pharmaceutically acceptable salt thereof.

Another PYY agonist has the formula (A),



having one or two pseudopeptide bonds where each pseudopeptide bond is independently selected from the group consisting of --CH_2 --NH--, --CH_2 --S--, --CH_2 --CH_2 --, --CH_2 --O-- and -CH_2 --CO--; wherein:

R^{10} is a chain of 0-5 amino acids, inclusive, where the N-terminal amino acid is bonded to R^1 and R^2 by the side chain of the N-terminal amino acid or by the nitrogen of the amino group of the N-terminal amino acid;

R^{20} is a chain of 0-4 amino acids, inclusive, where the C-terminal amino acid is bonded to R^3 and R^4 by the side chain of the C-terminal amino acid or by the carbon of the carboxyl group of the C-terminal amino acid;

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, (C_1 -C_{12})alkyl, (C_6 -C_{18})aryl, (C_1 -C_{12})acyl, phenyl(C_1 -C_{12})alkyl and ((C_1 -C_{12})alkyl)$_{1-5}$ -phenyl;

A^{22} is an aromatic amino acid, Ala, Aib, Anb, N-Me-Ala or is deleted;

A^{23} is Ser, Thr, Ala, N-Me-Ser, N-Me-Thr, N-Me-Ala or is deleted;

A^{24} is Leu, Ile, Nle, Val, Trp, Gly, Aib, Anb, N-Me-Leu or is deleted;

A^{25} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-p.epsilon.-NH-Z, Orn or is deleted;

A^{26} is His, Thr, 3-Me-His, 1-Me-His, β-pyrazolylalanine, N-Me-His, Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-Z, Orn or is deleted;

A^{28} is Leu, Ile, Nle, Val, Trp, Aib, Anb or N-Me-Leu;

A^{29} is Asn, Ala, Gln, Gly, Trp or N-Me-Asn;

A^{30} is Leu, Ile, Nle, Fla, Val, Trp, Aib, Anb or N-Me-Leu;

A^{31} is Val, Nva, Ile, Trp, Aib, Anb or N-Me-Val; and

A^{32} is Thr, Ser, N-Me-Ser or N-Me-Thr;

where Z for each occurrence is independently selected from the group consisting of H, (C_1 -C_{10})alkyl and (C_6 -C_{18})aryl; or a pharmaceutically acceptable salt thereof. See U.S. Patent No. 6,046,167.

A particular group of compounds of the immediately foregoing group of compounds is where R^{10} is A^{17} -A^{18} -A^{19} -A^{20} -A^{21};

where A^{17} is Cys, Leu, Ile, Val, Nle, Nva, Aib, Anb or N-Me-Leu;

A^{18} is Cys, Ser, Thr, N-Me-Ser or N-Me-Thr;

A^{19} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R.sup.5, Cys or Orn;

A^{20} is an aromatic amino acid or Cys;

A^{21} is an aromatic amino acid or Cys;

R^{20} is A^{33} -A^{34} -A^{35} -A^{36},

A^{33} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R^5, Cys or Orn;

A^{34} is Cys, Gln, Asn, Ala, Gly, N-Me-Gln, Aib or Anb;

A^{35} is Arg, Lys, homo-Arg, diethyl-homo-Arg, Lys-ε-NH-R^5, Cys or Orn; and

A^{36} is an aromatic amino acid or Cys;

where R^5 for each occurrence is independently selected from the group consisting of H_1 (C_1 -C_{10})alkyl and (C_6 -C_{18}) aryl.

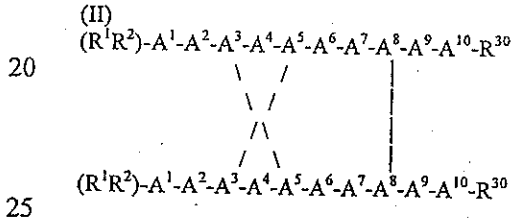
A particular group of compounds of the foregoing group of compounds are the compounds of the formula N-α-Ac-[Fla^{27})]PYY(25-36)-NH_2 and N-α-Ac-[Fla^{27}]PYY(22-36)-NH_2 or a pharmaceutically acceptable salt thereof.

Another group of PYY agonist has the formula:

(I)

$(R^1 R^2)$-A^1 -A^2 -A^3 -A^4 -A^5 -A^6 -A^7 -A^8 -A^9 -A^{10} -R^{30},

(II)

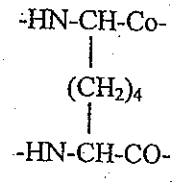


(III)

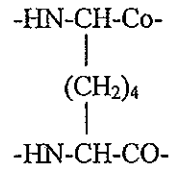
$(R^1 R^2)$-[A^5 -A^6 -A^7 -A^8 -A^9 -A^{10}]$_m$ R^{30},

or a pharmaceutically acceptable salt thereof wherein

------represents an optional bond between the amino acids shown connected where each bond is independently selected from the group consisting of --S--S-- only when the amino acids connected are Cys-Cys, -CO-NH-, -CH_2 -NH- and



provided that when the optional bond is



it replaces the two amino acids that the optional bond is attached to; q is 1-4; m is 1 to 4;

R^{30} is OH or -O-R^1, provided that when A^1 to A^7 are deleted then R^{30} is also NH-R^1, where R^{30} is attached to the carbon atom of the carboxyl of the C-terminal amino acid;

R^1 and R^2 for each occurrence are each independently selected from the group consisting of H, (C_1 -C_{12})alkyl, (C_6 -C_{18})aryl, (C_1 -C_{12})acyl, phenyl(C_1 -C_{12})alkyl and ((C_1 -C_{12})alkyl)$_{1-5}$ -phenyl where R^1 and R^2 are attached to the nitrogen of the amine of the N-terminal amino acid;

A^1 is deleted or D- or L- of the following amino acids: Trp, Tyr, Fla, Bth, Nal, Tic, Tic-OH, Dip, Bip or optionally substituted Phe where the Phe is optionally substituted with one to five substituents selected from the group consisting of (C_1 -C_4)alkyl, halo, (C_1 -C_4)alkoxy, amino and nitro;

A^2 is deleted or D- or L- of the following amino acids: Ile, Val, Leu, Nle, Anb, Aib, Pro, Gln or Asn;

A^3 is deleted or D- or L- of the following amino acids: Asn, Gln, Glu, Asp, Orn, Lys, Dpr or Cys;

A^4 is deleted or D- or L- of the following amino acids: Ile, Val, Leu, Nle, Anb, Aib or Pro;

A^5 is deleted or D- or L- of the following amino acids: Ile, Val, Leu, Nle, Anb, Aib, Pro, Glu, Asp, Orn, Lys, Dpr or Cys;

A^6 is deleted or D- or L- of the following amino acids: Thr, Ser, Trp, Tyr, Fla, Bth, Nal, Tic, Tic-OH, Dip, Bip or optionally substituted Phe where the Phe is optionally substituted with one to five substituents selected from the group consisting of (C_1 -C_4)alkyl, halo, (C_1 -C_4)alkoxy, amino and nitro;

A^7 is deleted or D- or L- of the following amino acids: Arg, Lys, homo-Arg, dialkyl-homo-Arg, Lys-ε-NH-R^7 or Orn;

A^8 is deleted or D- or L- of the following amino acids: Nva, Val, Ile, Leu, Nle, Anb, Aib, Pro, Gln, Asn, Glu, Asp, Orn, Lys, Dpr or Cys;

A^9 is deleted or D- or L- of the following amino acids: Arg, Lys, homo-Arg, dialkyl-homo-Arg, Lys-ε-NH-R^7 or Orn; and

A^{10} is deleted or D- or L- of the following amino acids: Tyr, Trp, Fla, Bth, Nal, Tic, Tic-OH, Dip, Bip, tyramine or optionally substituted Phe where the Phe is optionally substituted with one to five substituents selected from the group consisting of (C_1 -C_4)alkyl, halo, (C_1 -C_4)alkoxy, amino and nitro, or the corresponding decarboxylated optionally substituted Phe;

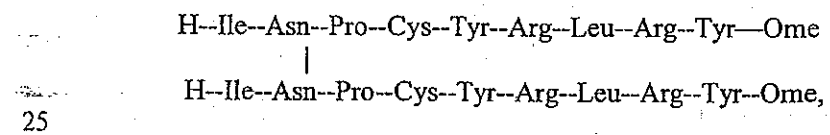
where R^7 for each occurrence is independently selected from the group consisting of H.sub.1 (C_1 -C_{10})alkyl and (C_6 -C_{18}) aryl, provided that not all of A_1 to A_{10} are deleted at the same time. See U.S. Patent No. 6,046,167.

A particular group of compounds of the immediately foregoing group of compounds is

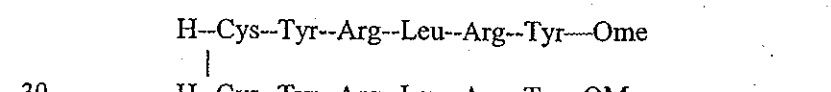
(SEQ ID NO: 310)

H--Ile--Asn--Pro--Ile--Tyr--Arg--Leu--Arg--Tyr--OMe

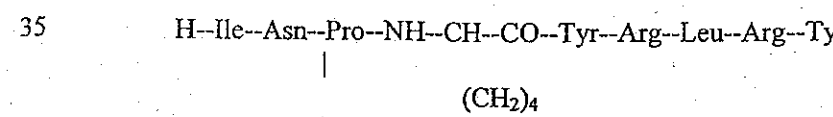
(SEQ ID NO: 311)



(SEQ ID NO: 312)



(SEQ ID NO: 313)



H--Ile--Asn--Pro--NH--CH--CO--Tyr--Arg--Leu--Arg--Tyr--OMe,

(SEQ ID NO: 314)

H-[Tyr-Arg-Leu-Arg-Tyr]$_2$ –Ome

or a pharmaceutically acceptable salt thereof.

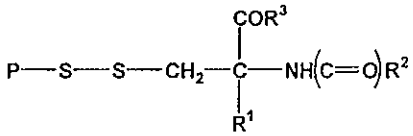
PYY and PYY agonists may be modified by well known processes such as amidation, glycosylation, acylation (e.g. acetylation), sulfation, phosphylation, cyclization, lipidization and pegylation. Methods for lipidization with fatty acid derivatives of sulfhydryl-containing compounds are disclosed in U.S. Patent No. 5,936,092; U.S. Patent No. 6,093,692; and U.S. Patent No. 6,225,445. Fatty acid derivatives of sulfhydryl-containing PYY and PYY agonists comprising fatty acid-conjugated products with a disulfide linkage are employed for delivery of the PYY and PYY agonists to neuronal cells and tissues. This modification markedly increases the absorption of the compounds relative to the rate of absorption of the unconjugated compounds, as well as prolonging blood and tissue retention of the compounds. Moreover, the disulfide linkage in the conjugate is quite labile in the cells and thus facilitates intracellular release of the intact compounds from the fatty acid moieties.

Fatty acids, as constituents of phospholipids, make up the bulk of cell membranes. Due to their lipidic nature, fatty acids can easily partition into and interact with the cell membrane in a non-toxic way. Therefore, fatty acids represent potentially a useful carrier ligand for the delivery of proteins and peptides. Strategies that may use fatty acids in the delivery of proteins and peptides include the covalent modification of proteins and peptides and the use of fatty acid emulsions.

To prepare such conjugates, a sulfhydryl-containing PYY and PYY agonist is attached to a fatty acid derivative via a reversible, biodegradable disulfide bond. Such a conjugate is expected to bind to the apical side of a cell membrane, reach the basolateral membrane of the GI-epithelium as a result of membrane transport and

turnover, and become released into interstitial fluid as the result of disulfide bond reduction.

Such lipidized PYY and PYY agonist compounds have the general formula



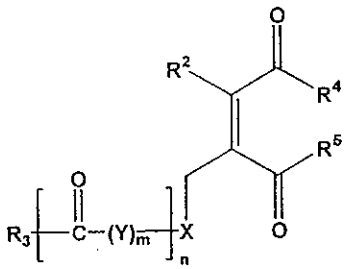
in which P is a residue derived from a PYY or PYY agonist; R^1 is hydrogen, lower alkyl or aryl; R^2 is a lipid-containing moiety and R^3 is --OH, a lipid-containing moiety or an amino acid chain comprising one or 2 amino acids and terminating in $-CO_2H$ or $-COR^2$. See U.S. Patent No. 5,936,092. These conjugates are particularly useful for increasing the absorption and prolonging blood and tissue retention of PYY and PYY agonists.

Typical alkyl groups include C_{1-6} alkyl groups including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, and the like.

Preferred aryl groups are C_{6-14} aryl groups and typically include phenyl, naphthyl, fluorenyl, phenanthryl, and anthracyl groups.

The term "lipid-containing moiety" refers to either a lipid group per se or a hydrocarbon-based group (in particular, one or more amino acids) comprising a lipid group. By the term "lipid group" is meant a hydrophobic substituent consisting of 4 to 26 carbon atoms, preferably 5 to 19 carbon atoms. Suitable lipid groups include, but are not limited to, the following: palmityl ($C_{15}H_{31}$,), oleyl ($C_{15}H_{29}$), stearyl ($C_{17}H_{35}$), cholate; and deoxycholate.

PCT Application No. WO 00/34236 describes drug-carrier conjugates and synthetic strategies for their production, as well as synthetic methods, intermediates, and final products useful for the uptake and release of biologically-active amino group containing compounds. Such lipidized PYY and PYY agonist compounds have general Formula I



in which R^2 is selected from the group consisting of hydrogen, halo, alkyl, or aryl, wherein the alkyl or aryl groups are optionally substituted with one or more alkoxy, alkoxyalkyl, alkanoyl, nitro, cycloalkyl, alkenyl, alkynyl, alkanoyloxy, alkyl or halogen atoms;

R^3 is a lipophilic group; one of R^4 and R^5 is a PYY or a PYY agonist and the other of R^4 and R^5 is OR^6 where R^6 is hydrogen, an alkali metal or a negative charge;

X is oxygen or sulfur;

Y is a bridging natural or unnatural amino acid; n is zero or 1; and m is an integer from zero to 10.

Typical alkyl groups include C_{1-6} alkyl groups including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, and the like.

Typical alkoxy groups include oxygen substituted by any of the alkyl groups mentioned above.

Typical alkoxyalkyl groups include any of the above alkyl groups substituted by an alkoxy group, such as methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, pentoxymethyl, hexoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, methoxypentyl, methoxyhexyl, and the like.

Preferred aryl groups are C_{6-14} aryl groups and typically include phenyl, naphthyl, fluorenyl, phenanthryl, and anthracyl groups.

Typical alkoxy substituted aryl groups include the above aryl groups substituted by one or more of the above alkoxy groups, e.g., 3-methoxyphenyl, 2-ethoxyphenyl, and the like.

Typical alkyl substituted aryl groups include any of the above aryl groups substituted by any of the C_{1-6} alkyl groups, including the group $Ph(CH_2)n$, where n is

1-6, for example, tolyl, o-, m-, and p-xylyl, ethylphenyl, 1-propylphenyl, 2-propylphenyl, 1-butylphenyl, 2-butylphenyl, t-butylphenyl, 1-pentylphenyl, 2-pentylphenyl, 3-pentylphenyl.

Typical alkenyl groups include C_{2-6} alkenyl groups, e.g. ethenyl, 2-propenyl, isopropenyl, 2-butenyl, 3-butenyl, 4-pentenyl, 3-pentenyl, 2-pentenyl, 5-hexenyl, 4-hexenyl, 3-hexenyl, and 2-hexenyl groups.

Typical alkynyl groups include C_{2-6} alkynyl groups e.g. enthynyl, 2-propenyl, 2-butynyl, 3-butynyl, 4-pentynyl, 3-pentynyl, 2-pentynyl, 5-hexynyl, 4hexynyl, 3-hexynyl, and 2-hexynyl groups.

Typical alkenyl or alkynyl substituted aryl groups include any of the above C_{6-14} aryl groups substituted by any of the above C_{2-6} alkenyl or C_{2-6} alkynyl groups, e.g., ethenylphenyl, 1-propenylphenyl, 2-propenylphenyl, 1butenylphenyl, 2-butenylphenyl, 1-pentenylphenyl, 2-pentenylphenyl, 3-pentenylphenyl, 1-hexenylphenyl, 2-hexenylphenyl, 3-hexenylphenyl, ethynylphenyl, 1-propynylphenyl, 2-propynylphenyl, 1-butynylphenyl, 2-butynylphenyl, 1-pentynylphenyl, 2-pentynylphenyl, 3-pentynylphenyl, 1-hexynylphenyl, 2-hexynylphenyl, 3-hexynylphenyl groups.

Typical halo groups include fluorine, chlorine, bromine, and iodine.

Typical halo substituted alkyl groups include C_{1-6} alkyl groups substituted by one or more fluorine, chlorine, bromine, or iodine atoms, e.g., fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, and trichloromethyl groups.

Typical alkanoyl groups include $C_{1-5}C(=O)-$ alkanoyl groups, e.g., acetyl, propionyl, butanoyl, pentanoyl, and hexanoyl groups, or by an arylalkanoyl group, e.g., a $C_{1-5}C(=O)$ – alkanoyl group substituted by any of the above aryl groups.

Typical cycloalkyl groups include C_{3-8} cycloalkyl groups including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups.

The term "lipophilic group" as used herein refers to either a naturally occurring lipid per se, a hydrophobic branched or unbranched hydrocarbon comprising about 4 to about 26 carbon atoms, preferably about 5 to about 19 carbon atoms, a fatty acid or ester thereof, or a surfactant. Suitable lipophilic groups

include, but are not limited to, long chain alkanoyl groups including: palmityl ($C_{15}H_{31}$), oleyl ($C_{15}H_{29}$), stearyl ($C_{17}H_{35}$), lauryl ($C_{11}H_{23}$), cholyl, and myristyl ($C_{13}H_{27}$)

The term "natural or unnatural amino acid" as used herein refers to any of the 21 naturally occurring amino acids as well as D-form amino acids, blocked L-and D-form amino acids such as those blocked by amidation or acylation, substituted amino acids (e.g., those substituted with a sterically hindered alkyl group or a cycloalkyl group such as cyclopropyl or cyclobutyl) in which the substitution introduces a conformational restraint in the amino acid. The preferred naturally occurring amino acids for use in the present disclosure as amino acids or components of a peptide or protein are alanine, arginine, asparagine, aspartic acid, citrulline, cysteine, cystine, γ-glutamic acid, glutamine, glycine, histidine, isoleucine, norleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, hydroxyproline, serine, threonine, tryptophan, tyrosine, valine, γ -carboxyglutamate, or O-phosphoserine. The preferred non-naturally occurring amino acids for use in the present disclosure as amino acids or components of peptides or proteins are any of the β-amino acids, e.g., α-alanine, γ-amino butyric acid, γ-amino butyric acid, γ-(aminophenyl)butyric acid, α-amino isobutyric acid, ε-amino caproic acid, 7-amino heptanoic acid, amino benzoic acid, aminophenyl acetic acid, aminophenyl butyric acid, cysteine (ACM), methionine sulfone, phenylglycine, norvaline, ornithine, δ-ornithine, ρnitro-phenylalanine, 1,2,3,4-terahydroisoquinoline-3-carboxylic acid and thioproline.

The present disclosure is also directed to methods of preparing lipidized conjugates of PYY and PYY agonists, pharmaceutical compositions comprising lipidized conjugates of PYY and PYY agonists, and methods of increasing the delivery of amino group-containing PYY and PYY agonists into a cell.

Also provided by the disclosure are chemically modified derivatives of PYY and PYY agonists which 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). Such modified derivatives include PYY and PYY agonists modified by pegylation. The terms "pegylated" and "pegylation" refer to the process of reacting a poly(alkylene glycol), preferably an activated poly(alkylene glycol), with a facilitator such as an amino acid, e.g. lysine,

to form a covalent bond. Although "pegylation" is often carried out using poly(ethylene glycol) or derivatives thereof, such as methoxy poly(ethylene glycol), the term is not intended to be so limited here, but is intended to include any other useful poly(alkylene glycol), such as, for example poly(propylene glycol).

The chemical moieties for derivitization may also be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides 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.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and 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) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., 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.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72, 1996; Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750, 1999; and Caliceti et al., *Bioconjug. Chem.* 10:638-646, 1999.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the polypeptides or proteins with consideration of effects on functional

or antigenic domains of the polypeptides or proteins. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384 (coupling PEG to G-CSF), see also Malik et al., *Exp. Hematol.* 20:1028-1035, 1992 (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins and polypeptides via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins and polypeptides via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the polypeptide or protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein or polypeptide.

One may specifically desire proteins and polypeptides chemically modified at the N-terminus. Using polyethylene glycol as an illustration, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (or peptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished

by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins and polypeptides may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein or polypeptide either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins and polypeptides are described in Delgado et al., *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304, 1992; Francis et al., *Intern. J. of Hematol.* 68:1-18, 1998; U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466.

One system for attaching polyethylene glycol directly to amino acid residues of proteins and polypeptides without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of the protein or polypeptide with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein or polypeptide. Thus, the disclosure includes protein-polyethylene glycol conjugates produced by reacting proteins and polypeptides with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

Polyethylene glycol can also be attached to proteins and polypeptides using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460 discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein or polypeptide by a linker can also be produced by reaction of proteins or polypeptides with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG- ρ -nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins and polypeptides are described in WO 98/32466.

The number of polyethylene glycol moieties attached to each protein or polypeptide (i.e., the degree of substitution) may also vary. For example, the pegylated proteins and polypeptides may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein or polypeptide molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304, 1992.

The proteins and polypeptides containing substantially non-antigenic polymers, preferably poly(alkylene glycols) may be prepared, for example, as described in U.S. Patent No. 5,428,128; U.S. Patent No. 6,127,355; and U.S. Patent No. 5,880,131.

To effect covalent attachment of poly(ethylene glycol) (PEG) to a protein or polypeptide, the hydroxyl end groups of the PEG must first be converted into reactive functional groups. This process is frequently referred to as "activation" and the product is called "activated PEG." Methoxy poly(ethylene glycol) (mPEG), distally capped with a reactive functional group is often used. One such activated PEG is succinimidyl succinate derivative of PEG (SS-PEG). See also Abuchowski et al., *Cancer Biochem. Biophys.* 7:175-186, 1984; and U.S. Patent No. 5,122,614 which discloses poly(ethylene glycol)-N-succinimide carbonate and its preparation.

Alternative substantially non-antigenic polymers that may be employed in the practice of the present disclosure include materials such as dextran, polyvinyl pyrrolidones, polysaccharides, starches, polyvinyl alcohols, polyacrylamides, or other similar non-immunogenic polymers. Those of ordinary skill in the art will realize that the foregoing are merely illustrative and not intended to restrict the type of polymeric substances suitable for use herein.

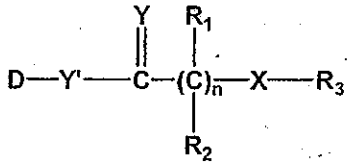
In one aspect of the disclosure, the polymer is introduced into the peptide or protein molecule after being functionalized or activated for reaction and attachment to one or more amino acids. By activation, it is understood by those of ordinary skill in the art that the polymer is functionalized to include a desired reactive group. See, for example, U.S. Patent No. 4,179,337 and U.S. Patent No. 5,122,614. In this

embodiment, the hydroxyl end groups of poly(alkylene glycols) are converted and activated into reactive functional groups.

In another aspect of the disclosure, the polymer is conjugated to a facilitator moiety prior to being introduced into the polypeptide or protein molecule. The facilitator moiety is preferably an amino acid such as lysine, however, non-amino acid moieties are also contemplated. Within the aspect, there are included multifunctionalized organic moieties such as alkyls or substituted alkyls. Such moieties can be prepared to have a nucleophilic functional group such as an amine and an electrophilic group such as an acid as well as a suitably functionalized region for conjugating with the desired polymer or polymers.

The facilitator moieties allow easier inclusion of a polymer into the peptide or protein molecule during synthesis. For example, poly(alkylene glycols) coupled to facilitator amino acids or amino acid residues in polypeptides or proteins by means of suitable coupling agents are illustrative. A useful review of a number of coupling agents known in the art appears in Dreborg et al., *Critical Reviews in Therapeutic Drug Carrier Systems* 6(4):315-165, 1990, see especially, pp. 317-320.

Pegylated PYY peptides and agonists can also be of the general formula



wherein:

D is a residue of a PYY peptide or agonist;

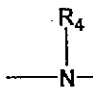
X is an electron withdrawing group;

Y and Y' are independently O or S;

(n) is zero (0) or a positive integer, preferably from 1 to about 12;

R_1 and R_2 are independently selected from the group consisting of H, C_{1-6} alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls, and substituted C_{1-6} alkyls;

R_3 is a substantially non-antigenic polymer, C_{1-12} straight or branched alkyl or substituted alkyl, C_{5-8} cycloalkyl or substituted cycloalkyl, carboxyalkyl, carboalkoxy alkyl, dialkylaminoalkyl, phenylalkyl, phenylaryl or

; and

R_4 and R_5 are independently selected from the group consisting of H, C_{1-6} alkyls, aryls, substituted aryls, aralkyls, heteroalkyls, substituted heteroalkyls and substituted C_{1-6} alkyls or jointly form a cyclic C_5-C_7 ring. See U.S. Patent No. 6,127,355.

Typical alkyl groups include C_{1-6} alkyl groups including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, and the like.

Preferred aryl groups are C_{6-14} aryl groups and typically include phenyl, naphthyl, fluorenyl, phenanthryl, and anthracyl groups.

Typical alkyl substituted aryl groups include any of the above aryl groups substituted by any of the C_{1-6} alkyl groups, including the group $Ph(CH_2)_n$, where n is 1-6, for example, tolyl, o-, m-, and p-xylyl, ethylphenyl, 1-propylphenyl, 2-propylphenyl, 1-butylphenyl, 2-butylphenyl, t-butylphenyl, 1-pentylphenyl, 2-pentylphenyl, 3-pentylphenyl.

Typical cycloalkyl groups include C_{3-8} cycloalkyl groups including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups.

Typical electron withdrawing groups include O, NR_1, S, SO and SO_2, wherein R_1 is defined above.

PYY Antagonists

Also contemplated, are the use of Y receptor antagonist. A Y receptor antagonist is a substance (typically a ligand) which binds to a Y receptor and blocks the physiological effect of a Y receptor agonist (such as, PYY, NPY, or PP (see Tables 1-3, *infra*). These antagonists could be either peptide antagonist or non-peptide antagonist of PYY, NPY, or PP.

Peptide antagonist include modifications, mutants, fragments, and/or variants thereof, of the PYY, NPY, or PP peptide's natural amino acid sequence (*e.g.*, by deletions, amino acid substitutions, deletions, insertions, and modifications of the N-

terminal amino and/or C-terminal carboxyl group) resulting in a peptide which acts as an antagonist to a Y receptor. In addition, PYY, NPY, or PP amino acid sequences may be fusion or chimera proteins which act as antagonists at the Y receptor. These peptides may also be modified by processes such as, lipidation, pegylation, amidation, glycosylation, acylation, sulfation, phosphorylation, acetylation and cyclization.

Many non-peptide antagonist of the Y receptors are known in the art and are contemplated for use with this invention. (See Table 5, *infra*). Any known PYY, NPY, or PP non-peptide antagonist may be useful in this invention.

TABLE 5 – PYY AND NPY ANTAGONIST

Exemplary antagonists of the Y receptor include, but are not limited to the following:

BIBO3304

Ref: Berglund, MM. *Biochem Pharmacol* 60(12):1815-22, Dec 15, 2000.

SR120819A

1-[2-[2-(2-naphtylsulfamoyl)-3-phenylpropionamido]-3-[4-[N- [4-(dimethylaminomethyl)-cis-cyclohexylmethyl]amidino]phenyl]propiony l] pyrrolidine, (S,R) stereoisomer

Ref: Berglund, MM. *Biochem Pharmacol* 60(12):1815-22, Dec 15, 2000.

BIIE0246

(S)-N2-[[1-[2-[4-[(R,S)-5,11-dihydro-6(6h)-oxodibenz[b,e]azepin-11-yl]-1-piperazinyl]-2-oxoethyl]cyclopentyl]acetyl]-N-[2-[1,2-dihydro-3,5 (4H)-dioxo-1,2-diphenyl-3H-1,2,4-triazol-4-yl]ethyl]-argininamid

Ref: Malmstrom, *Life Sci* 69(17):1999-2005, Sep 14, 2001.

BIBP 3226

[(R)-N2-(diphenylacetyl)-N-[(4-hydroxyphenyl)methyl]-D-arginine-amide], and a recently described peptidic structure [Ile-Glu-Pro-Orn-Tyr-Arg-Leu-Arg-Tyr-NH2, cyclic (2,4'), (2',4)-diamide].

Ref: Doods, H.N. *J Pharmacol Exp Ther* 275(1):136-42, Oct, 1995.

BIBP 3435

Ref: Lundberg J.M., Modin A. *Br J Pharmacol* 116(7):2971-82, Dec, 1995.

H 394/84

1,4-Dihydro-4-[3-[[[[3-[spiro(indene-4,1'-piperidin-1-yl)]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethylester

Ref: Malmstrom, R.E. *Eur J Pharmacol* 418(1-2):95-104, Apr 20, 2001.

H 409/22

(2R)-5-([amino(imino)methyl]amino)-2-[(2,2-diphenylacetyl)amino]-N-[(IR)-1-(4-hydroxyphenyl)ethyl]-pentanamide

Ref: Malmstrom, R.E. *Life Sci* 69(17):1999-2005, Sep 14, 2001.

1229U91

Ref: Schober, DA. *Peptides* 19(3):537-42, 1998.

L-152,804

Ref: Kanatani, A. *Biochem Biophys Res Commun* 272(1):169-73, May 27, 2000.

Aminoalkyl substituted pyrazolo[1,5,-a]-1,5- pyrimidines and pyrazolo[1,5-a]-1,3,5-triazines

Ref: U.S. Patent No. 6,372,743

Alkyl and cycloalkyl derivatives of 1,4-dihydropyridine (e.g., 1,4-dihydro-2,6-dimethyl-4-[4-[[[[3-[4-(3-methoxyphenyl)-1-piperidinyl]prop yl]amino]carbonyl]amino]butyl]-3,5-pyridine dicarboxylic acid, dimethyl ester)

Ref: U.S. Patent No. 6,444,675

4-(3-substituted-phenyl)-1,4-dihydropyridine derivatives

Ref: U.S. Pat. No. 5,635,503

Squarate derivatives of 4-phenyl-1,4-dihydropyridines e.g., 1,4-dihydro-4-[3-[[2-[[3-[4-(3-methoxyphenyl)-1-piperidinyl]propyl]amino]-3 ,4-dioxo-1-cyclobuten-1-yl]amino]phenyl]-2,3-dimethyl-3,5-pyridinedicarboxy lic acid, dimethyl ester

Ref: U.S. Patent No. 6,432,960

Substituted amide Y receptor antagonist, such as:

N-(4-Diethylamino-phenyl)-2-phenyl-2-pyridin-4-yl-acetamide;

2-(4-Fluoro-phenyl)-2-pyridin-4-yl-N-(3,4,5,6-tetrahydro-2H-[1,2']bipyridin yl-5'-yl)-acetamide;

2-Phenyl-2-pyridin-4-yl-N-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-acetamide;

N-(4-Diethylamino-phenyl)-2-phenyl-2-pyridin-2-yl-acetamide;

N-(6-Diethylamino-pyridin-3-yl)-2,2-diphenylacetamide;

N-(4-Diethyl-sulfamoyl-phenyl)-2-phenyl-2-pyridin-4-yl-acetamide;

2,2-Diphenyl-N-(6-pyrrolidin-1-yl-pyridin-3-yl)-acetamide;

2,2-Diphenyl-N-(3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-yl)-acetamide;

N-[6-(2,5-Dimethyl-pyrrolidin-1-yl)-pyridin-3-yl]-2,2-diphenyl-acetamide;

N-(4-Diethylsulfamoyl-phenyl)-2,2-diphenyl-acetamide; and

N-(4-Dimethylsulfamoyl-phenyl)-2,2-diphenyl-acetamide.

Ref: U.S. Patent No. 6,407,120

Carbazole Y receptor antagonist, such as:

2-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

3-Diethylamino-N-(9-ethyl-9H-carbazol-3-yl)-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-2-fluoro-benzamide;

4-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-butyramide;

N-(9-Ethyl-9H-carbazol-3-yl)-2-hydroxy-2,2-diphenyl-acetamide;

N-(9-Ethyl-9H-carbazol-3-yl)-2-hydroxy-2-methyl-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-2-hydroxy-2-methyl-butyramide;

N-(9-Ethyl-9H-carbazol-3-yl)-2-hydroxy-2-phenyl-propionamide;

(R)-N-(9-Ethyl-9H-carbazol-3-yl)-2-hydroxy-2-phenyl-propionamide;

2-Bromo-N-(9-ethyl-9H-carbazol-3-yl)-acetamide; and

3-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-propionamide.

2-[Bis-(2-hydroxy-ethyl)-amino]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

2-Benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

3-Diphenylamino-N-(9-ethyl-9H-carbazol-3-yl)-propionamide; and

N-(9-Ethyl-9H-carbazol-3-yl)-3-(4-piperidin-1-ylmethyl-phenoxy)-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-3-[methyl-(1,2,3,4-tetrahydro-naphthalen-2-yl) -amino]-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-3-(quinolin-7-yloxy)-propionamide; and

2-[Bis-(2-hydroxy-ethyl)-amino]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide.

3-Bromo-N-(9-ethyl-9H-carbazol-3-yl)-propionamide; N-(9-Isopropyl-9H-carbazol-3-yl)-trifluoroacetamide;

4-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-N-methyl-butyramide; N-(9-Methyl-9H-carbazol-3-yl)-trifluoroacetamide;

1-Hydroxy-cyclopropanecarboxylic acid (9-ethyl-9H-carbazol-3-yl)-amide; and

2-(4-Chloro)-benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide.

2-(4-fluoro)-benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

(R)-N-(9-Ethyl-9H-carbazol-3-yl)-2-(1-phenyl-ethylamino)-acetamide;

(R)-N-(9-Ethyl-9H-carbazol-3-yl)-2-(1-(4-chloro)-phenyl-ethylamino)-acetamide;

2-(3-Diethylamino-2-hydroxy-propylamino)-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

2-(Benzyl-isopropyl-amino)-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

N-3-Bromo-(9-ethyl-9H-carbazol-6-yl)-trifluoroacetamide;

N-(9-Ethyl-6-formyl-9H-carbazol-3-yl)-trifluoroacetamide;

N-(9-Ethyl-6-hydroxymethyl-9H-carbazol-3-yl)-trifluoroacetamide;

N-(9-Ethyl-9H-carbazol-3-yl)-methanesulfonamide;

N-(9-Ethyl-9H-carbazol-3-yl)-chloromethanesulfonamide;

2-Bromo-N-(9-ethyl-9H-carbazol-3-yl)-acetamide; and

3-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-propionamide.

2-[Bis-(2-hydroxy-ethyl)-amino]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

2-Benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

3-Diphenylamino-N-(9-ethyl-9H-carbazol-3-yl)-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-3-(4-piperidin-1-ylmethyl-phenoxy)-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-3-[methyl-(1,2,3,4-tetrahydro-naphthalen-2-yl) -amino]-propionamide;

N-(9-Ethyl-9H-carbazol-3-yl)-3-(quinolin-7-yloxy)-propionamide;

2-[Bis-(2-hydroxy-ethyl)-amino]-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

3-Bromo-N-(9-ethyl-9H-carbazol-3-yl)-propionamide; and

N-(9-Isopropyl-9H-carbazol-3-yl)-acetamide.

4-Dimethylamino-N-(9-ethyl-9H-carbazol-3-yl)-N-methyl-butyramide;

N-(9-Methyl-9H-carbazol-3-yl)-trifluoroacetamide;

1-Hydroxy-cyclopropanecarboxylic acid (9-ethyl-9H-carbazol-3-yl)-amide;

2-(4-Chloro)-benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide; and

2-(4-fluoro)-benzylamino-N-(9-ethyl-9H-carbazol-3-yl)-acetamide.

(R)-N-(9-Ethyl-9H-carbazol-3-yl)-2-(1-phenyl-ethylamino)-acetamide;

(R)-N-(9-Ethyl-9H-carbazol-3-yl)-2-(1-(4-chloro)-phenyl-ethylamino)-acetami de;

(R)-, (S)- or a mixture of (R)- and (S)-2-(3-Diethylamino-2-hydroxy-propylamino)-N-(9-ethyl-9H-carbazol-3-yl)- acetamide;

(S)-N-(6-tert-Butyl-9-ethyl-9H-carbazol-3-yl)-2-(3-diethylamino-2-hydroxy-p ropylamino)-acetamide, 2-(Benzyl-isopropyl-amino)-N-(9-ethyl-9H-carbazol-3-yl)-acetamide;

N-3-Bromo-(9-ethyl-9H-carbazol-6-yl)-trifluoroacetamide;

N-(9-Ethyl-6-formyl-9H-carbazol-3-yl)-trifluoroacetamide; and

N-(9-Ethyl-6-hydroxymethyl-9H-carbazol-3-yl)-trifluoroacetamide.

N-(9-Ethyl-9H-carbazol-3-yl)-methanesulfonamide; and

N-(9-Ethyl-9H-carbazol-3-yl)-chloromethanesulfonamide.

Ref: U.S. Patent No. 6,399,631

Various dihydropyridine derivatives:

Ref: U.S. Patent No. 4,829,076

Cyanoguanidine derivatives of the 4-(3-substituted-phenyl)-1,4-dihydropyridines

Ref: U.S. Patent No. 6,001,836

Amide derivatives that are NPY Y5 receptor antagonists

Ref: U.S. Patent No. 6,410,792

Thiourea linked piperazine and piperidine derivatives of 4-phenyl-1,4-dihydropyridines, such as:

1,4-dihydro-4-[3-[[[[3-[4-(3-methoxyphenyl)piperidinyl]propyl]amino]carbono thioyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-phenylpiperidinyl)propyl]amino]carbonothioyl]amin o]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester, and

1,4-dihydro-4-[4-[[[[3-(4-cyclohexyl-1-piperazinyl)propyl]amino]carbonothio yl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester.

1,4-dihydro-4-[4-fluoro-3-[[[[3-(4-phenylpiperidinyl)propyl]amino]carbonoth ioyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-methyl-1-piperidinyl)propyl]amino]carbonothioyl]a mino]-4-fluorophenyl)-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-ethyl-1-piperidinyl]propyl]amino]carbonothioyl]am ino]-4-fluorophenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-(4-propyl-1-piperidinyl)propyl]amino]carbonothioyl]a

mino]-4-fluorophenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-[4-1,1-dimethylethyl)-1-piperidinyl]propyl]amino]carbonothioyl]amino]-4-fluorophenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester,

1,4-dihydro-4-[3-[[[[3-[4-(1-methylethyl)-1-piperidinyl]propyl]amino]carbonothioyl]amino]-4-fluorophenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester, and

1,4-dihydro-4-[4-[[[[3-(4-cyclohexyl-1-piperazinyl)propyl]amino]carbonothio yl]amino]-4-fluorophenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester.

Ref: U.S. Patent No. 6,391,881

Novel aryl sulfonamide and sulfamide compounds

Ref: U.S. Patent No. 6,391,877

Amine and amide derivative Y receptor antagonist, such as:

Amino-6-[(2-fluorophenylsulfonyl)amino]-N-[cis-1,2,3,4-tetrahydro-6-metho xy-1-(3-pyridinylmethyl)-2-naphthenyl]-(2S)-hexanamide bis-hydrochloride,

N-[5-amino-6-[[cis-1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-nap hthalenyl]amino]hexyl]-2-fluorobenzenesulfonamide tris-hydrochloride,

N-[5-amino-6-[[cis-1,2,3,4-tetrahydro-6-hydroxy-1-(3-pyridinylmethyl)-2-nap hthalenyl]amino]hexyl]-2-fluorobenzenesulfonamide tris-hydrochloride,

(2S)-2-(Acetylamino)-6-[(2-fluorophenylsulfonyl)amino]-N-[cis-1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthenyl]hexanamide bis-hydrochloride,

(2S)-2-(Acetylamino)-6-[(2-fluorophenylsulfonyl)amino]-N-[cis-1,2,3,4-tetrahydro-6-hydroxy-1-(3-pyridinylmethyl)-2-naphthenyl]hexanamide bis-hydrochloride,

3-[(Phenylsulfonyl)amino]-N-[cis-1,2,3,4-tetrahydro-6-fluoro-1-(3-pyridinylmethyl)-2-naphthalenyl]-1-pyrrolidineacetamide bis-trifluoroacetate,

4-Oxo-1-phenyl-N-[cis-1,2,3,4-tetrahydro-1-(3-pyridinylmethyl)-2-naphthalenyl]-1,3,8-triazaspiro[4.5]decane-8-acetamide bis-hydrochloride,

trans-N-[2-(4-fluorophenyl)-3-(3-pyridinyl)propyl]-4-[((2-fluorophenylsulfonyl)amino)methyl]-1-cyclohexanamide hydrochloride,

trans-N-[[[[[2-(4-fluorophenyl)-3-(3-pyridinyl)propyl]amino]methyl]-4-cyclo hexyl]methyl] 2-fluorobenzenesulfonamide bis-hydrochloride.

Ref: U.S. Patent No. 6,380,224.

Alkylene diamine-substituted pyrazlo (1,5-a)-1,5-pyrimidines and pyrazolo (1,5-a) 1,3,5-triazines, such as:

2-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-butan-1-ol;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-methyl-cyclohexane-1,4-diamine;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-ethyl-cyclohexane-1,4-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(4-morpholin-4-yl-cyclohexyl)-ethane-1,2-diamine;

4-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-cyclohexanol;

3-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-propane-1,2-diol;

N-{2-[3(2,6-dichloro-4-methoxy-phenyl)-2,5-dimnethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N'-isobutyl-cyclohexane-1,4-diamine;

N-{2-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethyl}-N-isobutyl-cyclohexane-1,4-diamine;

4-{2-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-1-methyl-ethylamino}-cyclohexanol;

2-{2-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-ethylamino}-cyclohexanol;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazol[1,5-a]pyrimidin-7-yl]-N-(4,4,4-trifluoro-butyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2,2,2-trifluoro-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-trifluoromethyl-cyclohexyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(4-trifluoromethyl-cyclohexyl)-ethane 1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2,2-difluoro-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N- (2-fluoro-1-methyl-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-fluoro-cyclohexyl)-ethane-1,2-diamine.

N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-5-a]pyrimidin-7-yl]-N -(2,2, 6, 6-tetramethyl-piperidin-4-yl)-ethane-1,2diamine;

N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-19 piperidin-4-yl-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-3-yl)-ethane-1,2-diamine;

N-(1benzyl-pyrrolidin-3-yl)-N'-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-pyrimidin-2-yl-ethane-1,2-diamine;

N-(1-benzylpiperidin-4-yl)-N'-[3-(2,4-dichloro-6-methoxy-phenyl)-2,5-diethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-(1-benzyl-piperidin-4-yl)-N'-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-[3(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-methyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5 dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-4-yl)-ethane-1,2-di amine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-isopropyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-(2,2,6,6-tetramethyl-piperidin-4-yl)ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-ethyl-piperidin-3-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4methoxy-phenyl)-2, 5-dimethyl-pyrazol to [1, 5-a] pyrimidin-7-yl]-N'-piperidin-4-yl-ethane 1,2-diamine;

N.sup.2 -(1-Benzyl-piperidin-4-yl)-N'-[3-(2,6-dichloro-phenyl)-2,5-dimethyl-pyrazo lo[1,5-ajpyrimidin-7-yl]-propane-1,2-diamine;

N-[3-(2,6-Dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-3-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-Dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(1-pyridin-4-ylmethyl-piperidin4-yl)-ethane-1,2-diamine;

3,5-Dichloro-4-12,5-dimethyl-7-[2-(1-phenyl-pyrrolidin-3-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl]-phenol;

N-[3-(2,6-dicloro-4-methoxy-phenyl)-2,5-dimethyl-purazolo[1,5-a]pyrimdin-7-yl]-N'-(1-pyridin-2-ylmethyl-piperidin-4-yl)-ethane-1,2-diamine;

3,5-dichloro-4-(2,5-dimethyl-7-[2-(1-pyrimidin-2-yl-piperidin-4-ylamino)-ethylamino]-pyrazolo[1,5-a]pyrimidin-3-yl}-benzonitrile;

N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5 a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-(1-benzyl-piperidin-4-yl)-N'-[3(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-5isopropyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)ethane-1,2-diamine;

N-[3-(2,4-dichloro-phenyl)-5-isopropyl-2-methyl-pyrazolo[1,5a]pyrimidin-7-y l]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-ethoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-5isopropyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N2-(1-pyrimidin-2-yl-piperidin-4-yl)propane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-5-ethyl-2-methylpyrazoto [1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-dia mine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N -(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N- [3-(2,6-dichloro-4-methoxy-phenyl)5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-ylpiperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-2-methyl-5-propylpyrazoto [1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-dia mine;

N-[3-(2,6-dichloro-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N2-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,6-dichloro-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl] -N.sup.2 -(1-pyrimidin-2-yl-piperidin-4-yl)-propane1,2-diamine;

N-[5-ethyl-2-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-y l]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[5-ethyl-2-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,6dichloro-4-ethynyl-phenyl)-2,5-dimethylpyrazolo[1,5-a]pyrimidin-7-yl]-N'-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[2-methyl-5-propyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-N'-(1pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N' -(1-pyridin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-Dimethyl-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl] -N-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,6-dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl] –N- (1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,6-Dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-NZ-(1-pyrimidin-2-yl-piperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,6dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-ylpiperidin-4-yl)-propane-1,2-diamine;

N-[3-(2,4-dimethyl-phenyl)-5-ethyl-2-methyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine;

N-[3-(2,4-dimethyl-phenyl)-2-methyl-5-propyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(1-pyrimidin-2-yl-piperidin-4-yl)-ethane-1,2-diamine; and

1-[4-(1-{[3-(2,6-dichloro-4-methoxyphenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-ylamino]-methyl]-propylamino)piperidin-1-yl]-ethanone.

N-[2,5-dimethyl-3-(2,4,6-trimethylphenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-N-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo1,5-a]pyrimidin-7-yl]-N-[2-(4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N'-[2-(3-ethoxy-4-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo 1,5-a]pyrimidin-7-yl]-N-[2-(4-ethoxy-3-methoxy-phenyl)-ethyl]-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,a]pyrimidin-7-yl]-N'-(1,2,3,4-tetrahydro-naphthalen-2-yl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-pyridin-2-yl-ethyl)-ethane-1,2-diamine;

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-N-(2-pyridin-3-yl-ethyl)-ethane-1,2-diamine; and

N-[3-(2,6-dichloro-4-methoxy-phenyl)-2,5-dimethyl-pyrazolo [1,5-a]pyrimidin-7-yl]-N-(2-pyridin4-yl-ethyl)-ethane-1,2-diamine.

Ref: U.S. Patent No. 6,372,743

Spiroisoquinolinone derivative Y antaponist, such as:

2-(3-Chloropropyl)-2-phenyl-1,3-dioxolane,

2-(3-Chloropropyl)-2-(4-methoxyphenyl)-1,3-dioxolane,

2-(3-Chloropropyl)-2-(4-phenoxyphenyl)-1,3-dioxolane,

2-(3-Chloropropyl)-2-(4-bromophenyl)-1,3-dioxolane,

2-(3-Chloropropyl)-2-(4-chlorophenyl)-1,3-dioxolane,

N-3-Chloropropyl-N-methylbenzenemethanamine Hydrochloride,

N-(3-Chloropropyl)-N-(phenylmethyl)benzenemethanamine Hydrochloride,

N-(2-Hydroxyethyl)-N-methylbenzenemethanamine,

Chloro-1-(4-phenoxyphenyl)ethanone,

3-Chloro-1 -(4-phenoxyphenyl)propanone,

1'-[3-(4-Phenoxyphenyl)-3-oxopropyl]spiro[isoquinoline-1-(2H)-4'-piperidine -3-(4H)-one Hydrochloride,

1'-[3-(4-Bromophenyl)-3-oxopropyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3 -(4H)-one],

1'-[2-[(1,1'-Biphenyl)-4-yl]-2-oxoethyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3-(4H)-one],

1'-[2-(4-Bromophenyl)-2-oxoethyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3- (4H)-one],

1'-[2-(4-Phenoxyphenyl)-2-oxoethyl]spiro[isoquinoline-1-(2H-4'-piperidine-3 -(4H)-one], Hydrochloride,

1'-[2-[Bis(phenylmethyl)amino]ethyl]spiro[isoquinoline-1-(2H)-4'-piperidine -3-(4H)-one] Dihydrochloride,

1'-(4-Phenyl-4-oxobutyl)spiro[isoquinoline-1-(2H)-4'-piperidine-3-(4H)-one] Hydrochloride,

1'-[4-(4-Methoxyphenyl)-4-oxobutyl]spiro[isoquinoline-1-(2H)-4'-piperidine- 3-(4H)-one] Hydrochloride,

1'-[4-(4-Phenoxyphenyl)-4-oxobutyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3-(4H)-one] Hydrochloride,

1'-[4-(4-Bromophenyl)-4-oxobutyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3- (4H)-one],

1'-[4-(4-Chlorophenyl)-4-oxobutyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3 -(4H)-one] Hydrochloride,

1'-[2-[(1,1'-Biphenyl)-3-yl]-2-oxoethyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3-(4H)-one] Hydrochloride,

1'-[3-[(1,1'-Biphenyl)-4-yl]-3-oxopropyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3-(4H)-one] Hydrochloride,

1'-[4-[(1,1'-Biphenyl)-4-yl]-4-oxobutyl]spiro[isoquinoline-1-(2H)4'-piperidine-3-(4H)-one] Hydrochloride,

1'-[2-[(1,1'-Biphenyl)-4-yl]-2-hydroxyethyl]spiro[isoquinoline-1-(2H)-4'-piperidine-3-(4H-one] Hydrochloride,

Ref: U.S. Patent No. 6,348,472

Triazine derivative Y receptor antagonists, such as:

N1-{[4-({[4-(Isopropylamino)-6-(methylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4-(ethylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide)-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfenamideN1-{[4-({[4,6-Di(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4-(isopropylamino)-6-(propylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl3methyl-1-naphthalenesulfonamide,

N1-[4-([4-(butylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(cyclobutylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(cyclopropylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(isopropylamino)-6-(pentylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-[(2-cyanoethyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-[(2-hydroxyethyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-(4-[(4-(isopropylamino)-6-((2-methoxyethyl)amino]-1,3,5-triazin-2-yl]amino)methyl]cyclohexylmethyl)-1-naphthalenesulfonamide,

N1-(4-[(4-(isopropylamino)-6-[(3-methoxypropyl)amino]-1,3,5-triazin-2-ylamino)methyl]cyclohexylmethyl)-1-naphthalenesulfonamide,

N1-{[4-({[4-}[2-(dimethylamino)ethyl]amino}-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl) cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4-[3-(1H-1-imidazolyl)propyl]amino-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-({4-[({4-(isopropylamino)-6-1(4-methoxyphenethyl)amino]-1,3,5-triazin-2- yl}amino)methyl]cyclohexyl}methyl)-1-naphthalenesulfonamide,

N1-{[4-({[4-(dimethylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4-[ethyl(methyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(diethylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl) cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(isopropylamino)-6-tetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl]am inomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-(4-[(4-(isopropylamino)-6-[(2S)-2-(methoxymethyl)tetrahydro-1H-1-pyrrolyl]-1,3,5-triazin-2-ylamino)methyl]cyclohexylmethyl)-1-naphthalenesulfonamide,

N1-{[4-({[4-(isopropylamino)-6-piperidino-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-napnthalenesulfonamide,

N1-4-([4-(isopropylamino)-6-(2-methylpiperidino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-[4-([4-(isopropylamino)-6-morpholino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-{[4-({[4-[(2R,6S)-2,6-dimethyl-1,4-oxazinan-4-yl]-6-(isopropylamino)-1,3 ,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4-[(2-hydroxyethyl)(methyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide,

N1-{[4-({[4-(4-acetylpiperazino)-6-(isopropylamino)-1,3,5-triazin-2-yl]amnio}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-{[4-({[4-(isopropylamino)-6-(4-isopropylpiperazino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -4-(tert-butyl)-1-benzenesulfonamide,

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -4-fluoro-1-benzenesulfonamide,

N1-[4-([4,6-di (ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-methoxy-5-methyl-1-benzenesulfonamide,

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-fluoro-1-benzenesulfonamide,

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-methyl-1-benzenesulfonamide,

N3-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-3-pyridinesulfonamide, N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-4-methoxy-1-benzenesulfonamide,

N5-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2,4-dimethyl-1,3-oxazole-5-sulfonamide,

N2-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-thiophenesulfonamide, N4-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-methyl-1H-4-imidazolesulfonamide,

N1-4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl- 4-methyl-1-benzenesulfonamide, N5-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -2,1,3-benzothiadiazole-5-sulfonamide,

N8-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl -8-quinolinesulfonamide-yl]aminomethyl)cyclohexyl]methylme thanesulfonamide

N1-[4-([4-(isopropylamino)-6-tetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-pyrrolidinesulfonamide,

N4-[4-([4-(isopropylamino)-6-morpholino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-4-morpholinesulfonamide,

N1-[4-([4-(isopropylamino)-6-piperidino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-piperidinesulfonamide,

N1-[(4-[(4,6-ditetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl)amino]methylcyclohexyl)methyl]-4-(tert-butyl)-1-benzenesulfonamide,

N-cyclopropyl-N'-[4-([4-(cyclopropylamino)-6-(isopropylamino)-1,3,5-triazin -2-yl]aminomethyl)cyclohexyl]methylsulfamide,

N'-[4-([4-(cyclopropylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-N,N-dimethylsulfamide,

N1-{[4-({[4-chloro-6-(isopropylamino)-1,3,5-triazin-2-yl]amnio}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide,

N'-[(4-[(4,6-dimorpholino-1,3,5-triazin-2-yl)amino]methylcyclohexyl)methyl] -N,N-dimethylsulfamide,

N1-[4-([4-chloro-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohex yl]methyl-4-(tert-butyl)-1-benzenesulfonamnide,

N1-[4-([4-(cyclopropylamino)-6-tetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl] aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide,

N'-((4-(((4,6-dichloro-1,3,5-triazin-2-yl)amino)methyl)cyclohexyl)methyl)-N ,N-dimethylsulfamide,

N1-[(4-[(4,6-ditetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl)amino]methylcyclohexyl)methyl]-2-methoxy-5-methyl-1-benzenesulfonamide,

N1-[4-([4-(cyclopropylamino)-6-(2-pyridyl)-1,3,5-triazin-2-l]aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide,

N1-[4-(aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide,

N1-[4-(aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide,

N2, N4-diethyl-N6-[5-(1H-1-pyrazolyl)pentyl]-1,3,5-triazine-2,4,6-triamine

N2, N4-diethyl-N6-[3-(1H-1-imidazolyl)propyl]-1,3,5-triazine-2,4,6-triamine

N2, N4-diethyl-N6-(2-pyridylmethyl)-1,3,5-triazine-2,4,6-triamine

Ref: U.S. Patent No. 6,340,683

Tricyclic compound Y receptor antagonists, such as:

trans-N2-(4-Dimethylaminosulfonylaminomethyl)cyclohexyl-9-fluoro-5,6-dihydro -4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

1-Aza-9-fluoro-4,5-dihydro-2-{5-(dimethylaminosulfonyl-amino)pentyl}amino-3 -thia-benzo[e]azulene;

1-Aza-9-fluoro-2-(5-(2-fluorophenyl)sulfonylamino)pentylamino-4,5-dihydro-3 -thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(1-naphthyl)sulfonylamino)-pentylamino-3-th ia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-(methanesulfonylamino)-butyl)amino-3-thia-b enzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-(dimethylaminosulfonyl-amino)butyl)amino-3- thia-benzo[e]azulene;

1-Aza-9-fluoro-2-(4-(2-fluorophenyl)sulfonylamino)butylamino-4,5-dihydro-3- thia-benzo[e]azulene -3-thia -benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-((2(S)-methoxymethyl)-pyrrolidine-1-yl)sulfonyl)phenylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(methylsulfonylamino)-pentyl)amino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(methylsulfonylamino-methyl)cyclohexyl)amino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(2,4-difluorophenyl)sulfonylamino)pentylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-isopropylsulfonylamino)-pentylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(diethylaminosulfonyl-amino)pentyl)amino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(2-methoxy-5-methylphenyl)sulfonylamino)pen tylamino-3-thia-benzo[e]azulene;

1-Aza-2-(5-benzylsulfonylamino)pentylamino-9-fluoro-4,5-dihydro-3-thia-benz o[e]azulene;

1-Aza-2-(5-(3,4-difluorophenyl)sulfonylamino)pentylamino-9-fluoro-4,5-dihyd ro-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(4-methoxyphenyl)sulfonylamino)pentylamino- 3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(2-thienyl)sulfonylamino)-pentylamino-3-thi a-benzo[e]azulene;

1-Aza-9-fluoro-2-(5-(2-trifluoroethyl)sulfonylamino)pentylamino-4,5-dihydro -3-thia-benzo[e]azulene;

1-Aza-9-fluoro-2-(5-ethylsulfonylamino)pentylamino-4,5-dihydro-3-thia-benzo[e]azulene;

1-Aza-2-(4-diethylaminosulfonylamino)butylamino-9-fluoro-4,5-dihydro-3-thia -benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(1-methylimidazol-4-yl)sulfonylamino)pentylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(3,5-dimethylisoxazol-4-yl)sulfonylamino)pentylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-aminosulfonylamino)pentylamino-3-thia-benzo[e]azulene;

trans-1-aza-9-fluoro-2-(4-(2-fluorophenyl)sulfonylamino-methyl)cyclohexylam ino-4,5-dihydro-3-thia-benzo[e]-azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(4-methoxyphenyl)-sulfonylaminomethyl}cyclohexylamino-3-thia-benzo[e]azulene;

trans-N2-(4-(2,6-Difluorophenylsulfonyl)aminomethyl)cyclohexyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]-thiazol-2-amine;

trans-1-Aza-2-{4-benzylsulfonylaminomethyl}cyclohexylamino-9-fluoro-4,5-dih ydro-3-thia-benzo[e]azulene;

trans-N2-(4-(2-Thienylsulfonyl)aminomethyl)cyclohexyl-9-fluoro-5,6-dihydro- 4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-N2-(4-Ethylsulfonylaminomethyl)cyclohexyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(1-methylimidazolyl-4-yl)sulfonylaminomethyl}cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(3,5-dimethylisoxazol-4-yl)sulfonylaminomethyl}cyclohexylamino-3-thia-benzo[e]azulene)-cyclohexylamino- 3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-diethylaminosulfonylamino)-cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(4-methoxyphenyl)sulfonylamino)-cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2-thienyl)sulfonyl-amino)-cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2,2,2-trifluoro-ethyl)sulfonylamino)-cyclohexylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-(2,2,2-trifluoroethyl)-sulfonylamino)butylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-2-{4-(3,4-difluorophenyl)sulfonyl-aminomethy}cyclohexy lamino-4,5-dihydro-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-2-{4-trifluoromethylsulfonylaminomethyl}cyclohexylamino-4,5-dihydro-3-thiabenzo[e]-azulene;

trans-1-Aza-9-fluoro-2-{4-(2-fluoro)phenylsulfonylamino}-cyclohexylmethylamino-4,5-dihydro-3-thia-benzo[e]azulene;

trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine: A mixture of trans-N2-(4-amino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclo hepta[d][1,3]thiazol-2-aminedihydrochloride;

trans-N2-(4-Aminosulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-N2-(4-Amino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-N2-(4-Aminosulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine: 6-Bromo-3-fluoro-6;7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one;

N1-(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)-5-bromopentanamide;

1-5-[(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-yl)amino]-5-oxopentyl-1,2-triazadien-2-ium;

N1-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)-5-aminopentanamide;

N1-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)-5-[(methylsulfonyl)amino]pentanamide;

trans-N2-(4-Aminosulfonylaminomethyl)cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

trans-N2-(4-Methylsulfonylaminomethyl)cyclohexyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

trans-1-Aza-4,5-dihydro-2-{4-(2-methoxy-5-methyl)phenyl-sulfonylaminomethyl}cyclohexylamino-6-oxa-3-thia-benzo[e]azulene;

N1-(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-yl)-5-[(2-methoxy-5-methylphenyl)sulfonyl]-aminopentanamide;

N1-(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]-thiazol-2-yl)-5-aminopentanamide;

trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

trans-1-Aza-4,5-dihydro-2-{4-(2-methoxy-5-methylphenyl)-sulfonylamino}cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene;

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-ben zo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-isopropylsulfonylamino}cyclohexylmethylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(3-pyridylsulfonylamino)cyclohexyl)amino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(5-(3-pyridyl)sulfonylamino)pentylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-(4-(3-pyridyl)sulfonylamino)butylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-{2-(2-methylsulfonylamino)ethoxy}ethylamino-3-thia-benzo[e]azulene;

1-Aza-9-fluoro-4,5-dihydro-2-{2-[2-(2-methoxy-5-methylphenyl)sulfonylamino] ethoxy}ethylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(3-pyridyl)sulfonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene;

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-8-methoxy-4,5-dihydro-benzo [2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

trans-1-Aza-4,5-dihydro-8-methoxy-2-{4-methylsulfonyl-amino)cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-{4-(3-pyridyl)sulfonylamino}cyclohexylmethylamino-3-thia-benzo[e]azulene;

trans-1-Aza-4,5-dihydro-9-methoxy-2-{4-methylsulfonyl-amino}cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene;

trans-N2-(4-Ethylsulfonylamino)cyclohexylmethyl-9-methoxy-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

trans-N2-(4-Methylsulfonylamino)cyclohexylmethyl-7-methoxy-4,5-dihydro-benzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine hydrochloride;

trans-1-Aza-4,5-dihydro-7-methoxy-2-{4-dimethylaminosulfonylamino}cyclohexylmethylamino-6-oxa-3-thia-benzo[e]azulene;

trans-N2-(4-Dimethylphosphonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4 H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-N2-(4-Ethoxycarbonylamino)cyclohexylmethyl-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine hydrochloride;

1-Aza-9-fluoro-4,5-dihydro-2-(2-(2-isopropylsulfonylamino)-ethoxy)ethylamino-3-thia-benzo[e]-azulene;

2-(4-Methylsulfonylaminomethyl)cyclohexylamino-4H-chromeno[4,3-d]thiazole;

trans-1-Aza-4,5-dihydro-8-methoxy-2-(4-methylsulfonyl-amino)cyclohexylmethylamino-3-thia-benzo[e]-azulene;

trans-1-Aza-4,5-dihydro-8-methoxy-2-(4-methylsulfonylamino-methyl)cyclohexylamino-3-thia-benzo[e]-azulene;

trans-1-Aza-4,5-dihydro-2-(4-isopropylsulfonylaminomethyl)-cyclohexylamino-8-methoxy-3-thia-benzo[e]-azulene;

trans-1-Aza-4,5-dihydro-2-(4-methylsulfonylaminomethyl)-cyclohexylamino-7-m ethoxy-3-thia-benzo[e]-azulene;

trans-1-Aza-4,5-dihydro-2-(4-ethylcarbonylaminomethyl)-cyclohexylamino-9-fl uoro-3-thia-benzo[e]azulen;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(4-morpholinyl)-sulfonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2-methoxy)ethoxy-carbonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene 2-methoxyethyl N-(t4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3]thiazol-2-yl) amino]cyclohexyl}methyl)-carbamate;

tert-butyl N-[(4-{[(benzoylamino)carbothioyl]amino}cyclo-hexyl)methyl]carbamate;

tert-butyl-N-({4-[(aminocarbothioyl)amino]cyclohexyl}-methyl)carbamate;

6-Bromo-3-fluoro-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one;

tert-Butyl-N-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta-[d][1,3]th iazol-2-yl)amino]cyclohexyl}methyl)-carbamate;

trans-N2-[4-(Aminomethyl)cyclohexyl]-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(2-methoxy)ethoxy-carbonylaminomethyl)cyclohexylamino-3-thia-benzo[e]azulene 2-methoxyethyl N-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)a mino]cyclohexyl}-methyl)carbamate;

trans-N2-(4-(1-Morpholinylsulfonylaminomethyl)cyclohexyl-8-methoxy-5,6-dihy dro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine hydrochloride;

3-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)am ino]cyclohexyl}methyl)-1,3-oxazolan-2-one;

2-chloroethyl-N-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta[d][1,3] thiazol-2-yl)amino]cyclohexyl}methyl)-carbamate;

3-({4-[(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)am ino]cyclohexyl}methyl)-1,3-oxazolan-2-one;

N1-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta-[d][1,3]thiazol-2-yl) amino]cyclohexyl}methyl)-2-methoxyacetamide;

N1-({4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]-cyclohepta-[d][1,3]thiazol-2-yl)amino]cyclohexyl}methyl)acetamide;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(N-propylformamido)-methyl)cyclohexylamino-3-thia-benzo[e]azulene;

trans-1-Aza-9-fluoro-4,5-dihydro-2-(4-(N-isopropylformamido)methyl)cyclohex ylamino-3-thia-benzo[e]azulene;

N1-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-2-methoxyacetamide;

Benzyl-N-(4-{[(aminocarbothioyl)amino]methyl}cyclohexyl)-carbamate;

Benzyl-N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}carbamate;

N2-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine

N-{[4-(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-N-propylformamide;

N1-{[4-(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}propanamide;

N2-{4-[(Propylamino)methyl]cyclohexyl}-4,5-dihydrobenzo-[2,3]oxepino[4,5-d] [1,3]thiazol-2-amine;

N-{[4-(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-N-propylformamide;

N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-(2-methoxyethyl)formamide;

N2-({4-[(2-methoxyethyl)amino]cyclohexyl}methyl)-4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-(2-methoxyethyl)formamide;

trans-1-Aza-2-(4-(n-(ethyl)formamido)cyclohexyl)methyl-amino-4,5-dihydro-6-oxa-3-thia-benzo[e]azulene;

trans-2-(4-Acetamido)cyclohexylmethylamino-1-aza-4,5-dihydro-6-oxa-3-thia-benzo[e]azulene;

Benzyl-N-[4-({[(benzoylamino)carbothioyl]amino}methyl)-cyclohexyl]carbamate;

Benzyl-N-(4-{[(aminocarbothioyl)amino]methyl}cyclohexyl)-carbamate; Benzyl-N-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}carbamate;

N2-[(4-aminocyclohexyl)methyl]-4,5-dihydrobenzo[2,3]-oxepino[4,5-d][1,3]thiazol-2-amine

N1-{4-[(4,5-dihydrobenzo[2,3]oxepino[4,5-d][1,3]-thiazol-2-ylamino)methyl]cyclohexyl}acetamide;

N2-{[4-(Ethylamino)cyclohexyl]methyl}-4,5-dihydrobenzo-[2,3]oxepino[4,5-d][1,3]thiazol-2-amine;

N-{4-[(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-ethylformamide;N-(4-[(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-propylformamide;

N2-{[4-(propylamino)cyclohexyl]methyl}-4,5-dihydrobenzo-[2,3]oxepino[4,5-d] [1,3]thiazol-2-amine;

N-{4-[(4,5-Dihydrobenzo[2,3]oxepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl}-N-propylformamide;

N1-{4-[(9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)amino]benzyl}-2-methoxyacetamide;N-{4-[(9-Fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-yl)amino]benzyl}methanesulfonamide;

N2-[4-(Aminomethyl)phenyl]-9-fluoro-5,6-dihydro-4H-benzo[6,7]cyclohepta[d][1,3]thiazol-2-amine

Ref: U.S. Patent No. 6,225,330

Bicyclic compound Y receptor antagonists, such as:

2-(5-Diethylaminosulfonylamino)pentylamino-4-(2-pyridyl)-thiazole hydrogen chloride

4-(2-Pyridyl)-2-(5-(2-thienyl)sulfonylaminopentyl)-amino-thiazole hydrogen chloride

2-(5-(2-Fluorophenyl)sulfonylamino)pentylamino-4-(2-pyridyl)-thiazole hydrogen chloride

2-(5-(4-Methoxyphenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(3,4-Difluorophenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(2-Methoxy-5-methylphenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Benzylsulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Ethylsulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Trifluoromethylsulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(Aminosulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride

2-(5-(2-Fluorophenyl)sulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride

2-(5-(2-Methoxy-5-methyl)phenylsulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride

2-(5-(2-Fluoro)phenylsulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride 2-(5-(2-Methoxy-5-methyl)phenylsulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride

N1-{5-[(4-Benzo[b]thiophen-2-yl-1,3-thiazol-2-yl)amino]-pentyl}-2-methoxy-5-methyl-1-benzenesulfonamide

N1-(5-{[4-(5-Chloro-3-methylbenzo[b]thiophen-2-yl)-1,3-thiazol-2-yl]amino}pentyl)-2-methoxy-5-methyl-1-benzene-sulfonamide

N1-(4-{[4-(5-Phenyl-3-isoxazolyl)-1,3-thiazol-2-yl)amino}-pentyl)-2-methoxy-5-methyl-1-benzenesulfonamide

N1-(5-{[4-(3-Thienyl)-1,3-thiazol-2-yl]amino}pentyl)-2-methoxy-5-methyl-1-benzenesulfonamide

N1-[5-({4-[1-(Phenylsulfonyl)-1H-3-pyrrolyl]-1,3-thiazol-2-yl}amino)pentyl] -2-methoxy-5-methyl-1-benzenesulfonamide

trans-N8-[(4-{[4-(3-Phenyl-5-isoxazolyl)-1,3-thiazol-2-yl]amino}cyclohexyl) methyl]-8-quinolinesulfonamide

N,N-Dimethyl-N'-(5-{[4-(3-Thienyl)-1,3-thiazol-2-yl]amino}pentyl)sulfamide

trans-2-(4-(2-Methoxy-5-methylphenyl)sulfonylamino)cyclohexylmethylamino-4- (2-pyridyl)thiazole dihydrogen chloride

trans-2-(4-(2-Fluorophenyl)sulfonylamino)cyclohexylmethyl-amino-4-(2-pyridyl)thiazole dihydrogen chloride

trans-2-(4-(3,5-Dimethyl-4-isoxazolyl)sulfonylamino)cyclohexylmethylamino-4-(2-pyridyl)thiazole dihydrogen chloride

trans-2-(4-(2-Fluorophenyl)sulfonylamino)cyclohexylmethyl-amino-4-(3-pyridyl)thiazole dihydrogen chloride

trans-2-(4-(2-Methoxy-5-methylphenyl)sulfonylamino)cyclohexylmethylamino-4-(4-pyridyl)thiazole dihydrogen chloride

N1-(5-[4-(1,3-thiazol-2-yl)-1,3-thiazol-2-yl]aminopentyl)-2-methoxy-5-methy l-1-benzenesulfonamide

trans-N1-[(4-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminocyclo hexyl)methyl]-2-methoxy-5-methyl-1-benzenesulfonamide

trans-N,N-dimethyl-N'-[(4-[4-(-1,3-thiazol-2-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]sulfamide

N,N-Dimethyl-N'-(5-{[4-(2-thienyl)-1,3-thiazol-2-yl]amino}-pentyl)sulfamide

N1-(5-{[4-(2-Thienyl)-1,3-thiazol-2-yl]amino}pentyl)-2-methoxy-5-methyl-1-b enzenesulfonamide

N1-(5-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-2-me thoxy-5-methyl-1-benzenesulfonamide

N1-(5-[4-(2,5-Dimethyl-1,3-thlazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-4-fl uoro-1-benzenesulfonamide

N1-(5-[4-(1,3-Thiazol-2-yl)-1,3-thiazol-2-yl]aminopentyl)-4-fluoro-1-benzenesulfonamide

N'-(5-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-N,N-dimethylsulfamide

trans-N1-[(4-[4-(2,5-dimethyl-1,3-thiazol-4-yl])-1,3-thiazol-2-yl]aminocyclohexyl)methyl]-4-fluoro-1-benzene-sulfonamilde

trans-N'-[(4-[4-(2,5-dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]-N,N-dimethylsulfamide

trans-N'-[4-([5-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]methyl-N,N-dimethyl-sulfamide

trans-N4-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]methyl-4-morpholine-sulfonamide

trans-N-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]-N-(2-methoxyethyl)formamide

trans-N-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]-N-isopropylformamide

Ref: U.S. Patent No. 6,218,408

N-aralkylaminotetralin Y receptor antagonist, such as:

rac-cis-1-(Phenylmethyl)-6-methoxy-N-(2-(3,4-dimethoxyphenyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine;

rac-cis-1-(Phenylmethyl)-6-methoxy-N-(2-(3-indolyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine hemifumarate;

rac-cis-1-(Phenylmethyl)-N-(4-fluorophenylmethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monohydrobromide;

rac-cis-1-(Phenylmethyl)-N-(2-methoxyphenylmethyl)-1,2,3,4-tetrahydro-2-naphthalenamine;

rac-cis-1-(Phenylmethyl)-N-(2-methoxyphenylmethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monohydrobromide;

rac-cis-1-(4-Fluorophenylmethyl)-N-(2-methoxyphenylmethyl)-1,2,3,4-tetrahyd ro-2-naphthalenamine monohydrobromide;

rac-trans-1-(4-Fluorophenylmethyl)-N-(2-methoxyphenylmethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monooxalate;

rac-cis-1-(Phenylmethyl)-N-(4-fluorophenylmethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monohydrobromide;

rac-cis-1-(Phenylmethyl)-7-methoxy-N-(2-methoxyphenylmethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monohydrobromide;

rac-trans-1-(4-Fluorophenylmethyl)-N-(2-(3-indolyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monooxalate;

rac-cis-1-(Phenylmethyl)-N-(2-methoxyphenyl-2-oxomethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monohydrobromide;

rac-cis-1-(Phenylmethyl)-7-methoxy-N-(2-(3-indolyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine 0.8 fumarate 0.8 methanol 0.2 hydrate;

rac-trans-1-(Phenylmethyl)-7-methoxy-N-(2(3-indolyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monooxalate;

rac-cis-1-(2-Naphthylmethyl)-N-(2-(3-indolyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine hemifumarate methanol;

rac-trans-1-(2-Naphthylmethyl)-N-(2-(3-indolyl)ethyl)-1,2,3,4-tetrahydro-2-naphthalenamine monooxalate;

rac-cis-1-(2-Naphthylmethyl)-N-(2-methoxyphenylmethyl)-1,2,3,4-tetrahydro-2 -naphthalenamine monohydrobromide;

rac-cis-1-(Phenylmethyl)-N-(2-methoxyphenyl-2-oxoethyl)-1,2,3,4-tetrahydro- 2-naphthalenamine;

rac-cis-1-(4-Fluorophenylmethyl)-N-(3-phenylpropyl)-1,2,3,4-tetrahydro-2-na phthalenamine monohydrobromide;

rac-cis-1-(3-pyridylmethyl)-N-(2-(3,4-dimethoxyphenyl)ethyl-1,2,3,4-tetrahydro-2-naphthalenamine monohydrobromide

Ref: U.S. Patent No. 6,201,025

Amide derivative Y receptor antagonist:

Ref: U.S. Patent No. 6,048,900

N-substituted aminotetralin Y receptor antagonist, such as:

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]4-cyclohexyl]methyl]2-naphthalenesulfo namide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(phenylmethyl)-2-naphthalenyl]amino]-5-pentyl]2-naphthalenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-pyridinylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]2-naphthalenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-fluoro-1-(phenylmethyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]2-fluorobenzenesulfonamide;

rac-[1α,2α (trans)]-N-[[[[[1,2,3,4-tetrahydro-6-fluoro-1-phenyl-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl]2-naphthalenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(1-propene-3-yl)-2-naphthalenyl]amino]methyl]4-cyclohexyl]methyl] benzenesulfonamide;

rac-[1α,2α(trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(3-hydroxypropyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide;

rac-[1α,2 α (trans)]-N-[[[[[1,2,3,4-tetrahydro-6-methoxy-1-(n-propyl)-2-naphthalenyl]amino]methyl]-4-cyclohexyl]methyl] benzenesulfonamide.

Ref: U.S. Patent No. 6,140,354

4-phenyl-1,4-dihydropyrimidinone derivative Y receptor antagonist:

Ref: U.S. Patent No. 5,889,016

Piperidine derivative dihydropyridine Y receptor antagonist:

4-Dihydro-[3-[[[[3-[4-(3-methoxyphenyl)-1-piperidinyl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-hydroxy-4-(3-methoxyphenyl)piperidin-1-yl]propyl] amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-(2-methoxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-(4-phenylpiperidin-1-yl)propyl]amino]carbonyl]amino] phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1. 4-Dihydro-4-[3-[[[[3-(4-hydroxy-4-phenylpiperidin-1-yl)propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-2,6-dimethyl-4-[3-[[[[3-[4-[3-(2-propynyloxy)phenyl]-1-piperidinyl]propyl]amino]carbonyl]amino]phenyl]-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-cyano-4-phenylpiperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-(3-hydroxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-naphthalen-1-ylpiperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

4-[3-[[[[3-[4-(1,1'-Biphenyl-3-yl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-(phenylmethyl)-piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

4-[3-[[[[3-(4-cyclohexyl-1-piperidinyl)propyl]amino]carbonyl]amino]phenyl]-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-dihydro-4-[3-[[[[3-[4-hydroxy-4-(2-phenoxyphenyl)-1-piperidinyl]propyl] amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-(4-phenyl-1-piperidinyl)propyl]amino]carbonyl]amino] phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1,4-Dihydro-4-[3-[[[[3-[(4-phenylmethyl)-1-piperidinyl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1,4-Dihydro-4-[3-[[[3-[4-hydroxy-4-(2-methoxyphenyl)-piperidin-1-yl]propyl] amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1. 4-Dihydro-4-[3-[[[[3-[4-hydroxy-4-(3-methoxyphenyl)-piperidin-1-yl]propy l]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, ethyl methyl ester;

1,4-Dihydro-2,6-dimethyl-4-[3-[[[[3-[4-[3-(2-propoxy)phenyl]-1-piperidinyl]-propyl]amino]carbonyl]amino]phenyl]3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[2-[4-(3-methoxyphenyl)-1-piperidinyl]ethyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester hydrochloride;

1,4-Dihydro-4-[3-[[[[4-[4-(3-methoxyphenyl)-1-piperidinyl]butyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester hydrochloride;

1,4-Dihydro-4-[3-[[[[3-[4-(3-methoxyphenyl)-1-piperidinyl]propyl]methylamino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester hydrochloride;

4-Dihydro-4-[3-[[[[3-[1,2,3,6-tetrahydro -4-(3-methoxyphenyl)pyridin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-d imethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-(1,2,3,6-tetrahydro-4-phenylpyridin-1-yl)propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[1,2,3,6-tetrahydro-4-(3-hydroxyphenyl)pyridine]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridine dicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[1,2,3,6-tetrahydro-4-(1-naphthalenyl)-1-pyridinyl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[3-(4-phenylpiperidin-1-yl)-1-oxo-1-propyl]amino]phenyl]- 2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1. 4-Dihydro-4-[3-[[4-(4-phenylpiperidin-1-yl)-1-oxo-1-butyl]amino]phenyl]- 2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[5-(4-phenylpiperidin-1-yl)-1-oxo-1-pentyl]amino]phenyl]- 2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[6-(4-phenylpiperidin-1-yl)-1-oxo-1-hexyl]amino]phenyl]-2 ,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[5-(4-hydroxy-4-phenylpiperidin-1-yl)-1-oxo-1-pentyl]amin o]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[5-(4-cyano-4-phenylpiperidin-1-yl)-1-oxo-1-pentyl]amino] phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[4-[4-(3-methoxyphenyl)-1-piperidinyl]butyl]carbonyl]ami no]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-dihydro-4-[3-[[[[3-[4-(3-methoxyphenyl)-1-piperidinyl]propyl]oxy]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester hydrochloride;

1,4-Dihydro-4-[3-[[[[3-[4-(3-methoxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-(2-methoxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-(3-hydroxyphenyl)piperidin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[4-naphthalenylpiperidin-1-yl]propyl]amino]carbonyl] amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

4-[3-[[[[3-(4-cyclohexyl-1-piperidinyl)propyl]amino]carbonyl]amino]phenyl]- 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[[3-[1,2,3,6-tetrahydro-4-(3-methoxyphenyl)pyridin-1-yl]propyl]amino]carbonyl]amino]phenyl]-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester;

1,4-Dihydro-4-[3-[[[3-[1,2,3,6-tetrahydro-4-(1-naphthalenyl)pyridin-1-yl]propyl]amino]carbonyl]amino]phenyl-2,6-dimethyl-3,5-pyridinedicarboxylic acid, dimethyl ester.

Ref: U.S. Patent No. 5,668,151

As disclosed herein, when administered to humans, PYY was found to reduce appetite. When infused into humans at physiological post-prandial levels, PYY_{3-36} significantly decreased appetite and reduced food intake by a third over 12 hours, and even by a third over 24 hours. Both the effect itself and the duration of the effect are surprising and unpredictable, as they occurred for many hours after the

hormone had been cleared from the circulation. The effects, which are produced at physiological levels of the peptide, are strong indications that PYY acts in vivo to regulate feeding behavior.

As disclosed herein, peripheral administration of PYY 3-36 in the rat caused an increase of c-fos immunoreactivity in the arcuate nucleus of the hypothalamus and a decrease in hypothalamic neuropeptide Y (NPY) mRNA. Further, electrophysiological studies demonstrated that PYY 3-36 inhibits synaptic activity of the NPY nerve terminals and thus activates POMC neurons, which are known to receive inhibitory NPY synaptic inputs.

Without being bound by theory, these results demonstrate that the gut hormone PYY $_{3-36}$ can act via the neuropeptide Y Y2 receptor. This hypothesis is supported by the observation that when PYY $_{3-36}$ was administered to neuropeptide Y Y2 receptor null mice (Y2R gene knock out mice), no inhibition of feeding was observed. Administration of PYY $_{3-36}$ to wild type littermates of the Y2R null mice was fully effective in inhibiting feeding.

Thus, a novel gut-brain pathway that inhibits feeding after meals is described. Without being bound by theory, the natural pathway involves release of PYY from the gut, its conversion to PYY $_{3-36}$, which acts as an agonist on the neuropeptide Y Y2 receptor (NPY Y2 receptor) in the brain. The NPY Y2 receptor acts as a inhibitory pre-synaptic receptor reducing release of neuropeptide Y, which is a most potent stimulator of feeding, and also acting on the anorexigenic melanocortin systems, the result of the NPY Y2 receptor activity being to suppress appetite and decrease food intake. The action of PYY $_{3-36}$ may occur in the arcuate nucleus of the hypothalamus, but other areas may be also be involved.

The results obtained show that PYY $_{3-36}$, a gut hormone that circulates in the blood, inhibits appetite at physiological concentrations, and that the inhibitory effect is observed even for some hours after the hormone has been cleared from the blood. This effect has been observed in all species tested, i.e. in mouse, rat and human. The circulating gut hormone appears to act via hypothalamic circuits. The reduction of messenger RNA, necessary for the synthesis of brain appetite regulating hormones, in particular of hypothalamic NPY mRNA may be a possible mechanism for the long action of PYY $_{3-36}$.

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

EXAMPLES

Example 1

Material and Methods

Generation of POMC-EGFP mice: The *EGFP* cassette contains its own Kozak consensus translation initiation site along with *SV40* polyadenylation signals downstream of the *EGFP* coding sequences directing proper processing of the 3' end of the EGFP mRNA. The *EGFP* cassette was introduced by standard techniques into the 5' untranslated region of exon 2 of a mouse *Pomc* genomic clone containing 13 kb of 5' and 2 kb of 3' flanking sequences (Young et al., *J Neurosci* 18, 6631-40, 1998). The transgene was microinjected into pronuclei of one-cell stage embryos of C57BL/6J mice (Jackson Laboratories) as described (Young et al., *J Neurosci* 18, 6631-40, 1998). One founder was generated and bred to wildtype C57BL/6J to produce N_1 hemizygous mice. In addition, N_2 and subsequent generations of mice homozygous for the transgene were also generated. The mice are fertile and have normal growth and development.

Immunofluorescence and GFP co-localization: Anesthetized mice were perfused transcardially with 4% paraformaldehyde and free-floating brain sections prepared with a vibratome. Sections were processed for immunofluorescence and colocalization of GFP fluorescence using standard techniques. Primary antisera and their final dilutions were rabbit anti-β-endorphin, 1:2500 v/v; rabbit anti-NPY, 1:25,000 v/v (Alanex Corp.); rabbit anti-ACTH, 1:2000 v/v; and mouse anti-TH, 1:1000 v/v (Incstar). After rinsing, sections were incubated with 10mg/ml biotinylated horse anti-mouse/rabbit IgG (Vector Laboratories) followed by Cy-3 conjugated streptavidin, 1:500 v/v (Jackson Immunoresearch Laboratories). Photomicrographs were taken on a Zeiss Axioscop using FITC and RITC filter sets (Chroma Technology Corp.).

Electrophysiology (Example 2): 200 μm thick coronal slices were cut from the ARC of four-week old male POMC-EGFP mice. Slices were maintained in (in mM) [NaCl, 126; KCl, 2.5; $MgCl_2$, 1.2; $CaCl_2.2H_2O$, 2.4; $NaH_2PO_4.H_2O$, 1.2; $NaHCO_3$, 21.4; Glucose, 11.1] (Krebs) at 35°C and saturated with 95% O_2 5% CO_2 for 1 hour(hr) prior to recordings. Recordings were made in Krebs at 35° C. Slices were visualized on an Axioskop FS2 (Zeiss) through standard infra red optics and using epifluoresence through a FITC filter set (see Fig. 1c). Whole cell recordings were made from fluorescent neurons using an Axopatch 1D amplifier (Axon Instruments) and Clampex 7 (Axon Instruments). Resting membrane potentials were determined using an event detection protocol on a PowerLab system (AD Instruments, Mountain View, CA) to average expanded traces of the membrane potential. Drugs were applied to the bath over the times indicated. The resting membrane potential was stable for up to an hour in cells treated with Krebs alone. I-V relationships for the Met-Enk currents were established using a step protocol; (–60 mV holding potential, sequentially pulsed (40 ms) from –120 to –50 mV, cells were returned to –60 mV for 2 s between voltage steps). The protocol was repeated after Met Enk addition. The net current was the difference between the two I-V relationships. This protocol was repeated in Krebs with 6.5 mM K^+. I-V relationships to identify the postsynaptic leptin current were performed similarly with slow voltage ramps (5 mV/ s from –100 to –20 mV) before and 10 minutes after the addition of leptin (100 nM). GABAergic IPSCs were recorded using a CsCl internal electrode solution (in mM) [CsCl, 140; Hepes, 10; $MgCl_2$, 5; Bapta, 1; (Mg)-ATP, 5; (Na)GTP, 0.3]. Both mini IPSCs and large amplitude (presumably multisynaptic) IPSCs were observed in the untreated slices. TTX (1 μM) abolished large IPSCs. Data were acquired before and after addition of drug for the times indicated on the figures at a –50 mV holding potential in 2 s. sweeps every 4 s. Mini postsynaptic currents were analyzed using Axograph 4 (Axon Instruments). IPSCs and excitatory postsynaptic currents (EPSCs) were distinguished on the basis of their decay constants; additionally picrotoxin (100 μM) blocked all IPSCs. POMC neurons receive a low EPSC tone and the frequency was not modulated by any of the treatments described here.

Immunostaining for light and electron microscopy: Double immunocytochemistry for NPY and POMC using different color diaminobenzidine(DAB) chromogens was carried out on fixed mouse hypothalami according to published protocols (Horvath et al., *Neuroscience* 51, 391-9, 1992). For electron microscopy, preembedding immunostaining for β-endorphin was using an ABC Elite kit (Vector Laboratories) and a DAB reaction followed by post-embedding labeling of GABA and NPY using rabbit anti-GABA, 1:1000 v/v and gold conjugated (10 nm) goat anti-rabbit IgG or sheep anti-NPY and gold conjugated (25 nm) goat anti-sheep IgG. Finally, sections were contrasted with saturated uranyl acetate (10 minutes) and lead citrate (20-30 s) and examined using a Philips CM-10 electron microscope.

Animals: Male Wistar rats (200-250g), 7-8 weeks old (Charles River Laboratories, United Kingdom) were maintained under controlled temperature (21-23° C) and light conditions (lights on 07:00-19:00) with *ad libitum* access to water and food (RM1 diet; SDS Ltd., Witham, United Kingdom) except where stated. Arcuate and paraventricular nuclei cannulations and injections were performed as previously described (Glaum et al., *Mol. Pharmacol.* 50, 230-5, 1996; Lee et al., *J. Physiol (Lond)* 515, 439-52; 1999; Shiraishi et al., *Nutrition* 15, 576-9, 1999). Correct intranuclear cannula placement was confirmed histologically at the end of each study period (Glaum et al., *Mol. Pharmacol* 50, 230-5, 1996; Lee et al., *J. Physiol (Lond)* 515, 439-52, 1999; Shiraishi et al., *Nutrition* 15, 576-9, 1999). All animal procedures were approved under the British Home Office Animals (Scientific Procedures) Act, 1986. All injection studies on fasting animals were performed in the early light-phase (0800-0900). All dark-phase feeding studies injections were performed just prior to lights off.

Male *Pomc-EGFP* mice were studied at 5-6 weeks of age and were generated as described above. *Y2r*-null mice were generated using *Cre*-lox P

mediated recombination, which results in the germline deletion of the entire coding region of the Y2 receptor. All *Y2r*-null mice were maintained on a mixed C57/Bl6-129SvJ background. Male mice aged 8-12 weeks and between 20-30 g bodyweight were kept under controlled temperature (21-23° C) and light conditions (lights on 06:00-18:00) with *ad libitum* access to water and food (Gordon's Speciality Stock feeds) except where stated. All studies were performed in the early light-phase (0700-0800).

Intraperitoneal injections: Rats were accustomed to IP injection by injections of 0.5 ml saline on the two days prior to study. For all studies, animals received an IP injection of either PYY_{3-36} or saline in 500 µl (for rats) or 100 µl (for mice).

Electrophysiology: Whole cell patch clamp recordings were made from POMC neurons in the hypothalamus of 180 µm thick coronal slices from *Pomc*-EGFP mice, as previously reported (Cowley et al., *Nature* 411, 480-484, 2001). "Loose cell-attached'' recordings were made using extracellular buffer in the electrode solution, and maintaining seal resistance between 3-5Mohm throughout the recording. Firing rates were analysed using mini-analysis protocols (MiniAnalysis, Jaejin Software, NJ). Vehicle controls were used in this system, previously validated for the electrophysiological actions of neuropeptides (Cowley et al., *Nature* 411, 480-484, 2001). Data were analysed by ANOVA, Neuman-Keuls posthoc comparison, and Wilcoxon Signed Rank Test.

Hypothalamic explants: Male Wistar rats were killed by decapitation and the whole brain immediately removed, mounted with the ventral surface uppermost and placed in a vibrating microtome (Biorad, Microfield Scientific Ltd., Devon, UK). A 1.7 mm slice was taken from the base of the brain to include the PVN and the ARC and immediately transferred to 1ml of artificial CSF (aCSF) (Kim et al., *J. Clin. Invest.* 105, 1005-11, 2000) equilibrated with 95% O_2 and 5% CO_2 and maintained at 37° C. After an initial 2-hour equilibration period, with aCSF replaced every 60 minutes, the hypothalami were then incubated for 45 minutes in 600µl aCSF (basal period) before being exposed to the Y2A (50nM) in 600µl aCSF. Finally, the

viability of the tissue was verified by a 45 minute exposure to 56 mM KCL; isotonicity was maintained by substituting K^+ for Na^+. At the end of each period, the aCSF was removed and frozen at -20° C until assayed for NPY and αMSH by radioimmunoassay.

C-fos expression: C-fos expression was measured in adult Wistar rats and Pomc-EGFP mice 2 hours after IP administration of saline or PYY_{3-36} (5μg/100g) using standard immunohistochemical techniques (Hoffman et al., *Front. Neuroendocrinol.* 14, 173-213, 1993). Data were obtained from 3 rats and 5 mice in each group. For the *Pomc*-EGFP mice 5 anatomically matched arcuate nucleus sections (Franklin et al., *The Mouse Brain in Stereotaxic Coordinates*, Academic Press, San Diego, 1997) were counted from each animal, and images acquired using a Leica TSC confocal microscope (Grove et al., *Neuroscience* 100, 731-40, 2000).

RNase protection assay (RPA): Total RNA was extracted from hypothalami (Trizol, Gibco). RPAs were performed (RPAIII kit, Ambion) using 5μg RNA and probes specific for NPY, αMSH and β actin (internal standard). For each neuropeptide, the ratio of the optical density of the neuropeptide mRNA band to that of β actin was calculated. Neuropeptide mRNA expression levels are expressed relative to saline control (mean ± s.e.m. n = 4 per group). The statistical analysis used was ANOVA, with Bonferroni post hoc analysis.

Plasma assays: Human leptin was measured using a commercially available radioimmunoassay (RIA) (Linco Research, USA). All other plasma hormone levels were measured using established in-house RIAs (Tarling et al., *Intensive Care Med.* 23, 256-260, 1997). Glucose concentrations were measured using a YSI 2300STAT analyser (Yellow Springs Instruments Inc., Ohio, USA). Plasma paracetamol levels were measured using an enzymatic colorimetric assay (Olympus AU600 analyzer).

Human Studies: PYY_{3-36} was purchased from Bachem (California, USA). The Limulus Amoebocyte Lysate assay test for pyrogen was negative and the peptide was sterile on culture. Ethical approval was obtained from the Local Research Ethics Committee (project registration 2001/6094) and the study was

performed in accordance with the principles of the Declaration of Helsinki. Subjects gave informed written consent.

Each subject was studied on two occasions with at least 1 week between each study. Volunteers filled out a food diary for three days prior to each infusion, and for the following 24 hours. All subjects fasted and drank only water from 20:00 on the evening prior to each study. Subjects arrived at 08:30 on each study day, were cannulated and then allowed to relax for 30 minutes prior to the onset of the study protocol. Blood samples were collected every 30 minutes into heparinised tubes containing 5,000 Kallikrein Inhibitor Units (0.2 ml) of aprotinin (Bayer) and centrifuged. Plasma was separated and then stored at -70° C until analysis. Subjects were infused with either saline or 0.8 pmol.kg^{1}.min^{-1} PYY_{3-36} for 90 minutes (about 72 pmol total infusion), in a double blind randomized crossover design.

Two hours after the termination of the infusion, subjects were offered an excess free-choice buffet meal (Edwards et al., *Am. J. Physiol. Endocrinol. Metab.* 281, E155-E166, 2001), such that all appetites could be satisfied. Food and water were weighed pre- and postprandially and caloric intake calculated. Appetite ratings were made on 100 mm visual analogue scores (VAS) with the text expressing the most positive and the negative rating anchored at each end (Raben et al., *Br. J. Nutr.* 73, 517-30, 1995). VAS was used to assess hunger, satiety, fullness, prospective food consumption and nausea. Caloric intake following saline and PYY_{3-36} were compared using a paired t test. The postprandial response curves were compared by ANOVA using repeated paired measures, with time and treatment as factors.

Measurements of Energy Expenditure: To determine the actions of PYY on energy expenditure the OXYMAX system is utilized with rodents following PYY injection into a treatment cohort. This system is also utilized with rodents following a saline injection (control cohort). The equipment measures O_2 consumption and CO_2 production; the efficiency with which the body produces CO_2 from O_2 gives a reliable index of caloric or metabolic efficiency. A similar system is used with human volunteers.

Example 2

Neural Network in the Arcuate Nucleus

A strain of transgenic mice was generated expressing green fluorescent protein (EGFP Clontech), under the transcriptional control of mouse *Pomc* genomic sequences that include a region located between –13 kb and –2 kb required for accurate neuronal expression (Young et al., *J Neurosci* 18, 6631-40, 1998) (Fig. 1a). Bright green fluorescence (509 nm) was seen in the two CNS regions where POMC is produced: the ARC and the nucleus of the solitary tract. Under ultraviolet (450–480 nm) excitation POMC neurons were clearly distinguished from adjacent, non-fluorescent neurons (Fig. 1b) visualized under infrared optics. Double immunofluorescence revealed >99% cellular co-localization of EGFP and POMC peptides within the ARC (Fig. 1c). There was close apposition of both tyrosine hydroxylase (TH)- and NPY-stained terminals on EGFP-expressing POMC neurons, but no evidence of co-localization of the TH or NPY immunoreactivity with EGFP. Total fluorescent cell counts performed on coronal hypothalamic sections revealed 3148 ± 62 (mean ± SEM: n=3) POMC-EGFP neurons distributed through the entire ARC (Franklin et al., *The Mouse Brain in Stereotaxic Coordinates*, Academic Press, San Diego, 1997) (Fig. 1d). POMC neurons in the mouse are located both medially and ventrally within the ARC, in contrast to a predominantly lateral position in the rat ARC.

POMC-EGFP neurons in hypothalamic slices had a resting membrane potential of –40 to –45 mV and exhibited frequent spontaneous action potentials. The non-selective opioid agonist met-enkephalin (Met-Enk: 30 μM; Sigma) caused a rapid (35- 40 s), reversible hyperpolarization (10-20 mV) of the membrane potential of POMC cells (n=10) and prevented spontaneous action potential generation (Fig. 2a). In normal (2.5 mM K^+) Krebs buffer, the reversal-potential of the inwardly-rectifying opioid current was approximately –90mV, while in 6.5 mM K^+ Krebs the reversal-potential was shifted to approximately –60 mV (n=3: Fig. 2b). The μ opioid receptor (MOP-R) antagonist CTAP (1 μM; Phoenix Pharmaceuticals) completely prevented the current induced by Met-Enk in POMC cells (n=3: Fig. 2c). These characteristics indicate the opioid current was due to activation of MOP-R and increased ion conductance through G protein coupled, inwardly-rectifying

potassium channels (GIRK) (Kelly et al., *Neuroendocrinology* 52, 268-75, 1990). The similar opioid responses in EGFP-labeled POMC neurons to that of a guinea pig (Kelly et al., *Neuroendocrinology* 52, 268-75, 1990) or mouse (Slugg et al., *Neuroendocrinology* 72, 208-17, 2000). POMC cells, identified by post-recording immunohistochemistry, suggests that expression of the EGFP transgene does not compromise either expression of receptors nor their coupling to second messenger systems in POMC neurons.

Next, the direct effects of leptin on identified POMC cells in slice preparations were investigated. Leptin (0.1 – 100 nM) depolarized 72 of 77 POMC cells by 3-30 mV (Fig. 3a; mean ± SEM depolarization at 100 nM leptin = 9.7 ± 1.2 mV, n= 45) within 2-10 minutes, in a concentration responsive manner (Fig. 3b). There were two components to the depolarization and neither were fully reversible within 40 minutes. Firstly, the depolarization was due to a small inward current which reversed at approximately -20 mV (Fig. 3c), suggesting the involvement of a non-specific cation channel (Powis et al., *Am J Physiol* 274, R1468-72, 1998). Secondly, leptin treatment decreased the GABAergic tone onto POMC cells. GABAergic inhibitory postsynaptic currents (IPSCs) were observed in POMC cells and leptin (100 nM) decreased their frequency by 25% (Fig. 3d) in 5 out of 15 cells suggesting that it acted presynaptically to reduce GABA release (leptin had no effect on IPSCs in10 out of 15 POMC neurons). The effect on IPSC frequency occurred with a similar lag to the effect on membrane potential. Thus, leptin not only directly depolarizes POMC neurons but also acts at GABAergic nerve terminals to reduce the release of GABA onto POMC neurons, allowing them to adopt a more depolarized resting potential. The consistent depolarization of POMC cells by leptin was specific because leptin had no effect on 5 of 13 adjacent non-fluorescent cells tested (Fig. 3e), while it hyperpolarized 5 (Fig. 3f) and depolarized 3 other non-POMC neurons in the ARC. The electrophysiological effects of leptin reported here are consistent with leptin's biological actions; leptin rapidly causes release of α-MSH from rat hypothalami (Kim et al., *J Clin Invest* 105, 1005-11, 2000), presumably by activating POMC neurons.

Previous reports of neuronal hyperpolarization by leptin (Glaum et al., *Mol Pharmacol* 50, 230-5, 1996; Spanswick et al., *Nature* 390, 521-5, 1997), and the

demonstrated co-localization of GABA and NPY (Horvath et al., *Brain Res* 756, 283-6, 1997) within subpopulations of ARC neurons, led us to speculate that leptin hyperpolarizes NPY/GABA cells that directly innervate POMC neurons, and thus reduces GABAergic drive onto POMC cells. Both the leptin and NPY Y2 receptors are expressed on NPY neurons in the ARC (Hakansson et al., *J Neurosci* 18, 559-72, 1998; Broberger et al., *Neuroendocrinology* 66, 393-408, 1997). Furthermore, activation of Y2 receptors inhibits NPY release from NPY neurons (King et al., *J Neurochem* 73, 641-6, 1999), and presumably would also diminish GABA release from NPY/GABA terminals. This is an alternative pharmacological approach, independent of leptin, to test the hypothesized innervation of POMC neurons by GABAergic NPY neurons. Indeed, NPY (100 nM; Bachem) decreased the frequency of GABAergic IPSCs by 55% within 3 minutes, in all 12 POMC cells tested (Fig. 4a). Both NPY and leptin still inhibited IPSCs in the presence of tetrodotoxin (TTX) (6 of 6 and 3 of 5 cells respectively), indicating that some of the inhibition of IPSCs was occurring through direct effects at presynaptic nerve terminals. POMC neurons express the NPY Y1 receptor (Broberger et al., *Neuroendocrinology* 66, 393-408, 1997) and NPY also hyperpolarized all POMC neurons tested, by an average of 9±6 mV (n=3).

Another pharmacological test to confirm the origin of GABAergic innervation on POMC neurons from NPY/GABA terminals was to test the effect of the recently characterized and highly selective MC3-R agonist D-Trp^8-γMSH (Grieco et al., *J Med Chem* 43, 4998-5002, 2000) on local GABA release. D-Trp^8-γMSH (7 nM) increased the frequency of GABAergic IPSCs (280 ± 90%) recorded from 3 of 4 POMC neurons (Fig. 4b). It had no effect on one cell. The positive effect of MC3-R activation, together with the negative effects of NPY and leptin, demonstrate the dynamic range of the NPY/GABA synapse onto POMC neurons and point to the important role of this synapse in modulating signal flow within the ARC. D-Trp^8-γMSH (7 nM) also hyperpolarized (-5.5 ± 2.4 mV) 9 of 15 POMC neurons tested and decreased the frequency of action potentials (Fig 4c); the remaining cells showed no significant response to D-Trp^8-γMSH. These effects could be due entirely to increased GABA release onto the POMC cells, or could be due to an additional postsynaptic action of D-Trp^8-γMSH on POMC neurons,

approximately half of which also express the MC3-R (Bagnol et al., *J Neurosci (Online)* 19, RC26, 1999). Thus, MC3-R acts in a similar autoreceptor manner to MOP-Rs on POMC neurons, diminishing POMC neuronal activity in response to elevated POMC peptides.

To further determine that the IPSCs in POMC neurons were due to local innervation by NPY/GABA cells, multi-label immunohistochemistry was performed using light and electron microscopy. Although independent NPY (Csiffary et al., *Brain Res* 506, 215-22, 1990) and GABA (Horvath et al., *Neuroscience* 51, 391-9, 1992) innervation of POMC cells has been reported, co-localization of NPY and GABA in nerve terminals forming synapses onto POMC cells has not been shown. Similar to the rat (Csiffary et al., *Brain Res* 506, 215-22, 1990), a dense innervation of POMC cells by NPY axon terminals was detected in the mouse (Fig. 4d). Electron microscopy confirmed the coexpression of NPY and GABA in axon terminals and revealed that these boutons established synapses on the perikarya of all 15 ARC POMC neurons analyzed (representative example, Fig. 4e).

A detailed model of regulation of this circuit shows dual mechanisms of leptin action in the ARC, interactions between NPY/GABA and POMC neurons, and autoregulatory feedback from opioid and melanocortin peptides as well as NPY (Fig. 4f). In this model, leptin directly depolarizes the POMC neurons and simultaneously hyperpolarizes the somata of NPY/GABA neurons, and diminishes release from NPY/GABA terminals. This diminished GABA release disinhibits the POMC neurons, and result in an activation of POMC neurons and an increased frequency of action potentials.

Example 3

Administration of PYY Inhibits Food Intake

The orexigenic NPY and the anorectic alpha melanocortin stimulating hormone (α-MSH) systems of the hypothalamic arcuate nucleus are involved in the central regulation of appetite (Schwartz et al., *Nature* 404, 661-671, 2000). However the potential mechanisms signaling meal ingestion directly to these hypothalamic-feeding circuits are unclear. PYY_{3-36} is a gut-derived hormone that is released postprandially in proportion to the calories ingested (Pedersen-Bjergaard et

al., *Scand. J. Clin. Lab. Invest.* 56, 497-503, 1996). The effects of peripheral administration of PYY_{3-36} on feeding were investigated.

An intraperitoneal injection (IP) of PYY_{3-36} to freely feeding rats, prior to the onset of the dark-phase, significantly decreased subsequent food intake (Fig. 5a). A similar inhibition of feeding was seen following IP injection in rats fasted for 24 hours (Fig. 5b). A time course of the plasma PYY_{3-36} levels achieved following IP injection of PYY_{3-36} demonstrated a peak level at 15 minutes post injection, which was within the normal postprandial range (peak PYY_{3-36} levels 15 minutes post IP injection of 0.3μg/100g = 99.3 ± 10.4 pmol/l vs. peak postprandial level = 112.1 ± 7.8 pmol/l, n = 8-10 per group), suggesting that physiological concentrations of PYY_{3-36} inhibit feeding. PYY_{3-36} did not affect gastric emptying (percentage of food ingested remaining in the stomach at 3 hours: PYY_{3-36} = 36 ± 1.9 %, saline = 37.4 ± 1.0 % n = 12) (Barrachina et al., *Am. J. Physiol.* 272, R1007-11, 1997). PYY_{3-36} administered IP twice daily for 7 days reduced cumulative food intake (7-day cumulative food intake: PYY_{3-36} = 187.6 ± 2.7g vs. saline = 206.8 ± 2.3, n = 8 per group, $P < 0.0001$) and decreased body weight gain (Fig. 5d) (PYY_{3-36} = 48.2 ± 1.3g vs. saline = 58.7 ± 1.9, n = 8 per group, $P < 0.002$).

Example 4

PYY Administration Affects c-fos Expression

To investigate whether this inhibition of food intake involved a hypothalamic pathway, c-fos expression was examined in the arcuate nucleus, an important center of feeding control (Schwartz et al., *Nature* 404, 661-671, 2000; Cowley et al., *Nature* 411, 480-484, 2001), following a single IP injection of PYY_{3-36}. There was a 2-fold increase in the number of cells positive for c-fos in the lateral arcuate of the rat (PYY_{3-36}=168 ± 2, saline = 82.7 ± 5, n = 3, $P < 0.0001$). Likewise in *Pomc-EGFP*-transgenic mice (Cowley et al., *Nature* 411, 480-484, 2001) IP administration of PYY_{3-36} resulted in a 1.8-fold increase in the number of arcuate cells positive for c-fos (Fig. 6b), compared with saline control animals (Fig. 6a) (PYY_{3-36} = 250 ± 40, saline = 137 ± 15, n = 5, $P < 0.05$). IP PYY_{3-36} caused a 2.6 fold increase in the proportion of POMC neurons that express c-fos (PYY_{3-36} = 20.4 ± 2.9%, saline = 8 ± 1.4%, n = 5, $P < 0.006$) (Figs. 6c and d).

These observations suggested that PYY_{3-36} may act via the arcuate nucleus. Thus, the actions of PYY_{3-36}, and its effects upon NPY and POMC circuits in the hypothalamus, were studied. In view of the sustained inhibition of food intake and the effects on weight gain following peripheral administration of PYY_{3-36} both *Pomc* and *Npy* hypothalamic messenger RNA (mRNA) were measured using RNase protection assays. A significant decrease in *Npy* mRNA in response to PYY_{3-36} was observed 6 hours post IP injection, compared with saline treated animals (saline = 17.3 ± 2.0, $PYY_{3-36} = 8.8 \pm 1.0$, relative optical density units, $P < 0.02$). A non-significant increase occurred in *Pomc* mRNA levels.

Example 5

Y2 receptors

PYY_{3-36} shows a 70% amino acid sequence identity to NPY and acts through NPY receptors (Soderberg et al., *J. Neurochem.* 75, 908-18, 2000). The Y2R is a putative inhibitory presynaptic receptor and is highly expressed on the arcuate NPY neurons (Broberger et al., *Neuroendocrinology* 66, 393-408, 1997), though not on the neighboring POMC neurons. PYY_{3-36} is a high affinity agonist at the Y2 receptor (Grandt et al., *Regul. Pept.* 51, 151-159, 1994). It was hypothesized that peripheral PYY_{3-36} inhibits food intake via the Y2R in the arcuate nucleus, an area known to be directly accessible to circulating hormones (Kalra et al., *Endocr. Rev.* 20, 68-100, 1999).

To investigate this hypothesis, PYY_{3-36} was injected directly into the arcuate nucleus (Kim et al., *Diabetes* 49, 177-82, 2000). In rats fasted for 24 hours, food intake was significantly decreased by doses as low as 100 fmol (Fig. 7a), resulting in a similar inhibition to that seen following IP administration. To establish whether these effects were via the Y2R, aY2R selective agonist was used (Potter et al., *Eur. J. Pharmacol.* 267, 253-262, 1994), N-acetyl (Leu ^{28}, Leu ^{31}) NPY (24-36) [Y2A]. Its affinity was confirmed using receptor-binding studies (Small et al., *Proc. Natl. Acad. Sci. U.S.A.* 94, 11686-91, 1997) on cell lines expressing the NPY Y1, Y2 and Y5 receptors (Y2 $IC_{50} = 1.3 \pm 0.2$ nM, Y1 $IC_{50} > 5000$ nM, Y5 $IC_{50} > 5000$ nM). Intra-arcuate nucleus injection of Y2A in rats previously fasted for 24 hours dose-dependently (100 fmol – 1 nmol) inhibited food intake (chow ingested 2 hours post-

injection, 0.1 nmol Y2A = 6.2 ± 0.5 g, saline = 8.2 ± 0.6 g, n = 8 per group, P < 0.05).

To confirm the anatomical specificity of this effect Y2A (100 fmol - 1 nmol) was injected into the paraventricular nucleus (PVN) (Kim et al., *J. Clin. Invest.* 105, 1005-11, 2000) of rats fasted for 24 hours and found no alteration of food intake (2 hour post-injection saline = 8.3 ± 0.4 g, 0.1nmol Y2A = 8.0 ± 0.6 g, n = 8 per group). To further determine the role of the Y2R in the feeding inhibition caused by peripheral PYY_{3-36}, the effect of PYY_{3-36} on *Y2r*-null mice and littermate controls was examined. PYY_{3-36} inhibited daytime feeding in a dose responsive manner in fasted male wild-type mice but did not inhibit food intake in fasted male *Y2r*-null mice (Figs. 7b and 7c). Food intake measured in response to a fast demonstrated that male *Y2r*-null mice eat significantly more at 2, 4 and 24 hours compared with their littermate controls (24-hour cumulative food intake; *Y2r*-null mice = 7.1 ± 0.48g vs. wild-type = 5.3 ± 0.7g, n = 8 per group, P < 0.05).

The electrophysiological response of hypothalamic POMC neurons to administration of both PYY_{3-36} and Y2A was examined. These neurons were identified using mice with targeted expression of green fluorescent protein in POMC neurons (Cowley et al., *Nature* 411, 480-484, 2001). PYY_{3-36} disinhibited the POMC neurons, resulting in a significant depolarization of 19 of the 22 POMC neurons tested (Fig. 8a inset) (10.3 ± 2.1 mV depolarization, n = 22, P < 0.0003). A similar depolarization was seen with Y2A (8.7 ± 1.8 mV depolarization, n = 9, P < 0.002). The depolarization caused by PYY_{3-36} stimulated a significant increase in the frequency of action potentials in POMC neurons (Fig 8a) (93% increase over control, P < 0.05, n = 22). In the whole cell mode the effect of PYY_{3-36} was sometimes reversed upon washout, but only after a long latency (30 minutes). A similar washout of leptin effects upon these neurons was observed.

To exclude effects of cellular rundown, or seal deterioration, the effects of PYY_{3-36} in the "loose cell-attached" (or extracellular) configuration was examined. PYY_{3-36} caused a reversible 5-fold increase in the frequency of action potentials in loose cell-attached recordings of POMC neurons (Fig. 8b). This increase in firing rate occurred with the same latency as PYY_{3-36} reduced the frequency of inhibitory postsynaptic currents (IPSCs) onto all 13 POMC neurons tested (Fig. 8c) (51.9 ± 9.2

% reduction, n = 13, $P < 0.0001$), indicating a reduced frequency of GABA release onto POMC neurons. Interestingly, the firing rate of POMC neurons returned to basal, in spite of continued inhibition of IPSCs. A similar effect upon IPSC frequency was seen with Y2A (44.4 ± 9.3% reduction, n = 8, $P < 0.004$) suggesting this effect to be via Y2R. PYY_{3-36} (25 nM) caused a hyperpolarization (5.2 ± 1.16 mV, $P < 0.004$, n = 5) of unidentified, but presumably NPY-containing, non-POMC, neurons in the arcuate nucleus. There is a tonic GABAergic inhibition of POMC neurons by NPY neurons (Cowley et al., *Nature* 411, 480-484, 2001) and these results suggest that PYY_{3-36} acts by inhibiting NPY neurons, thus decreasing this GABAergic tone and consequentially disinhibiting POMC neurons. The effect of Y2A on peptide secretion was also examined using hypothalamic explants (Kim et al., *J. Clin. Invest.* 105, 1005-11, 2000). Y2A significantly decreased NPY release, with a concomitant increase in α-MSH release from hypothalamic explants (Figs. 8d and 4e). Taken together, these observations suggest that PYY_{3-36} modulates both the NPY and melanocortin systems in the arcuate nucleus.

Example 6

Human Studies

Because of the importance of the melanocortin system in man (Barsh et al., *Nature* 404, 644-651, 2000) and the profound effects of PYY_{3-36} on both feeding and weight change seen in rodents, the effects of PYY_{3-36} on appetite and food intake were investigated in human subjects. Twelve healthy fasted, non-obese volunteers (six men and six women, mean age 26.7 ± 0.7 years, BMI = 24.6 ± 0.94 $kg.m^{-2}$) were infused with PYY_{3-36} (0.8 $pmol.kg^{-1}.min^{-1}$) or saline for 90 minutes in a double-blind placebo controlled crossover study.

PYY_{3-36} plasma concentrations increased from mean basal concentration of 8.3 ± 1.0 pM to 43.5 ± 3 pM during the PYY_{3-36} infusion and mimicked postprandial levels (Pedersen-Bjergaard et al., *Scand. J. Clin. Lab. Invest.* 56, 497-503, 1996; Adrian et al., *Gastroenterology* 89, 1070-1077, 1985). Post-infusion, PYY_{3-36} concentrations returned to basal within 30 minutes. PYY_{3-36} infusion resulted in a significant decrease in hunger scores (Raben et al., *Br. J. Nutr.* 73, 517-30, 1995) (Fig. 9c), but not in the scores for sleepiness or sickness. Calorie intake during a

free-choice buffet meal (Tarling et al., *Intensive Care Med.* 23, 256-260, 1997) two hours after the termination of the infusion was reduced by over a third compared to saline (36 ± 7.4%, $p < 0.0001$) (Fig. 9a). There was no effect upon fluid intake and no difference in sensations of fullness or nausea reported by the volunteers. PYY_{3-36} administration had no effect on gastric emptying, as estimated by the paracetamol absorption method (Edwards et al., *Am. J. Physiol. Endocrinol. Metab.* 281, E155-E166, 2001; Tarling et al., *Intensive Care Med.* 23, 256-260, 1997), or on plasma glucose, plasma leptin, GLP-1, or insulin. Analysis of the food diaries revealed a significant inhibition of food intake in the 12-hour period following the PYY_{3-36} infusion (saline = 2205 ± 243 kcal, PYY_{3-36} = 1474 ± 207 kcal). However, food intake during a 12 to 24 hour period between the two groups was virtually identical. Overall there was a 33% decrease in cumulative total calorie consumption in the 24-hour period following the PYY_{3-36} infusion (Fig.9b). These findings demonstrate that infusion of PYY_{3-36}, matching postprandial levels, caused a marked inhibition of both appetite and food intake in man.

In an additional study, two groups of healthy subjects (n = 12 per group, 6 males and 6 females), one with increased Body Mass Index (BMI) (mean = 32.73 +/- 0.93 kg/m2) and another group with low BMI (mean = 20.49 +/- 2.05 kg/m2), were studied on two occasions with at least 1 week between each study. All subjects fasted and drank only water from 20:00 hours on the evening prior to each study. Subjects arrived at 08:30 on each study day, were cannulated and then allowed to relax for 30 minutes prior to the onset of the study protocol. Subjects were infused with either saline or 0.8 pmol.kg1.min-1 PYY_{3-36} for 90 minutes, in a double blind randomized crossover design. Two hours after the termination of the infusion, subjects were offered an excess free-choice buffet meal, such that all appetites could be satisfied. Food and water were weighed pre- and postprandially and caloric intake calculated. Caloric intake following saline and PYY_{3-36} were compared using a paired t test ($p<0.001$). The number of calories ingested following administration of PYY_{3-36} differed significantly from the number of calories ingested following administration of saline for both the overweight group and the lean group. The overweight group showed a 28.8 +/- 4.3 % reduction and the lean group a 31.1 +/- 4.4 % reduction. However, the reduction for the overweight group did not differ

significantly from the reduction for the lean group. These findings demonstrate that infusion of PYY_{3-36}, matching postprandial levels, caused a marked inhibition of both appetite and food intake in both lean and overweight subjects.

Without being bound by theory, cells within the arcuate nucleus could detect circulating peripheral satiety signals and relay these signals to other brain regions (Butler et al., *Nature Neuroscience* 4, 605-611, 2001). This is supported by the observation that leptin modifies the activity of both the POMC and NPY arcuate neurons (Cowley et al., *Nature* 411, 480-484, 2001). The results disclosed herein demonstrate, through a combination of electrophysiological and hypothalamic explant studies, that the gut hormone, PYY_{3-36}, can directly influence hypothalamic circuits, resulting in coordinate changes in POMC and NPY action. The results presented here demonstrate that NPY neurons in the ARC are not protected by the blood/brain barrier, and thus are accessible to circulating molecules. Furthermore, PYY_{3-36} administered directly into this brain region reduces food intake.

The data disclosed herein demonstrates that postprandial levels of PYY_{3-36} inhibit food intake in more than one mammalian species (e.g. rodents and human subjects) for up to 12 hours, thereby demonstrating a role in regulation of food intake. This role can be described as a long term role, such as over a period of several hours (e.g. at least two, three, four, eight, or twelve hours, or from about two to about fifteen hours). This is in contrast to previously characterized gut-derived 'short-term' satiety signals, e.g. cholecystokinin (Schwartz et al., *Nature* 404, 661-671, 2000; Moran, *Nutrition* 16, 858- 865, 2000), the effects of which are relatively short-lived (e.g., from about 1-4 hours).

The failure of PYY_{3-36} to inhibit food intake in the *Y2r*-null mice provides evidence that PYY_{3-36} reduces food intake via a Y2R dependent mechanism. The results disclosed herein suggest the existence of a novel gut-hypothalamic pathway in the regulation of feeding, involving postprandial PYY_{3-36} acting at the arcuate Y2R. Thus, PYY, and analogs thereof, such as PYY_{3-36} provide novel therapeutic agents for the treatment of obesity.

It will be apparent that the precise details of the methods or compositions described may be varied or modified without departing from the spirit of the

described disclosure. We claim all such modifications and variations that fall within the scope and spirit of the claims below.

CLAIMS

1. Use of PYY or an agonist thereof for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject
a) in the case of PYY, in an amount effective to achieve physiological levels of PYY_{3-36} observed postprandially, or
b) in the case of a PYY agonist, in an amount effective to mimic physiological levels of PYY_{3-36} observed postprandially.

2. Use as claimed in claim 1, wherein the subject is a human subject.

3. Use as claimed in claim 1 or claim 2, for the manufacture of a medicament for 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.

4. Use as claimed in claim 1 or claim 2, for the manufacture of a medicament for 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.

5. Use as claimed in claim 1 or claim 2, for the manufacture of a medicament for any one or more of the following: maintaining a desired body weight, maintaining a desired Body Mass Index, maintaining a desired appearance and maintaining good health.

6. Use as claimed in any one of claims 1 to 5, wherein the postprandial level of PYY_{3-36} is 40 to 60 pM.

7. Use as claimed in any one of claims 1 to 6, wherein the PYY is PYY_{3-36}.

8. Use as claimed in any one of claims 1 to 7, wherein the medicament is in a form suitable for the peripheral administration of PYY or the agonist thereof at a dose of from about 0.5 to about 135 pmol per kilogram body weight of the subject.

9. Use as claimed in claim 8, wherein the dose of PYY or the agonist thereof is from about 45 to about 135 pmol per kilogram body weight of the subject.

10. Use as claimed in claim 9, wherein the dose is about 72 pmol per kilogram body weight of the subject.

11. Use as claimed in any one of claims 1 to 7, wherein the medicament comprises a dose of from 5 to 50 nmols of PYY or the agonist thereof.

12. Use as claimed in claim 11, wherein the medicament comprises a dose of from 2 to 20 nmols of PYY or the agonist thereof.

13. Use as claimed in claim 12, wherein the medicament comprises a dose of about 10 nmols of PYY or the agonist thereof.

14. Use as claimed in any one of claims 1 to 13, wherein the medicament is for administration in divided doses.

15. Use as claimed in any one of claims 1 to 13, wherein the medicament comprises PYY or the agonist thereof in an amount sufficient to achieve the defined effect for 12 hours or more.

16. Use as claimed in claim 15, wherein the medicament comprises PYY or the agonist thereof in an amount sufficient to achieve the defined effect for 24 hours or more.

17. Use as claimed in any one of claims 1 to 16, wherein the medicament is for administration at least 30 minutes before a meal.

18. Use as claimed in any one of claims 1 to 17, wherein the medicament comprises an additional appetite suppressant.

19. Use as claimed in claim 18, wherein the additional appetite suppressant. is amfepramone (diethylpropion), phentermine, mazindol, phenylpropanolamine, fenfluramine, dexfenfluramine, or fluoxetine.

20. Use as claimed in any one of claims 1 to 19, wherein the medicament also comprises any one or more of plasma glucose-lowering agents, plasma lipid-altering agents and other food intake-reducing agents.

21. Use as claimed in any one of claims 1 to 4 and 8 to 20, wherein the PYY agonist increases the expression of c-fos in a section of an arcuate nucleus contacted with the compound.

22. Use as claimed in any one of claims 1 to 4 and 8 to 20, wherein the PYY agonist comprises a molecule that specifically binds the Y2 receptor.

23. Use as claimed in claim 22, wherein the PYY agonist specifically binds to a neuropeptide Y neuron and inhibits an activity of a neuropeptide Y neuron.

24. Use as claimed in claim 23, wherein the PYY agonist decreases the action potential firing rate of the neuropeptide Y neuron.

25. Use as claimed in claim 23 or claim 24, wherein the neuropeptide Y neuron synapses with a proopiomelanocortin neuron, and wherein binding of the PYY agonist to the neuropeptide Y neuron results in an increased activity of the proopiomelanocortin neuron.

26. Use as claimed in claim 25, wherein binding of the PYY agonist to the neuropeptide Y neuron the PYY agonist decreases the action potential firing rate of the neuropeptide Y neuron, which decreased activity of the neuropeptide Y neuron results in an increase in action potential firing on the proopiomelanocortin neuron.

27. Use as claimed in any one of claims 1 to 26, wherein the subject is overweight.

28. Use as claimed in any one of claims 1 to 26, wherein the subject is obese.

29. Use as claimed in any one of claims 1 to 26, wherein the subject is diabetic.

30. Use as claimed in any one of claims 1 to 29, wherein the medicament is in a form suitable for oral, subcutaneous, intravenous, intramuscular, intranasal, transdermal, intraperitoneal, topical, transmucosal or sublingual administration, or by pulmonary inhalation.

31. Use as claimed in any one of claims 1 to 29, wherein the medicament is in the form of a sustained release or depot preparation.

32. Use as claimed in claim 31, wherein the medicament is for administration orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray.

33. Use as claimed in any one of claims 1 to 29, wherein the medicament is in the form of a controlled release preparation.

34. Use as claimed in any one of claims 1 to 29, wherein the medicament is in the form of a pump or implantable drug infusion device.

35. Use as claimed in any one of claims 1 to 34, wherein the amount of PYY or an agonist thereof is effective to achieve a reduction in calorie intake, food intake, or appetite equivalent to the reduction in calorie intake, food intake, or appetite, or to increase the energy expenditure, caused by the postprandial level of PYY3-36.

36. Use as claimed in any one of claims 1 to 35, wherein the subject is obese or overweight, for treatment of a disorder wherein obesity or being overweight is a risk factor for the disorder.

37. Use as clamed in any one of claims 1 to 35, for treating, preventing, ameliorating or alleviating a condition or disorder caused by, complicated by, or aggravated by a relatively high nutrient availability.

38. Use of PYY or an agonist thereof for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject

a) in the case of PYY, in an amount effective to achieve physiological levels of PYY_{3-36}, or

b) in the case of a PYY agonist, in an amount effective to mimic physiological levels of PYY_{3-36}.

39. Use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject in an amount effective to achieve physiological levels of PYY_{3-36} observed postprandially.

40. Use as claimed in claim 39, wherein the postprandial level of PYY_{3-36} is 40 to 60 pM.

41. Use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject at a dose of from about 0.5 to about 135 pmol per kilogram body weight of the subject.

42. Use as claimed in claim 39 or claim 40, wherein the dose of PYY_{3-36} is from about 45 to about 135 pmol per kilogram body weight of the subject.

43. Use as claimed in claim 39 or claim 40, wherein the dose of PYY_{3-36} is about 72 pmol per kilogram body weight of the subject.

44. Use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject at a dose of not more than 100 nmoles.

45. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose in an amount of from 1 to 100 nmoles.

46. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose in an amount of from 2 to 90 nmoles.

47. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose in an amount of from 5 to 80 nmoles.

48. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose in an amount of from 5 to 70 nmoles.

49. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose in an amount of from 5 to 60 nmoles.

50. Use as claimed in claim 39 or claim 40, wherein the medicament comprises a dose of from 5 to 50 nmols of PYY_{3-36}

51. Use as claimed in claim 39 or claim 40, wherein the medicament comprises a dose of from 2 to 20 nmols of PYY_{3-36}.

52. Use as claimed in claim 39 or claim 40, wherein the medicament comprises a dose of about 10 nmols of PYY_{3-36}.

53. Use of PYY_{3-36} for the manufacture of a medicament for any one or more of the following: control of appetite, control of satiety, control of hunger, control of weight, weight treatment, reduction of obesity, and prevention of obesity, in a subject, which medicament is in a form suitable for peripheral administration to the subject at a dose of not more than 405 μg.

54. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose of from 4 to 405 μg.

55. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose of from 8 to 365 μg.

56. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose of from 20 to 324 μg.

57. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose of from 20 to 283 μg.

58. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose of from 20 to 243 μg.

59. Use as claimed in claim 39 wherein PYY_{3-36} is administered peripherally at a dose of from 20 to 202 μg.

60. Use as claimed in claim 1 or claim 2 wherein the medicament comprises a dose of from 1 to 100 nmoles of PYY or the agonist thereof.

61. Use as claimed in claim 1 or claim 2 wherein the medicament comprises a dose of from 2 to 90 nmoles of PYY or the agonist thereof.

62. Use as claimed in claim 1 or claim 2 wherein the medicament comprises a dose of from 5 to 50 nmoles of PYY or the agonist thereof.

63. Use as claimed in claim 1 or claim 2 wherein the medicament comprises a dose of from 2 to 20 nmoles of PYY or the agonist thereof

64. Use as claimed in any one of claims 53 to 63 wherein the medicament is in a form suitable for oral, subcutaneous, intravenous, intramuscular, intranasal, transdermal, intraperitonial, topical, transmucosal, or sublingual administration, or by pulmonary inhalation.

65. Use as claimed in any one of claims 53 to 63 wherein the medicament is in the form of a sustained release or depot preparation.

66. Use as claimed in any one of claims 53 to 63 wherein the medicament is for administration orally, rectally, parenterally, intracisternally, intravaginally, intraperitonially, topically (as by powders, ointments, gels, drops or transdermal patch), buccally or as an oral or nasal spray.

67. Use as claimed in any one of claims 53 to 63 wherein the medicament is in the form of a controlled release preparation.

68. Use as claimed in any one of claims 53 to 63 wherein the medicament is in the form of a pump or implantable drug infusion device.

SEQUENCE LISTING

<110> Cowley, Michael
Cone, Roger
Low, Malcolm
Bulter, Andrew

<120> Stimulation of Neurons in the Arcuate Nucleus to Modify Feeding Behavio
r

<130> 0899-63727

<150> 60/324,406
<151> 2001-09-24

<150> 60/392,109
<151> 2002-06-28

<160> 335

<170> PatentIn version 3.1

<210> 1
<211> 36
<212> PRT
<213> Homo sapiens

<400> 1

Tyr Pro Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 2
<211> 36
<212> PRT
<213> Homo sapiens

<400> 2

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 3
<211> 36
<212> PRT
<213> Homo sapiens

<400> 3

Ala Ser Leu Glu Pro Glu Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 4
<211> 3
<212> PRT
<213> Homo sapiens

<400> 4

000
1

<210> 5
<211> 36
<212> PRT
<213> Rattus sp.

<400> 5

Tyr Pro Ala Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Ser Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 6
<211> 36
<212> PRT
<213> Sus sp.

<400> 6

Tyr Pro Ala Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Ser Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 7
<211> 36
<212> PRT
<213> Cavia porcellus

<400> 7

Tyr Pro Ser Lys Pro Glu Ala Pro Gly Ser Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Ala Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 8
<211> 36
<212> PRT
<213> Rana sp.

<400> 8

Tyr Pro Pro Lys Pro Glu Asn Pro Gly Glu Asp Ala Ser Pro Glu Glu
1 5 10 15

Met Thr Lys Tyr Leu Thr Ala Leu Arg His Tyr Ile Asn Leu Val Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 9
<211> 36
<212> PRT
<213> Raja sp.

<400> 9

Tyr Pro Pro Lys Pro Glu Asn Pro Gly Asp Asp Ala Ala Pro Glu Glu
1 5 10 15

Leu Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 10
<211> 36
<212> PRT
<213> Dogfish sp.

<400> 10

Tyr Pro Pro Lys Pro Glu Asn Pro Gly Glu Asp Ala Pro Pro Glu Glu
1 5 10 15

Leu Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 11
<211> 36
<212> PRT
<213> Lampetra sp.

<400> 11

Phe Pro Pro Lys Pro Asp Asn Pro Gly Asp Asn Ala Ser Pro Glu Gln
1 5 10 15

Met Ala Arg Tyr Lys Ala Ala Val Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 12
<211> 36
<212> PRT
<213> Petromyzontidae gen. sp.

<400> 12

Met Pro Pro Lys Pro Asp Asn Pro Ser Pro Asp Ala Ser Pro Glu Glu
1 5 10 15

Leu Ser Lys Tyr Met Leu Ala Val Arg Asn Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 13
<211> 36
<212> PRT
<213> Rattus sp.

<400> 13

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 14
<211> 36
<212> PRT
<213> Oryctolagus cuniculus

<400> 14

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 15
<211> 36
<212> PRT
<213> Canis familiaris

<400> 15

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 16
<211> 36
<212> PRT
<213> Sus sp.

<400> 16

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 17
<211> 36
<212> PRT
<213> Bos taurus

<400> 17

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 18
<211> 36
<212> PRT
<213> Ovis aries

<400> 18

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Asp Asp Ala Pro Ala Glu Asp
1 5 10 15

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 19
<211> 36
<212> PRT
<213> Cavia porcellus

<400> 19

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 20
<211> 36
<212> PRT
<213> Avian

<400> 20

Tyr Pro Ser Lys Pro Asp Ser Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 21
<211> 36
<212> PRT
<213> Rana sp.

<400> 21

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Met Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 22
<211> 36
<212> PRT
<213> Carassius auratus

<400> 22

Tyr Pro Thr Lys Pro Asp Asn Pro Gly Glu Gly Ala Pro Ala Glu Glu
1 5 10 15

Leu Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 23
<211> 36
<212> PRT
<213> Dogfish sp.

<400> 23

Tyr Pro Ser Lys Pro Asp Asn Pro Gly Glu Gly Ala Pro Ala Glu Asp
1 5 10 15

Leu Ala Lys Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 24
<211> 36
<212> PRT
<213> Lampetra sp.

<400> 24

Pro Pro Asn Lys Pro Asp Ser Pro Gly Glu Asp Ala Pro Ala Glu Asp
1 5 10 15

Leu Ala Arg Tyr Leu Ser Ala Val Arg His Tyr Ile Asn Leu Ile Thr
20 25 30

Arg Gln Arg Tyr
35

<210> 25
<211> 36
<212> PRT
<213> Ovis aries

<400> 25

Ala Pro Leu Glu Pro Val Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Asp Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 26
<211> 36
<212> PRT
<213> Sus sp.

<400> 26

Ala Pro Leu Glu Pro Val Tyr Pro Gly Asp Asp Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 27
<211> 36
<212> PRT
<213> Canis familiaris

<400> 27

Ala Pro Leu Glu Pro Val Tyr Pro Gly Asp Asp Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 28
<211> 36
<212> PRT
<213> Felis catus

<400> 28

Ala Pro Leu Glu Pro Val Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 29
<211> 36
<212> PRT
<213> Bos taurus

<400> 29

Ala Pro Leu Glu Pro Glu Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Ala Ala Glu Leu Arg Arg Tyr Ile Asn Met Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 30
<211> 36
<212> PRT
<213> Rattus sp.

<400> 30

Ala Pro Leu Glu Pro Met Tyr Pro Gly Asp Tyr Ala Thr His Glu Gln
1 5 10 15

Arg Ala Gln Tyr Glu Thr Gln Leu Arg Arg Tyr Ile Asn Thr Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 31
<211> 36
<212> PRT
<213> Mus musculus

<400> 31

Ala Pro Leu Glu Pro Met Tyr Pro Gly Asp Tyr Ala Thr Pro Glu Gln
1 5 10 15

Met Ala Gln Tyr Glu Thr Gln Leu Arg Arg Tyr Ile Asn Thr Leu Thr
20 25 30

Arg Pro Arg Tyr
35

<210> 32
<211> 37
<212> PRT
<213> Cavia porcellus

<400> 32

Ala Pro Leu Glu Pro Val Tyr Pro Gly Asp Asn Ala Thr Pro Glu Gln
1 5 10 15

Gln Met Ala Gln Tyr Ala Ala Glu Met Arg Arg Tyr Ile Asn Met Leu
20 25 30

Thr Arg Pro Arg Tyr
35

<210> 33
<211> 36
<212> PRT
<213> Gallus gallus

<400> 33

Gly Pro Ser Gln Pro Thr Tyr Pro Gly Asp Asp Ala Pro Val Glu Asp
1 5 10 15

Leu Ile Arg Phe Tyr Asn Asp Leu Gln Gln Tyr Leu Asn Val Val Thr
20 25 30

Arg His Arg Tyr
35

<210> 34
<211> 36
<212> PRT
<213> Alligator sp.

<400> 34

Thr Pro Leu Gln Pro Lys Tyr Pro Gly Asp Gly Ala Pro Val Glu Asp
1 5 10 15

Leu Ile Gln Phe Tyr Asn Asp Leu Gln Gln Tyr Leu Asn Val Val Thr
20 25 30

Arg Pro Arg Phe
35

<210> 35
<211> 36
<212> PRT
<213> Rana catesbeiana

<400> 35

Ala Pro Ser Glu Pro His His Pro Gly Asp Gln Ala Thr Pro Asp Gln
1 5 10 15

Leu Ala Gln Tyr Tyr Ser Asp Leu Tyr Gln Tyr Ile Thr Phe Ile Thr
20 25 30

Arg Pro Arg Phe
35

<210> 36
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 36

Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 37
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 37

Arg His Thr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 38
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 38

Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 39
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 39

Arg His Tyr Ile Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 40
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 40

Arg His Tyr Val Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 41
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 41
Arg His Tyr Leu Gln Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 42
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 42

Arg His Tyr Leu Asn Ile Val Thr Arg Gln Arg Tyr
1 5 10

<210> 43
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 43

Arg His Tyr Leu Asn Val Val Thr Arg Gln Arg Tyr
1 5 10

<210> 44
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 44

Arg His Tyr Leu Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 45
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 45

Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Tyr

1 5 10

<210> 46
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 46

Arg His Tyr Leu Asn Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 47
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 47

Arg His Tyr Leu Asn Leu Val Thr Lys Gln Arg Tyr
1 5 10

<210> 48
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 48

Arg His Tyr Leu Asn Leu Val Thr Arg Asn Arg Tyr
1 5 10

<210> 49
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 49

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Lys Tyr
1 5 10

<210> 50
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 50

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Thr
1 5 10

<210> 51
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 51

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Phe
1 5 10

<210> 52
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 52

Lys His Thr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 53
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 53

Lys His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 54
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 54

Lys His Tyr Ile Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 55
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 55

Lys His Tyr Val Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 56
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 56

Lys His Tyr Leu Gln Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 57
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 57

Lys His Tyr Leu Asn Ile Val Thr Arg Gln Arg Tyr
1 5 10

<210> 58
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 58

Lys His Tyr Leu Asn Val Val Thr Arg Gln Arg Tyr
1 5 10

<210> 59
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 59

Lys His Tyr Leu Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 60
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 60

Lys His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 61
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 61

Lys His Tyr Leu Asn Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 62
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 62

Lys His Tyr Leu Asn Leu Val Thr Lys Gln Arg Tyr
1 5 10

<210> 63
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 63

Lys His Tyr Leu Asn Leu Val Thr Arg Asn Arg Tyr
1 5 10

<210> 64
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 64

Lys His Tyr Leu Asn Leu Val Thr Arg Gln Lys Tyr
1 5 10

<210> 65
<211> 12
<212> PRT

<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 65

Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Thr
1 5 10

<210> 66
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 66

Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Phe
1 5 10

<210> 67
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 67

Arg His Thr Ile Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 68
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 68

Arg His Thr Val Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 69
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 69

Arg His Thr Leu Gln Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 70

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 70

Arg His Thr Leu Asn Ile Val Thr Arg Gln Arg Tyr
1 5 10

<210> 71
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 71

Arg His Thr Leu Asn Val Val Thr Arg Gln Arg Tyr
1 5 10

<210> 72
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 72

Arg His Thr Leu Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 73
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 73

Arg His Thr Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 74
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 74

Arg His Thr Leu Asn Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 75
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 75

Arg His Thr Leu Asn Leu Val Thr Lys Gln Arg Tyr
1 5 10

<210> 76
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 76

Arg His Thr Leu Asn Leu Val Thr Arg Asn Arg Tyr
1 5 10

<210> 77
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 77

Arg His Thr Leu Asn Leu Val Thr Arg Gln Lys Tyr
1 5 10

<210> 78
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 78

Arg His Thr Leu Asn Leu Val Thr Arg Gln Arg Thr
1 5 10

<210> 79
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 79

Arg His Thr Leu Asn Leu Val Thr Arg Gln Arg Phe
1 5 10

<210> 80
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 80

Arg His Phe Ile Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 81
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 81

Arg His Phe Val Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 82
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 82

Arg His Phe Leu Gln Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 83
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 83

Arg His Phe Leu Asn Ile Val Thr Arg Gln Arg Tyr
1 5 10

<210> 84
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 84

Arg His Phe Leu Asn Val Val Thr Arg Gln Arg Tyr
1 5 10

<210> 85
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 85

Arg His Phe Leu Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 86
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 86

Arg His Phe Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 87
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 87

Arg His Phe Leu Asn Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 88
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 88

Arg His Phe Leu Asn Leu Val Thr Lys Gln Arg Tyr
1 5 10

<210> 89
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 89

Arg His Phe Leu Asn Leu Val Thr Arg Asn Arg Tyr
1 5 10

<210> 90
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 90

Arg His Phe Leu Asn Leu Val Thr Arg Gln Lys Tyr
1 5 10

<210> 91
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 91

Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Thr
1 5 10

<210> 92
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 92

Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Phe
1 5 10

<210> 93
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 93

Arg His Tyr Leu Gln Ile Val Thr Arg Gln Arg Tyr
1 5 10

<210> 94
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Polypeptide variation

<400> 94

Arg His Tyr Leu Gln Val Val Thr Arg Gln Arg Tyr
1 5 10

<210> 95
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 95

Arg His Tyr Leu Gln Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 96
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 96

Arg His Tyr Leu Gln Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 97
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 97

Arg His Tyr Leu Gln Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 98
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 98

Arg His Tyr Leu Gln Leu Val Thr Lys Gln Arg Tyr
1 5 10

<210> 99
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 99

Arg His Tyr Leu Gln Leu Val Thr Arg Asn Arg Tyr
1 5 10

<210> 100
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 100

Arg His Tyr Leu Gln Leu Val Thr Arg Gln Lys Tyr
1 5 10

<210> 101
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 101

Arg His Tyr Leu Gln Leu Val Thr Arg Gln Arg Thr
1 5 10

<210> 102
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 102

Arg His Tyr Leu Gln Leu Val Thr Arg Gln Arg Phe
1 5 10

<210> 103
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 103

Arg His Tyr Leu Asn Ile Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 104
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 104

Arg His Tyr Leu Asn Ile Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 105
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 105

Arg His Tyr Leu Asn Ile Val Ser Arg Gln Arg Tyr
1 5 10

<210> 106
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 106

Arg His Tyr Leu Asn Ile Val Thr Lys Gln Arg Tyr
1 5 10

<210> 107
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 107

Arg His Tyr Leu Asn Ile Val Thr Arg Asn Arg Tyr
1 5 10

<210> 108
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 108

Arg His Tyr Leu Asn Ile Val Thr Arg Gln Lys Tyr
1 5 10

<210> 109

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 109

Arg His Tyr Leu Asn Ile Val Thr Arg Gln Arg Thr
1 5 10

<210> 110
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 110

Arg His Tyr Leu Asn Ile Val Thr Arg Gln Arg Phe
1 5 10

<210> 111
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 111
Arg His Tyr Leu Asn Val Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 112
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 112

Arg His Tyr Leu Asn Val Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 113
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 113

Arg His Tyr Leu Asn Val Val Ser Arg Gln Arg Tyr
1 5 10

<210> 114
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 114

Arg His Tyr Leu Asn Val Val Thr Lys Gln Arg Tyr
1 5 10

<210> 115
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 115

Arg His Tyr Leu Asn Val Val Thr Arg Asn Arg Tyr
1 5 10

<210> 116
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 116

Arg His Tyr Leu Asn Val Val Thr Arg Gln Lys Tyr
1 5 10

<210> 117
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 117

Arg His Tyr Leu Asn Val Val Thr Arg Gln Arg Thr
1 5 10

<210> 118
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 118

Arg His Tyr Leu Asn Val Val Thr Arg Gln Arg Phe
1 5 10

<210> 119
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 119

Arg His Tyr Leu Asn Leu Ile Ser Arg Gln Arg Tyr
1 5 10

<210> 120
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 120

Arg His Tyr Leu Asn Leu Ile Thr Lys Gln Arg Tyr
1 5 10

<210> 121
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 121

Arg His Tyr Leu Asn Leu Ile Thr Arg Asn Arg Tyr
1 5 10

<210> 122
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 122

Arg His Tyr Leu Asn Leu Ile Thr Arg Gln Lys Tyr
1 5 10

<210> 123
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 123

Arg His Tyr Leu Asn Leu Ile Thr Arg Gln Arg Thr
1 5 10

<210> 124
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 124

Arg His Tyr Leu Asn Leu Ile Thr Arg Gln Arg Phe
1 5 10

<210> 125
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 125

Arg His Tyr Leu Asn Leu Leu Ser Arg Gln Arg Tyr
1 5 10

<210> 126
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 126

Arg His Tyr Leu Asn Leu Leu Thr Lys Gln Arg Tyr
1 5 10

<210> 127
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 127

Arg His Tyr Leu Asn Leu Leu Thr Arg Asn Arg Tyr
1 5 10

<210> 128
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 128

Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Lys Tyr
1 5 10

<210> 129
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 129

Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Thr
1 5 10

<210> 130
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 130

Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Phe
1 5 10

<210> 131
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 131

Arg His Tyr Leu Asn Leu Val Ser Lys Gln Arg Tyr
1 5 10

<210> 132
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 132

Arg His Tyr Leu Asn Leu Val Ser Arg Asn Arg Tyr
1 5 10

<210> 133
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> Polypeptide variation

<400> 133

Arg His Tyr Leu Asn Leu Val Ser Arg Gln Lys Tyr
1 5 10

<210> 134
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 134

Arg His Tyr Leu Asn Leu Val Ser Arg Gln Arg Thr
1 5 10

<210> 135
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 135

Arg His Tyr Leu Asn Leu Val Ser Arg Gln Arg Tyr
1 5 10

<210> 136
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 136

Arg His Tyr Leu Asn Leu Val Thr Lys Asn Arg Tyr
1 5 10

<210> 137
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 137

Arg His Tyr Leu Asn Leu Val Thr Lys Gln Lys Tyr
1 5 10

<210> 138
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 138

Arg His Tyr Leu Asn Leu Val Thr Lys Gln Arg Thr
1 5 10

<210> 139
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 139

Arg His Tyr Leu Asn Leu Val Thr Lys Gln Arg Phe
1 5 10

<210> 140
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 140

Arg His Tyr Leu Asn Leu Val Thr Arg Asn Lys Tyr
1 5 10

<210> 141
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 141

Arg His Tyr Leu Asn Leu Val Thr Arg Asn Arg Thr
1 5 10

<210> 142
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 142

Arg His Tyr Leu Asn Leu Val Thr Arg Asn Arg Phe
1 5 10

<210> 143
<211> 12

<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 143

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Lys Thr
1 5 10

<210> 144
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 144

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Lys Phe
1 5 10

<210> 145
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 145

Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 146
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 146
Ile Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 147
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 147

Val Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 148

<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 148

Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 149
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 149

Thr Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 150
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 150

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 151
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 151

Ser Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 152
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 152

Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 153
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 153

Thr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 154
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 154

Phe Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 155
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 155

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
1 5 10 15

Tyr

<210> 156
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 156

Thr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
1 5 10 15

Tyr

<210> 157
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 157

Phe Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
1 5 10 15

Tyr

<210> 158
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 158

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
1 5 10 15

Arg Tyr

<210> 159
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 159

Lys Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
1 5 10 15

Arg Tyr

<210> 160
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 160

Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 161
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 161

Gln Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg

1 5 10 15

Gln Arg Tyr

<210> 162
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 162

Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 163
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 163

Ile Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 164
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 164

Val Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 165
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 165

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
1 5 10 15

Thr Arg Gln Arg Tyr
20

<210> 166
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 166

Asp Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val
1 5 10 15

Thr Arg Gln Arg Tyr
20

<210> 167
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 167

Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu
1 5 10 15

Val Thr Arg Gln Arg Tyr
20

<210> 168
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 168

Asp Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu
1 5 10 15

Val Thr Arg Gln Arg Tyr
20

<210> 169
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 169

Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn
1 5 10 15

Leu Val Thr Arg Gln Arg Tyr
20

<210> 170
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 170

Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu
1 5 10 15

Asn Leu Val Thr Arg Gln Arg Tyr
20

<210> 171
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 171

Thr Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu
1 5 10 15

Asn Leu Val Thr Arg Gln Arg Tyr
20

<210> 172
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 172

Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr
1 5 10 15

Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 173
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 173

Ser Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His Tyr
1 5 10 15

Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 174
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 174

Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
1 5 10 15

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 175
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 175

Glu Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg His
1 5 10 15

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 176
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 176

Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg
1 5 10 15

His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 177
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 177

Asp Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Arg
1 5 10 15

His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 178
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 178

Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu
1 5 10 15

Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 179
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 179

Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser
1 5 10 15

Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 180
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 180

Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala
1 5 10 15

Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 181
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 181

Ser Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala
1 5 10 15

Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 182
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 182

Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr
1 5 10 15

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 183
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 183

Asp Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr
1 5 10 15

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 184
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 184

Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr
1 5 10 15

Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 185
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 185

Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 186
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 186

Arg Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 187
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 187

Gln Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 188
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 188

Asn Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 189
<211> 34

<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 189

Leu Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
1 5 10 15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 190
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 190

Val Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
1 5 10 15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 191
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 191

Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 192
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 192

Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 193
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 193

Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 194
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 194

Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 195
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 195

Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg
1 5 10 15

Tyr

<210> 196
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 196

Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln
1 5 10 15

Arg Tyr

<210> 197
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 197

Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 198
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 198

Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 199
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 199

Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val
1 5 10 15

Thr Arg Gln Arg Tyr
20

<210> 200
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 200

Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu
1 5 10 15

Val Thr Arg Gln Arg Tyr
20

<210> 201
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 201

Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn
1 5 10 15

Leu Val Thr Arg Gln Arg Tyr
20

<210> 202
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 202

Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn
1 5 10 15

Leu Val Thr Arg Gln Arg Tyr
20

<210> 203
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 203

Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr Leu
1 5 10 15

Asn Leu Val Thr Arg Gln Arg Tyr
20

<210> 204
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 204

Asp Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His Tyr
1 5 10 15

Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 205
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 205

Glu Asp Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu Lys His
1 5 10 15

Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 206
<211> 28
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 206

Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser Leu
1 5 10 15

Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 207
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 207

Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr Tyr Ala Ser
1 5 10 15

Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 208
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 208

Ala Pro Gly Glu Asp Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala Ser
1 5 10 15

Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25

<210> 209
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 209

Glu Ala Pro Gly Glu Asp Ala Ser Glu Glu Leu Asn Arg Tyr Tyr Ala
1 5 10 15

Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 210
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 210

Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn Arg Tyr
1 5 10 15

Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 211
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 211

Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Glu Glu Leu Asn Arg Tyr
1 5 10 15

Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
20 25 30

<210> 212
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 212

Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Glu Glu Leu Asn Arg
1 5 10 15

Tyr Tyr Ala Ser Leu Lys His Tyr Leu Asn Leu Val Thr Arg Gln Arg
20 25 30

Tyr

<210> 213
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)

<223> ACETYLATION

<400> 213

Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 214
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> ACETYLATION

<400> 214

Leu Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 215
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 215

Leu Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 216
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 216

Pro Ala Glu Asp Leu Ala Gln Tyr Ala Ala Glu Leu Arg His Tyr Leu
1 5 10 15

Asn Leu Leu Thr Arg Gln Arg Tyr
20

<210> 217
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE

<222> (1)..(1)
<223> H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 217

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 218
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 218

Met Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 219
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 219

Ala Arg Tyr Tyr Ser Ala Leu Arg His Phe Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 220
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> D Ala

<220>
<221> MOD_RES
<222> (1)..(1)
<223> ACETYLATION

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 220

Xaa Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 221
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (18)..(18)
<223> AMIDATION

<400> 221

Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln
1 5 10 15

Arg Tyr

<210> 222
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 222

Xaa Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 223
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> D Ser

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 223

Xaa Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 224
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 224

Ala Ala Arg Tyr Ser His Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 225
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> D Ile

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 225

Xaa Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 226
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (1)..(1)
<223> ACETYLATION

<400> 226

Arg Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 227
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (18)..(18)
<223> AMIDATION

<400> 227

Gln Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln
1 5 10 15

Arg Tyr

<210> 228
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 228

Ala Arg Phe Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 229
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)

<223> MeLeu

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 229

Xaa Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 230
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (1)..(1)
<223> METHYLATION

<400> 230

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 231
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> desamino

<220>
<221> MOD_RES

<222> (19)..(19)
<223> AMIDATION

<400> 231

Xaa Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 232
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (1)..(1)
<223> FORMYLATION

<400> 232

Ala Arg Tyr Tyr Ser Glu Leu Arg Arg Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 233
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nva

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 233

Xaa Ala Arg Tyr Ala Ser Ala Leu Arg His Tyr Leu Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 234
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 234

Ala Arg Tyr Tyr Thr Gln Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 235
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> desamino

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 235

Leu Ala Arg Tyr Tyr Ser Asn Leu Arg His Tyr Ile Asn Val Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 236
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 236

Ala Arg Tyr Tyr Asp Ser Leu Arg His Tyr Ile Asn Thr Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 237
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 237

Ala Arg Tyr Tyr Ser Ala Leu Gln His Tyr Ile Asn Leu Leu Thr Arg
1 5 10 15

Pro Arg Tyr

<210> 238
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 238

Leu Ala Arg Tyr Tyr Ser Ala Leu Arg Gln Tyr Arg Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Phe

<210> 239
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (18)..(18)
<223> AMIDATION

<400> 239

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
1 5 10 15

Arg Phe

<210> 240
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 240

Ser Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 241
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> ACETYLATION

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 241

Ser Arg Tyr Tyr Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 242
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> Nle

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 242

Xaa Ala Arg Tyr Tyr Asn Ala Leu Arg His Phe Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 243
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> D isomer of Ala

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 243

Xaa Arg Tyr Glu Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

His Arg Tyr

<210> 244
<211> 21
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (21)..(21)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Bz

<400> 244

Xaa Leu Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile
1 5 10 15

Thr Arg Pro Arg Phe
20

<210> 245
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 245

Ala Leu Tyr Tyr Ser Ala Leu Arg His Phe Val Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 246
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> D Ala

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 246

Xaa Arg Tyr Tyr Ser Ala Leu Arg His Tyr Val Asn Leu Ile Phe Arg
1 5 10 15

Gln Arg Tyr

<210> 247
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> MeSer

<220>
<221> MOD_RES
<222> (18)..(18)
<223> AMIDATION

<400> 247

Xaa Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Met Ile Thr Arg Gln
1 5 10 15

Arg Phe

<210> 248
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 248

Arg Ile Arg Tyr Tyr Ser Ala Leu Arg His Phe Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Phe
20

<210> 249
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminal is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 249

Leu Ser Arg Tyr Tyr Ser Ala Leu Arg His Phe Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 250
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is MeIle

<400> 250

Xaa Arg Tyr Tyr Ser Ala Leu Gln His Phe Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 251
<211> 19
<212> PRT
<213> Artificial Sequence

<220>

<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> D Ser

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)
<223> AMIDATION

<400> 251

Xaa Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg
1 5 10 15

Gln Arg Phe

<210> 252
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 252

Met Ala Arg Tyr Tyr Ser Asp Leu Arg Arg Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 253
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MOD_RES
<222> (19)..(19)

<223> AMIDATION

<400> 253

Ala Arg Tyr Tyr Ser Glu Leu Arg His Tyr Ile Ile Leu Ile Thr Arg
1 5 10 15

Gln Arg Tyr

<210> 254
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> D Ala

<220>
<221> MOD_RES
<222> (20)..(20)
<223> AMIDATION

<400> 254

Xaa Ala Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr
1 5 10 15

Arg Gln Arg Tyr
20

<210> 255
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 255

Ala Ser Leu Arg His Trp Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 256
<211> 35
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (25)..(25)
<223> im DNP HIS; 2,2 diphenylalanine Hisitidine

<220>
<221> MOD_RES
<222> (35)..(35)
<223> AMIDATION

<400> 256

Tyr Pro Ala Lys Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu
1 5 10 15

Ser Thr Tyr Tyr Ala Ser Leu Arg Xaa Tyr Leu Asn Leu Val Thr Arg
20 25 30

Glx Arg Tyr
35

<210> 257
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 257

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 258
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 258

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Ala Arg Gln Arg Tyr
1 5 10 15

<210> 259
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation
<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 259

Ala Ala Leu Arg His Tyr Leu Asn Leu Val Ala Arg Gln Arg Tyr
1 5 10 15

<210> 260
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 260

Ala Ser Leu Arg His Tyr Glu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 261
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa is Ornithine

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 261

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Xaa Arg Tyr
1 5 10 15

<210> 262
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is p.Cl.Pro; 4 chlorophenylalanine

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>

<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 262

Ala Ser Leu Arg Xaa Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 263
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 263

Ala Ser Leu Arg His Tyr Glu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 264
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is N Me Tyr

<400> 264

Ala Ser Leu Arg His Phe Glu Asn Leu Val Thr Arg Gln Arg Xaa
1 5 10 15

<210> 265
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa is Ornithine

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is N Me Tyr

<400> 265

Ala Ser Leu Arg His Tyr Glu Asn Leu Val Thr Arg Xaa Arg Xaa
1 5 10 15

<210> 266
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> LIPID
<222> (1)..(1)
<223> N alpha myristoyl

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 266

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 267
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N alpha naphthateneacetyl

<220>
<221> MOD_RES

<222> (15)..(15)
<223> AMIDATION

<400> 267

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 268
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is N Me Tyr

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa is Ornithine

<400> 268

Ala Ser Leu Arg His Phe Glu Asn Leu Val Thr Arg Xaa Arg Xaa
1 5 10 15

<210> 269
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 269

Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 270

<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 3 benzothienyalanine

<220>
<221> MOD_RES
<222> (7)..(7)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<400> 270

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 271
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is 4,4' biphenylalanine

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (16)..(16)
<223> AMIDATION

<400> 271

Xaa Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 272
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)

<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 3 benzothienyalanine

<400> 272

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 273
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 3 benzothienyalanine

<400> 273

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 274
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 274

Ala Ser Leu Arg His Trp Leu Asn Leu Val Thr Arg Gln Arg Tyr

1 5 10 15

<210> 275
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 275

Ala Ser Leu Arg His Trp Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 276
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 2 thienylalanine

<400> 276

Ala Ser Leu Arg Asn Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 277
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)

<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is tetrahydroisoquinoline

<400> 277

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 278
<211> 3
<212> PRT
<213> Homo sapiens

<400> 278

000
1

<210> 279
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (11)..(11)
<223> AMIDATION

<400> 279

His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 280
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MOD_RES

<222> (1)..(1)
<223> ACETYLATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is 2 thienylalanine

<400> 280

Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Xaa
1 5 10 15

<210> 281
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (16)..(16)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 4 Thiazolylalanine

<400> 281

Ala Ser Leu Arg His Xaa Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 282
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (16)..(16)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 4 Thiazolylalanine

<400> 282

Ala Ser Leu Arg His Xaa Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 283
<211> 3
<212> PRT
<213> Homo sapiens

<400> 283

000
1

<210> 284
<211> 3
<212> PRT
<213> Homo sapiens

<400> 284

000
1

<210> 285
<211> 3
<212> PRT
<213> Homo sapiens

<400> 285

000
1

<210> 286
<211> 3
<212> PRT
<213> Homo sapiens

<400> 286

000
1

<210> 287
<211> 3
<212> PRT
<213> Homo sapiens

<400> 287

000
1

<210> 288
<211> 3
<212> PRT
<213> Homo sapiens

<400> 288

000

1

<210> 289
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 289

Phe Ser Leu Arg Asn Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 290
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 290

Tyr Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 291
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 291

Ala Ser Leu Arg His Tyr Trp Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 292
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 292

Ala Ser Leu Arg His Tyr Leu Asn Trp Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 293
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 293

Ala Ser Leu Arg Ala Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 294
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (14)..(14)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is 3' benzothienyalanine

<400> 294

Ala Ser Leu Arg Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 295
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 295

Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 296
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 296

Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Phe
1 5 10 15

<210> 297
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa is D form of Trp

<220>
<221> MOD_RES
<222> (11)..(11)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (11)..(11)
<223> N alpha ACETYLATION

<400> 297

Ala Ser Leu Arg His Phe Leu Asn Leu Val Xaa Arg Gln Arg Tyr
1 5 10 15

<210> 298
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (13)..(13)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to CH3CO

<400> 298

Leu Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 299
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (13)..(13)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to CH3CO

<400> 299

Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 300
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (13)..(13)
<223> AMIDATION

<400> 300

Leu Arg His Tyr Leu Asn Leu Leu Thr Arg Gln Arg Tyr
1 5 10

<210> 301
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (13)..(13)
<223> AMIDATION

<400> 301

Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln Arg Tyr
1 5 10

<210> 302
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES

<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Norleucine

<400> 302

Ala Ser Xaa Arg His Trp Xaa Asn Xaa Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 303
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>

<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 303

Ala Ser Xaa Arg His Trp Xaa Asn Trp Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 304
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 304

Ala Ser Xaa Arg His Phe Xaa Asn Xaa Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 305
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 305

Ala Ser Xaa Arg His Phe Xaa Asn Trp Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 306
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (12)..(12)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH

<400> 306

Arg His Tyr Leu Asn Trp Val Thr Arg Gln Xaa Xaa
1 5 10

<210> 307
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (12)..(12)
<223> AMIDATION

<400> 307

Arg His Tyr Leu Asn Trp Val Thr Arg Gln Arg Tyr
1 5 10

<210> 308
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a psuedopeptide bond consisting of CH2 NH2

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a psuedopeptide bond consisting of CH2 NH2

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 308

Ala Ser Leu Arg His Tyr Xaa Asn Trp Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 309
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<220>
<221> MISC_FEATURE
<222> (15)..(15)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH2

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is a pseudopeptide bond consisting of CH2 NH2

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Norleucine

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Norvaline

<400> 309

Ala Ser Xaa Arg His Tyr Xaa Asn Trp Xaa Thr Arg Gln Xaa Xaa
1 5 10 15

<210> 310
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> bonded to OCH3

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<400> 310

Ile Asn Pro Ile Tyr Arg Leu Arg Tyr
1 5

<210> 311
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> DISULFID
<222> (4)..(4)
<223> Sequence is linked to identical sequence by a disulfide bond

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> C terminus is bonded to NH2

<400> 311

Ile Asn Pro Cys Tyr Arg Leu Arg Tyr
1 5

<210> 312
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> C terminus is bonded to OCH3

<220>
<221> DISULFID
<222> (1)..(1)
<223> sequence is linked to an identical sequence

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<400> 312

Cys Tyr Arg Leu Arg Tyr
1 5

<210> 313
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (3)..(4)
<223> Connected by NH CH CO

<220>
<221> MISC_FEATURE
<222> (3)..(4)
<223> Identical peptide chains are connected by (CH2)4 at the CH o
f NH CH CO

<400> 313

Ile Asn Pro Tyr Arg Leu Arg Tyr
1 5

<210> 314
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminus is bonded to H

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> C terminus is bonded to OCH3

<400> 314

Tyr Arg Leu Arg Tyr Tyr Arg Leu Arg Tyr
1 5 10

<210> 315
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> DISULFID
<222> (18)..(22)
<223>

<400> 315

Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp Met Ala
1 5 10 15

Arg Cys Tyr Ser Ala Cys Arg His Tyr Ile Asn Leu Ile Thr Arg Gln
20 25 30

Arg Tyr

<210> 316
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 316

Arg His Tyr Leu Asn Leu Ile Gly Arg Gln Arg Tyr
1 5 10

<210> 317
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (3)..(7)
<223> ACETYLATION

<400> 317

Arg His Gly Leu Asn Leu Leu Gly Arg Gln Arg Tyr
1 5 10

<210> 318
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 318

Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10

<210> 319
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 319

His Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10

<210> 320
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 320

Arg His Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10

<210> 321
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 321

Tyr Ile Asn Leu Leu Tyr Arg Gln Arg Tyr
1 5 10

<210> 322
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is 6 amino hexanoic acid

<400> 322

Tyr Pro Ser Leu Xaa Tyr Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5 10 15

<210> 323
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 323

Ile Asn Leu Ile Tyr Arg Leu Arg Tyr
1 5

<210> 324
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (12)..(12)
<223> AMIDATION

<400> 324

Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10

<210> 325
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 325

Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 326
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> N terminal is bonded to H

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 326

Ala Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 327
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (9)..(9)
<223> AMIDATION

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<400> 327

Ala Ser Leu Arg Thr Arg Gln Arg Tyr
1 5

<210> 328
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is 2 thienylalanine

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 328

Ala Ser Leu Arg His Xaa Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 329
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<220>
<221> MOD_RES
<222> (1)..(1)
<223> N alpha ACETYLATION

<220>
<221> MOD_RES
<222> (15)..(15)
<223> AMIDATION

<400> 329

Tyr Ser Leu Arg His Phe Leu Asn Leu Val Thr Arg Gln Arg Tyr
1 5 10 15

<210> 330
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 330

Asp Asp Asp Asp Tyr
1 5

<210> 331
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 331

Gly Pro Arg
1

<210> 332
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 332

Ala Gly Gly
1

<210> 333

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 333

His Pro Phe His Leu
1 5

<210> 334
<211> 34
<212> PRT
<213> Homo sapiens

<400> 334

Ile Lys Pro Glu Ala Pro Gly Glu Asp Ala Ser Pro Glu Glu Leu Asn
1 5 10 15

Arg Tyr Tyr Ala Ser Leu Arg His Tyr Leu Asn Leu Val Thr Arg Gln
20 25 30

Arg Tyr

<210> 335
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> Polypeptide variation

<400> 335

Ser Lys Pro Asp Asn Pro Gly Glu Asp Ala Pro Ala Glu Asp Met Ala
1 5 10 15

Arg Tyr Tyr Ser Ala Leu Arg His Tyr Ile Asn Leu Ile Thr Arg Gln
20 25 30

Arg Tyr