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(54) Title: NOVEL COMPOUNDS

(57) Abstract: The invention provides novel compounds which are peptide hormone analogues, and which are useful in treating disorders such as diabetes and obesity. The compounds of the general sequence recited in the specification possess a tailored profile with regards to potency properties at the glucagon and GLP-1 receptors. With regard to in vivo properties, administration of example peptides of the invention have been shown, in animal models, to result in increased weight loss. Preferred compounds achieve this without reducing food intake significantly.

Novel Compounds

Field of the Invention

The present disclosure relates to compounds which are peptide hormone analogues, and which are useful in treating disorders such as diabetes and obesity.

Background

According to the National Health and Nutrition Examination Survey (NHANES, 2009–2010), 33.0% of adults in the United States aged 20 and over are overweight, 35.7% are obese, and 6.3% are extremely 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).

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 (type 1 diabetes) and non-insulin

dependent diabetes mellitus (type 2 diabetes). Diabetes type 1, or insulin dependent diabetes mellitus (IDDM) is caused by the destruction of β cells, which results in insufficient levels of endogenous insulin. Diabetes type 2, or non-insulin dependent diabetes, results from a defect in both the body's sensitivity to insulin, and a relative deficiency in insulin production. According to the National Diabetes Statistics Report, 2014 around 28.9 million adults in the United States aged 20 and over have diabetes (2009–2012 National Health and Nutrition Examination Survey estimates applied to 2012 U.S. Census data). In adults 90 to 95% of the diabetes is type 2 diabetes.

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. It has been shown that considerable weight loss can effectively cure type 2 diabetes (Lim *et al.*, *Diabetologia* June 2011).

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 as well as in subjects who are of normal weight.

A number of approaches to the development of agents useful in effecting weight loss have involved gastrointestinal peptide hormones and their analogues. For example, derivatives of peptides deriving from the preproglucagon molecule have been proposed for use in treatment of obesity and/or diabetes. Preproglucagon is a precursor peptide of glucagon-like peptide 1 (GLP-1), as well as other hormones including glucagon GLP-1 is produced *in vivo* in the intestinal L cell in response to the presence of nutrients in the lumen of the gut. GLP-1 possesses a number of physiological functions including increasing insulin secretion from the pancreas in a glucose-dependent manner, decreasing glucagon secretion from the pancreas, inhibiting gastric emptying and decreasing food intake by increasing satiety. Increased insulin secretion leads to a decrease in circulating glucose concentration.

Examples of research into analogues of such peptides are described in, for example, WO2013/004983 which describes peptide molecules containing sequence from both the GLP-1 and glucagon peptides. WO2015/132599 also discloses peptide hormone analogues, which are derivable from preproglucagon and which are useful in the therapy of disorders such as obesity and diabetes. WO2017/178829 discloses compounds that are analogues of exendin-4, GLP-1 and oxyntomodulin which have a modified ligand bias and therapeutically useful characteristics. Another example is the peptide liraglutide, a GLP-1 agonist which has the sequence of GLP-1(7-37) with an arginine residue substituted for the native lysine at position 34, and with the sidechain of the lysine residue at position 26 being acylated by a hexadecanoyl group(palmitic acid) attached to the lysine though a glutamic acid spacer. Liraglutide has been developed for use as a once daily injectable drug for the treatment of type II diabetes. The same active ingredient as in liraglutide is marketed as Saxenda for the treatment of obesity (once daily injection). Semaglutide, a once weekly injectable analogue of GLP-1, has two amino acid substitutions compared to human GLP-1 (AIB8, Arg34) and is derivatized at lysine 26 with a linker and a C_{18} diacid fatty acid.

However, despite significant advances, the process of identifying substances useful as drugs remains a complex and, in many cases, unpredictable field. In order to be useful as therapeutic agents, compounds must possess a suitable range of properties. In

addition to having good efficacy at the biological target of interest, compounds must have good *in vivo* pharmacokinetic properties, low toxicity and an acceptable side effect profile. For example, even with commercial agents such as liraglutide, side effects can include nausea and vomiting, and concerns have also been raised with regard to thyroid cancer and pancreatitis.

Thus, there remains a need for further compounds which are useful for the treatment of disorders and diseases such as diabetes and obesity. For example, it would be desirable to identify peptides having beneficial properties such as an improved activity profile, and/or which have reduced side effects. For example, it would be desirable for a peptide to be identified that reduces appetite and/or reduces food intake. Alternatively, or additionally, it would be desirable for a peptide to be identified that has these and other biological effects (for example the therapeutically useful biological effects described herein) for a sustained period. A compound that has a longer period of activity can be administered less frequently and at lower dose, which contributes to improved convenience for the subject, to fewer side effects and to lower cost.

Summary of the Invention

In a first aspect there is provided a compound of Formula (I):

Xaa1-AIB2-Xaa3-Gly4-Thr5-Phe6-Thr7-Ser8-Asp9-Xaa10-Ser11-Lys12-Gln13-Leu14-Glu15-Glu16-Xaa17-Xaa18-Val19-Xaa20-Xaa21-Phe22-Ile23-Glu24-Trp25-Leu26-Lys27-Xaa28-Xaa29-Gly30-Pro31-Ser32-Xaa33-Gly34-Xaa35-Xaa36-Pro37-Pro38-Xaa39-Xaa40-Xaa41-Lys42 (I) [SEQ ID NO: 528]

wherein:

Xaa1 is His, Tyr or Phe;

Xaa3 is His, Gln or Glu;

Xaa10 is Leu, Tyr or Val;

Xaa17 is Glu or Lys;

Xaa18 is Ala or Arg;

Xaa20 is Arg, Gln, Lys or His;

Xaa21 is Leu, Ala, Arg, Lys or Glu;

Xaa28 is Ala, Asn, Gln or His;

Xaa29 is Gly or Ala;

Xaa33 is Ser, His or Gln;

Xaa35 is Lys, Pro, His, Arg, Asn, Gln, Glu, Ser or Ala;

Xaa36 is Phe, His, Gln, Glu, Lys, Ser, Arg or absent

Xaa39 is Pro or Gly;

Xaa40 is Gly or absent;

Xaa41 is Lys or absent;

and the lysine residue at position 42 is substituted at its ε-amino group with a group Y and Y is:

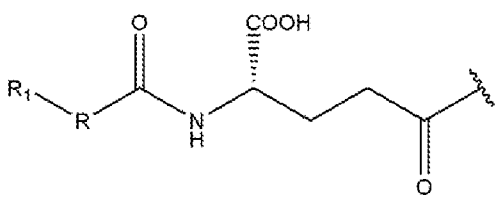
Z-Xaa43-Xaa44-

wherein:

Xaa43 is Asn or absent;

Xaa44 is His or absent;

and Z is a group of formula:



wherein R is a C_{16}–C_{18} alkylene or alkenylene group; and

R^1 is CO_2H;

or a derivative of the compound; or a salt or solvate of the compound or the derivative.

Also provided herein is a composition comprising a compound, derivative, salt or solvate of the invention together with a pharmaceutically acceptable carrier and optionally a further therapeutic agent.

Also provided herein is a compound, derivative, salt or solvate of the invention, or a composition comprising such a compound, derivative, salt or solvate and a pharmaceutically acceptable carrier, for use as a medicament, e.g. for use in the prevention or treatment of diabetes, obesity, heart disease, stroke or non-alcoholic fatty liver disease, improving insulin release in a subject, improving carbohydrate metabolism in a subject, improving the lipid profile of a subject, reducing appetite, reducing food intake, reducing calorie intake, improving carbohydrate tolerance in a subject, and/or for use as a cytoprotective agent, for example in the prevention or treatment of Parkinsonism, Alzheimer's disease and other types of neural and cellular degeneration.

Also provided herein is a method of treating or preventing a disease or disorder or other non-desired physiological state in a subject comprising administration of a therapeutically effective amount of a compound, derivative, salt or solvate of the invention, or of a composition comprising such a compound, derivative, salt or solvate and a pharmaceutically acceptable carrier, e.g. in a method of treating or preventing diabetes, obesity, heart disease, stroke or non-alcoholic fatty liver disease in a subject, improving insulin release in a subject, improving carbohydrate metabolism in a subject, improving the lipid profile of a subject, improving carbohydrate tolerance in a subject, reducing appetite, reducing food intake, reducing calorie intake, and/or providing cytoprotection in a subject.

Also provided herein is a use of a compound, derivative, salt or solvate of the invention for the manufacture of a medicament for the prevention or treatment of diabetes, obesity, heart disease, stroke or non-alcoholic fatty liver disease, improving insulin release in a subject, improving carbohydrate metabolism in a subject, improving the lipid

profile of a subject, improving carbohydrate tolerance in a subject, reducing appetite, reducing food intake, reducing calorie intake, and/or for use as a cytoprotective agent, for example in the prevention or treatment of Parkinsonism, Alzheimer's disease and other types of neural and cellular degeneration.

Also provided herein is a method of causing weight loss or preventing weight gain in a subject for cosmetic purposes comprising administration of an effective amount of a compound, derivative, salt or solvate of the invention.

Brief Description of the Drawings

Figure 1 shows the amino acid sequences of example compounds of the invention. The compounds are presented with the N-terminal residue at the left-hand side of the table (signified by the column titled "1"). The amino acid sequence for each compound is set out over two horizontal pages. Results of feeding and receptor binding experiments are shown in the far right hand columns.

Sequences

The amino acid sequences herein are shown with the N-terminus to the left, and where sequences are set out across multiple lines, the N-terminus is to the top left. Unless indicated otherwise, the amino acid residues in the sequences are L-amino acids.

The amino acid sequences listed in the application are shown using standard letter abbreviations for amino acids. The unnatural amino acid 2-aminoisobutyric acid has its usual abbreviation 'AIB'.

The specific sequences given herein relate to specific embodiments of the invention.

Detailed Description

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

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

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 behaviour.

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.

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 metres^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 (which is sometimes referred to as being "overweight" rather than 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.

Cardioprotection refers to the protection of cardiac cells (and especially the myocardial cells) from apoptosis, necrotic cell death or degeneration (loss of function). Cardioprotection is most often required following myocardial infarction, but may also be used in subjects suffering from ischemic heart disease (for example angina)

Cytoprotection refers to the protection of cells from apoptosis, necrotic cell death or degeneration (loss of function).

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.

Energy Metabolism: The body has to expend a certain amount of energy to maintain normal metabolism. In civilized man this is often set at about 2,800 Calories daily. If food consumption does not provide this, weight loss results. However, energy metabolism is also regulated, and, for example, administration of glucagon is thought to increase the metabolic rate so that a greater food intake is required to achieve energy balance and maintain weight. Thus, if food intake is maintained at the usual level, but energy metabolism is increased, weight loss will result.

Food intake: The amount of food consumed by an individual. Food intake can be measured by volume or by weight. For example, food intake may be the total amount of food consumed by an individual. In a feeding experiment, 'Food Intake' is the weight of a standardised chow consumed by an animal in a 24 hour period. Or, food intake may be 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.

GLP-1: Glucagon-like peptide 1 (GLP-1) is derived from the transcription product of the proglucagon gene. The biologically active forms of GLP-1 are truncated forms known as $GLP\text{-}1_{(7\text{-}37)}$ and $GLP\text{-}1_{(7\text{-}36)}\text{-}NH_2$ (the designation $\text{-}NH_2$ designates an amino acid

sequence in which the C-terminal amino acid has a $-C(O)NH_2$ group in place of a carboxylic acid group).

The sequence of human $GLP\text{-}1_{(7\text{-}37)}$ is His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-Gly. [SEQ ID NO: 529]

The sequence of human $GLP\text{-}1_{(7\text{-}36)}\text{-}NH_2$ is His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg—$CONH_2$. [SEQ ID NO: 530]

Glucagon: Glucagon is a peptide derived from the proglucagon gene. It is a 29-amino acid polypeptide in humans and has the sequence: His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr. [SEQ ID NO:531]

Neuroprotection refers to the protection of neurons within the nervous system (preferably within the central nervous system) from apoptosis, necrotic cell death or degeneration (loss of function). Neuroprotective treatments, including those relating to various aspects of the present invention may be required following a brain injury (for example those following physical trauma or non-traumatic injury such as stroke, brain tumours, infection, poisoning, hypoxia, ischemia, encephalopathy or substance abuse). Neuroprotective treatments, including those relating to various aspects of the present invention may also be indicated in subjects having a chronic neurodegenerative disease such as Alzheimer's disease, Parkinson's disease, Gehrig's disease or Huntington's disease.

Normal Daily Diet: The average food intake for an individual of a given species. A normal daily diet can be expressed in terms of caloric intake, protein intake, carbohydrate intake, and/or fat intake. A normal daily diet in humans generally comprises the following: about 2,000, about 2,400, or about 2,800 to significantly more calories. In addition, a normal daily diet in humans generally includes about 12 g to about 45 g of protein, about 120 g to about 610 g of carbohydrate, and about 11 g to

about 90 g of fat. A low calorie diet would be no more than about 85%, and preferably no more than about 70%, of the normal caloric intake of a human individual.

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

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

In another convention, waist circumference is used to assess obesity. In this convention, 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. For example, an overweight individual is any individual who desires to decrease their weight. In one

convention, an overweight individual is an individual with a BMI of 25.0 kg/m^2 to 29.9 kg/m^2.

Oxyntomodulin (OXM): Oxyntomodulin is a 37 amino acid peptide member of the glucagon superfamily comprising the entire 29 amino acid sequence of glucagon, with an eight amino acid carboxy terminal extension, resulting from the tissue-specific processing of the pre-pro-glucagon precursor in the brain and gut. The human OXM sequence is as follows:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala. [SEQ ID NO: 532]

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

pI: pI is an abbreviation for isoelectric point. An alternative abbreviation sometimes used is IEP. It is the pH at which a particular molecule carries no net electric charge. At a pH below its pI a protein or peptide carries a net positive charge. At a pH above its pI a protein or peptide carries a net negative charge. Proteins and peptides can be separated according to their isoelectric points using a technique called isoelectric focusing which is an electrophoretic method that utilises a pH gradient contained within a polyacrylamide gel.

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. Unless dictated otherwise by context, the terms "polypeptide", “peptide”, or “protein” as used herein encompass any amino acid sequence and include modified sequences such as glycoproteins. The term “polypeptide” covers naturally occurring proteins, as well as those which are recombinantly or synthetically produced. The term “polypeptide fragment” refers to a portion of a polypeptide, for example 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.

Subcutaneous administration: Subcutaneous administration is administration of a substance to the subcutaneous layer of fat which is found between the dermis of the skin and the underlying tissue. Subcutaneous administration may be by an injection using a hypodermic needle fitted, for example, to a syringe or a “pen” type injection device. Other administration methods may be used for example microneedles. Injection with a hypodermic needle typically involves a degree of pain on behalf of the recipient. Such pain may be masked by use of a local anaesthetic or analgesic. However, the usual method used to reduce the perceived pain of injections is to merely distract the subject immediately prior to and during the injection. Pain may be minimised by using a relatively small gauge hypodermic needle, by injecting a relatively small volume of substance and by avoiding excessively acidic or alkali compositions which may cause the subject to experience a “stinging” sensation at the injection site. Compositions having a pH of between pH 4 and pH 10 are usually regarded as tolerably comfortable.

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 some embodiments, a therapeutically effective amount of a compound of the invention is an amount sufficient to inhibit or halt weight gain, or an amount sufficient to decrease appetite.

Compounds of the invention

The present inventors have found that example compounds of the invention have properties including causing weight loss *in vivo*. The compounds also have a long half-life in the blood, meaning that they can be administered at a conveniently low frequency. In these respects, the compounds of the invention have an improved profile in comparison to the known compound semaglutide.

Compared with GLP-1 and derivatives of GLP-1 that have gone before, the compounds of the invention are extended at the C-terminus with particular residues, including that there is a lysine residue at position 42 and including that that lysine residue is functionalised in a particular way, to include the group R-R^1 where R^1 is CO_2H. These are functionalisations that have not previously been investigated and the beneficial properties found by the current inventors have not previously been seen.

As described above, compounds of the invention have Formula (I):

Xaa1- AIB2- Xaa3-Gly4-Thr5-Phe6-Thr7-Ser8-Asp9-Xaa10-Ser11- Lys12- Gln13-Leu14- Glu15- Glu16-Xaa17-Xaa18-Val19-Xaa20-Xaa21-Phe22- Ile23- Glu24-Trp25-Leu26- Lys27-Xaa28-Xaa29-Gly30-Pro31-Ser32-Xaa33-Gly34-Xaa35-Xaa36- Pro37-Pro38-Xaa39-Xaa40-Xaa41-Lys42; (I) [SEQ ID NO: 528]

wherein

Xaa1 is His, Tyr or Phe;

Xaa3 is His, Gln or Glu;

Xaa10 is Leu, Tyr or Val;

Xaa17 is Glu or Lys;

Xaa18 is Ala or Arg;

Xaa20 is Arg, Gln, Lys or His;

Xaa21 is Leu, Ala, Arg, Lys or Glu;

Xaa28 is Ala, Asn, Gln or His;

Xaa29 is Gly or Ala;

Xaa33 is Ser, His or Gln;

Xaa35 is Lys, Pro, His, Arg, Asn, Gln, Glu, Ser or Ala;

Xaa36 is Phe, His, Gln, Glu, Lys, Ser, Arg or absent

Xaa39 is Pro or Gly;

Xaa40 is Gly or absent;

Xaa41 is Lys or absent;

and the lysine residue at position 42 is substituted at its ε-amino group with a group Y and Y is:

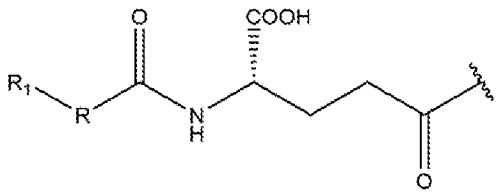
Z-Xaa43-Xaa44-

wherein:

Xaa43 is Asn or absent;

Xaa44 is His or absent;

and Z is a group of formula:



wherein R is a C_{16}–C_{18} alkylene or alkenylene group; and

R^1 is CO_2H.

Within the first portion of the molecule (Xaa1–Lys42), it is preferred that:

Xaa17 is Lys;

Xaa18 is Ala or Arg;

Xaa20 is Arg or His;

Xaa21 is Leu or Glu;

Xaa28 is Ala, Gln or His;

Xaa29 is Gly;

Xaa33 is Ser

Xaa35 is Lys, Glu, His, Gln or Asn;

Xaa36 is absent;

Xaa39 is Pro; and

Xaa41 is Lys.

In a more preferred embodiment, in the first portion of the molecule (Xaa1–Lys42):

Xaa1 is His or Phe;

Xaa3 is His or Glu;

Xaa10 is Tyr or Val;

Xaa17 is Lys;

Xaa18 is Ala or Arg;

Xaa20 is Arg or His;

Xaa21 is Glu;

Xaa28 is Ala or Gln;

Xaa29 is Gly;

Xaa33 is Ser

Xaa35 is Lys;

Xaa36 is absent;

Xaa39 is Pro;

Xaa40 is Gly; and

Xaa41 is Lys.

Considering the residues in turn, Xaa1 is selected from His, Tyr and Phe. For example, Xaa1 is selected from His and Tyr, or alternatively Xaa1 is selected from His and Phe. For example, Xaa1 is His. Alternatively, Xaa1 is Phe. In an especially preferred embodiment, Xaa1 is Phe. It has been found that compounds of the invention with Phe at the N-terminus (in particular ones that also have Xaa3 = Glu) have a GLP-1 receptor bias. Compounds with Phe at the N-terminus have been seen to fully activate the intracellular cAMP system, in a manner similar to native GLP1, whilst being weaker than GLP1 at activating the intracellular beta arrestin messenger system, so there is a bias at the GLP1 receptor. In some circumstances, this GLP1 receptor bias is an advantage in prolonging the action at the GLP1 receptor and producing relative enhancement of the action on the beta cell in releasing insulin while not enhancing other dose limiting effects such as inhibition of food intake and food aversion.

Xaa3 is selected from His, Gln and Glu. Preferably, Xaa3 is selected from His and Glu. For example, Xaa3 is His. Alternatively, Xaa3 is Glu. In an especially preferred embodiment, Xaa3 is Glu.

Xaa10 is selected from Leu, Tyr and Val. Preferably, Xaa10 is Tyr or Val, for example Xaa10 is Tyr. Alternatively, Xaa10 is Val.

Xaa17 is selected from Glu or Lys. Preferably, Xaa17 is Lys.

Xaa18 is selected from Ala or Arg. For example, Xaa18 is Ala. Alternatively, Xaa18 is Arg. In an especially preferred embodiment, Xaa18 is Arg.

Xaa20 is selected from Arg, Gln, Lys and His. Preferably, Xaa20 is Arg or His, for example Xaa20 is Arg. Alternatively, Xaa20 is His. In an especially preferred embodiment, Xaa20 is Arg.

Xaa21 is selected from Leu, Ala, Arg, Lys and Glu. Preferably, Xaa21 is Leu or Glu, for example, Xaa21 is Glu. Alternatively, Xaa21 is Leu. In an especially preferred embodiment, Xaa21 is Glu.

Xaa28 is selected from Ala, Asn, Gln and His. Preferably, Xaa28 is selected from Ala, Gln and His. In an especially preferred embodiment, Xaa28 is Ala or Gln, for example Xaa28 is Ala. Alternatively, Xaa28 is Gln.

Xaa29 is selected from Gly and Ala. Preferably, Xaa29 is Gly.

Xaa33 is selected from Ser, His and Gln. For example, Xaa33 is selected from Ser and His, or alternatively Xaa33 is selected from Ser and Gln. Preferably, Xaa33 is Ser.

Xaa35 is selected from Lys, Pro, His, Arg, Asn, Gln, Glu, Ser and Ala. Preferably, Xaa35 is selected from Lys, Gln, Glu, His and Asn. In an especially preferred embodiment, Xaa35 is Lys.

Xaa36 is selected from Phe, His, Gln, Glu, Lys, Ser, Arg, or Xaa36 is absent. Preferably, Xaa36 is absent.

Xaa39 is selected from Pro or Gly. Preferably, Xaa39 is Pro.

Xaa40 is Gly, or Xaa40 is absent. Preferably, Xaa40 is Gly.

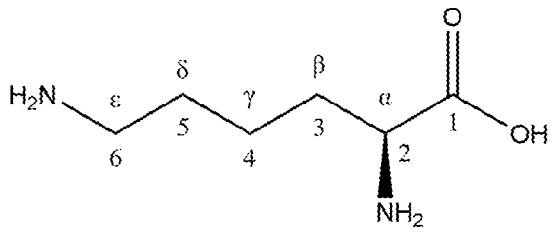
Xaa41 is Lys, or Xaa41 is absent. Preferably, Xaa41 is Lys.

In a preferred embodiment, Xaa36 is absent, and Xaa37-Xaa41 is Pro37-Pro38-Pro39-Gly40-Lys41 [SEQ ID NO: 533]. In an alternative preferred embodiment, Xaa36 is absent, Xaa40 is absent and Xaa37-Xaa41 is Pro37-Pro38-Pro39-Lys41 [SEQ ID NO: 534].

Group Y

In the compounds of the invention, the ε-amino group on Lys42 is attached to the acid group of the Xaa44 residue of the Y portion of the molecule, such that the bond is an amide bond. If Xaa44 or Xaa43 is absent, then the ε-amino group on Lys42 is attached to the acid group of the next residue that is present: the acid group of the Z group.

In a lysine residue, the ε-amino group is the amino group that is attached to the 6-carbon. Following standard IUPAC nomenclature, the atoms in lysine are numbered as follows, indicating the carbon atom numbering and also the α to ε positions:



The ε-amino group on Lys42 that is referred to herein is the amino group on the C-6 carbon atom as indicated.

Within the Y portion of the molecule:

Xaa43 may be Asn or absent; and

Xaa44 may be His or absent.

For example, Xaa43 is Asn and Xaa44 is His; or Xaa43 is Asn and Xaa44 is absent; or Xaa43 is absent and Xaa44 is His; or both Xaa43 and Xaa44 are absent. In a preferred embodiment, Xaa43 is absent and Xaa44 is absent.

For example, Y is:

Z-Asn-His-;

Z-Asn-;

Z-His-; or

Z-.

Group Z

Within the Z portion of the molecule, group R is an alkylene or alkenylene chain, which is linked at one end to residue Xaa43 (or, if Xaa43 is absent, Xaa44, or if both Xaa43 and Xaa44 are absent, Lys42) by the Glu residue through an amide bond. At its other end, the R alkylene or alkenylene chain is linked to the R^1 acid group (CO_2H).

Generally, R has an even number of carbon atoms. For example, R can be an alkylene or alkenylene chain that is found in naturally-occurring fatty acids. The root fatty acid has a chain length two higher than the number of carbon atoms in the R an alkylene or alkenylene chain.

R is a C_{16}–C_{18} alkylene or alkenylene group. For example, R is straight chain alkylene or alkenylene group. For example, R is a C_{16} or C_{18} straight chain alkylene group. For example, when R is a C_{16}, group, it can be provided by a octadecanedioic acid moiety. For example, when R is a C_{18}, group, it can be provided by an eicosanedioic acid moiety.

In a preferred embodiment, R is a C_{18} alkylene group.

In an embodiment, it is preferred that:

Xaa17 is Lys;

Xaa20 is Arg or His;

Xaa21 is Leu or Glu;

Xaa28 is Ala, Gln or His;

Xaa29 is Gly;

Xaa33 is Ser

Xaa35 is Lys, Glu, His, Gln or Asn;

Xaa36 is absent;

Xaa39 is Pro;

Xaa41 is Lys;

Xaa43 is absent;

Xaa44 is absent; and

R is a C_{18} alkylene group.

In a more preferred embodiment:

Xaa1 is His or Phe;

Xaa3 is His or Glu;

Xaa10 is Tyr or Val;

Xaa17 is Lys;

Xaa18 is Ala or Arg;

Xaa20 is Arg or His;

Xaa21 is Glu;

Xaa28 is Ala or Gln;

Xaa35 is Lys; and

Xaa40 is Gly.

For example, in such an embodiment:

Xaa1 is Phe;

Xaa3 is Glu;

Xaa10 is Val;

Xaa18 is Arg;

Xaa20 is Arg; and

Xaa28 is Gln.

For example, such a compound can be a compound of SEQ ID No: 502.

In especially preferred embodiments, the compound is one of the compounds of the invention set out in the Table of Figure 1.

Derivatives and Salts

The present invention provides compounds of formula (I), derivatives of such compounds, and salts or solvates of such compounds and derivatives.

The compounds, derivatives and salts may be produced by recombinant methods which are well-known in the art or alternatively they may be produced by synthetic methods, again which are well-known in the art.

Derivatives

Whilst in some embodiments, the invention relates to a compound of formula (I) and is not a derivative, in other embodiments the invention relates to a derivative of a compound of formula (I). The derivative may for example comprise one or more derivatisations selected from amidation, glycosylation, carbamylation, acylation, sulfation, phosphorylation, cyclization, lipidization, pegylation and fusion to another peptide or protein to form a fusion protein, for example the derivative may comprise one or more derivatisations selected from amidation, glycosylation, carbamylation, acylation, sulfation, phosphorylation, cyclization, lipidization and pegylation. The structure 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.

In certain embodiments it is preferred that the primary peptide chain of compounds of the invention may be amidated at their C-terminal. Such a modification is very common in nature with approximately half of naturally occurring peptides, including certain gastrointestinal peptide hormones, being susceptible to amidation at their C-

terminal. The present invention encompasses all of the generic and specific sequences disclosed herein, including in the sequence listing and drawings, in both amidated and non-amidated forms, the amidation, where present being especially preferred on the C-terminal of the primary peptide sequence.

The derivative may for example be a fusion protein, whereby the structure of formula (I) is fused to another protein or polypeptide (the fusion partner) using recombinant methods known in the art. Alternatively, such a fusion protein may be synthetically synthesized by any known method. Such a fusion protein comprises the structure of formula (I). Any suitable peptide or protein can be used as the fusion partner (e.g., serum albumin, carbonic anhydrase, glutathione-S-transferase or thioredoxin, etc.). Such fusion proteins may be made by linking the carboxy-terminus of the fusion partner to the amino-terminus of the structure of formula (I) or vice versa. Optionally, a cleavable linker may be used to link the structure of formula (I) to the fusion partner. A resulting cleavable fusion protein may be cleaved *in vivo* such that an active form of a compound of the invention is released. Examples of such cleavable linkers include, but are not limited to, the linkers Asp-Asp-Asp-Asp-Tyr [SEQ ID NO: 535], Gly-Pro-Arg, Ala-Gly-Gly and His-Pro-Phe-His-Leu [SEQ ID NO: 536], which can be cleaved by enterokinase, thrombin, ubiquitin cleaving enzyme and renin, respectively. For details, see for example U.S. Patent No. 6,410,707, the contents of which are incorporated herein by reference.

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

In addition to the derivatisation at Lys42, compounds of the invention can be further derivatised at additional positions. For example, pharmaceutically acceptable esters and amides of the compounds of the invention may comprise a C_{1-20} alkyl-, C_{2-20}

alkenyl-, C_{5-10} aryl-, C_{5-10} ar-C_{1-20} alkyl-, or amino acid- ester group or amide group attached at an appropriate site, for example formed by reaction of an alkyl, alkenyl aryl, aralkyl or amino alkyl group containing an alcohol or amino moiety with an acid moiety present in the compound of formula (I), or formed by reaction of an alkyl, alkenyl aryl, aralkyl or amino alkyl group containing an activated acyl group with an alcohol or amine group present in the compound of formula (I). Examples of suitable moieties are hydrophobic substituents with 4 to 26 carbon atoms, preferably 5 to 19 carbon atoms. Suitable lipid groups include fatty acids (e.g. lauroyl ($C_{12}H_{23}$), palmityl ($C_{15}H_{31}$), oleyl ($C_{15}H_{29}$) or stearyl ($C_{17}H_{35}$)) and bile acids (e.g. cholate or deoxycholate).

Methods for lipidization of sulfhydryl-containing compounds with fatty acid derivatives are disclosed in U.S. Patent No. 5,936,092; U.S. Patent No. 6,093,692; and U.S. Patent No. 6,225,445, the contents of which are incorporated herein by reference. Fatty acid derivatives of a compound of the invention comprising a compound of the invention linked to fatty acid via a disulfide linkage may be used for delivery of a compound of the invention to neuronal cells and tissues. Lipidisation markedly increases the absorption of the compounds relative to the rate of absorption of the corresponding unlipidised compounds, as well as prolonging blood and tissue retention of the compounds. Moreover, the disulfide linkage in a lipidised derivative is relatively labile in the cells and thus facilitates intracellular release of the molecule from the fatty acid moieties. Suitable lipid-containing moieties are hydrophobic substituents with 4 to 26 carbon atoms, preferably 5 to 19 carbon atoms. Suitable lipid groups include fatty acids (e.g. lauroyl ($C_{12}H_{23}$), palmityl ($C_{15}H_{31}$), oleyl ($C_{15}H_{29}$) or stearyl ($C_{17}H_{35}$)) and bile acids (e.g. cholate or deoxycholate). Whilst lipid functionalised compounds of the invention may have benefits in certain situations, it is expected that in most cases, it will be simplest and preferred if a compound of the invention is not further derivatised, such that there are not additional lipid groups present.

Cyclization methods include cyclization through the formation of a disulfide bridge, and head-to-tail cyclization using a cyclization resin. Cyclized peptides may have enhanced stability, including increased resistance to enzymatic degradation, as a result of their conformational constraints. Cyclization may in particular be expedient where the

uncyclized peptide includes an N-terminal cysteine group. Suitable cyclized peptides include monomeric and dimeric head-to-tail cyclized structures. Cyclized peptides may include one or more additional residues, especially an additional cysteine incorporated for the purpose of formation of a disulfide bond or a side chain incorporated for the purpose of resin-based cyclization.

The derivative may for example be a PEGylated structure of formula (I). Derivatives which are PEGylated compounds of the invention may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337, the contents of which are incorporated herein by reference).

Chemical moieties for derivatisation of a compound of the invention may also be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. A polymer moiety for derivatisation of a compound of the invention may be of any molecular weight and may be branched or unbranched. For ease in handling and manufacturing, the preferred molecular weight of a polyethylene glycol for derivatisation of a compound of the invention is from about 1 kDa to about 100 kDa, the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight. Polymers of other molecular weights may be used, depending on the desired therapeutic profile, for example the duration of sustained release desired, the effects, if any, on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog. For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

Salts

Salt forms of compounds of formula (I) and of derivatives of such compounds also form part of the invention. In some embodiments the salt is a salt of a compound of formula (I). In other embodiments the salt is a salt of a derivative of a compound of formula (I).

Salts of compounds of the invention include those which are pharmaceutically acceptable, i.e. which are suitable for use in medicine. However, salts having non-pharmaceutically acceptable counterions are also within the scope of the present invention, for example, for use as intermediates in the preparation of the compounds.

Suitable salts according to the invention include those formed with organic or inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed with hydrochloric, hydrobromic, sulphuric, nitric, citric, tartaric, acetic, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, perchloric, fumaric, maleic, glycolic, salicylic, oxaloacetic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic, and isethionic acids. Other acids such as oxalic acid may be useful as intermediates in obtaining the compounds of the invention in final form.

Pharmaceutically acceptable salts with bases include ammonium salts, alkali metal salts, for example potassium and sodium salts, alkaline earth metal salts, for example calcium and magnesium salts, and salts with organic bases, for example dicyclohexylamine and N-methyl-D-glucomine.

Solvates

Those skilled in the art of organic and/or medicinal chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. Such complexes are known as "solvates". For example, a complex with water is known as a "hydrate". The invention also encompasses solvates of the compounds of formula (I), solvates of derivatives of the compounds, and solvates of salts of the derivatives.

Those skilled in the art of organic and/or medicinal chemistry will also appreciate than many organic compounds can exist in different forms, including as amorphous material and/or in one or more crystalline forms. Different physical forms of organic compounds are known as polymorphs. The invention also encompasses all such different physical forms of the compounds of formula (I), as well as different physical forms of their derivatives and salts.

Biological Activity

Compounds of the invention have activity at the human GLP-1 receptor and can be considered GLP-1 receptor agonists. This may be assessed by, for example, an *in vitro* or cellular binding assay or by a reporter assay. Preferred compounds of the invention exhibit an activity at the human GLP-1 receptor that is at least 1/50th that of human GLP-1, preferably an activity which is at least 1/30th, 1/20th, 1/10th, 1/5th, 1/3rd or ½ that of human GLP-1, for example when tested in accordance with the assay described in the examples section below.

Methods of assessing activity at the GLP-1 receptor are well known. For example, Jones *et al.*, *Nat. Commun.*, 2018, 9(1), 1602 discloses a method of assaying for GLP-1 receptor binding. A specific method is described herein below.

Preferred compounds of the invention are effective in promoting insulin release/secretion. This may be assessed by, for example, an *in vitro* assay. Methods of assessing release of insulin from beta-cells are well known.

Compounds of the invention fulfil some, or more preferably all, of the following criteria:

1) Sustained bioactivity at the human GLP-1 receptor resulting in inhibition of appetite;
2) Activity in promoting insulin release from beta-cells;

3) High solubility in aqueous solution at pH 4.5 to allow an effective dose to be administered in a low volume injection (thereby resulting in lower pain of injection). Solubility may be easily assessed by simple *in vitro* tests;
4) Long period of activity *in vivo* (as assessed in humans or an animal model) so as to permit injections no more frequently than daily and preferably no more than twice, or more preferably no more than once a week, whilst still producing acceptable therapeutic or cosmetic benefits;
5) Good weight loss (as assessed in human subjects or an animal model);
6) Low antigenicity in humans. This may be assessed in humans or animal models (in particular mice which have been experimentally reconstituted with a human immune system so as to mimic human antibody repertoire) or predicted using predictive software such as that incorporating the "antigenic index" algorithm ((Jameson & Wolf (1988) *Comput. Appl. Biosci.* 4(1):181-6), or the PREDITOP algorithm (Pellequer & Westhof, (1993) *J. Mol. Graph.* 11(3):204-10), or using the methods of Kolaskar & Tongaonkar (1990) *FEBS Lett.* 10:276(1-2):172-4, the contents of which are incorporated herein by reference).

According to certain embodiments of the invention, especially embodiments relating to weight loss, obesity, carbohydrate metabolism and diabetes, the compounds, derivatives and salts of the invention have one, several or all of the following features:

A. Sufficient solubility between pH 4 and pH 5 to permit an effective dose to be administered in a volume of less than 1ml, less than 0.5ml or less than 0.3ml;
B. Activation of cAMP signalling in Chinese hamster ovary cells over-expressing the human GLP-1 Receptor;
C. One, several or all of the further 1 to 6 features listed above.

Pharmacokinetics, Duration of Action and Solubility

Compounds of the present invention exhibit potent and prolonged duration of action *in vivo* following subcutaneous administration. In order to achieve this, the compounds

are required to have both good activity at the biological target, and excellent pharmacokinetic properties.

Compounds of the present invention have a therapeutically useful duration of action and that manifests itself in the beneficial effects being observed in the experiments described herein below over several days. The half-life of compounds of the invention was assessed in a pig PK model. Preferred compounds of the invention were found to have a half-life significantly longer than semaglutide. As well as exhibiting a long *in vivo* half-life, the compounds of the invention have good storage stability, with no significant degradation seen on storage in solution for 4 weeks at 4°C.

Poor water solubility is a known problem for lipid containing molecules. In contrast, the compounds of the invention have very good solubility.

Certain compounds of the invention include His residues. Incorporation of His residue(s) into peptides having poor aqueous solubility typically leads to peptides having enhanced solubility at acidic pH (e.g. pH 5) due to the presence of charged His side-chain groups, but which are less soluble at physiological pH (pH 7.4). The pI of the side-chain group of histidine is about 6.0. Such properties enable formulation of His-containing peptides in weakly acidic media. Upon subcutaneous injection of such formulations, the solubility falls leading to subcutaneous precipitation of peptide which resolubilises over time. Zinc-containing formulations of His-containing peptides enhance this effect, because at pH 7.4 but not at pH 5 zinc ions co-ordinate with histidine residues and result in a further reduction in solubility which can contribute to increased precipitation at a subcutaneous injection site, or which can contribute to increased stability of the precipitate. However, where precipitation of peptide is not sufficiently rapid following subcutaneous administration, there may still be an initial "spike" or "burst" in blood concentration levels of the peptide. Such properties are undesirable since they increase the possibility of subjects experiencing side effects associated with high concentration levels of the peptides, such as nausea, even if only temporary. In contrast to peptides not having the multi-His containing C-terminal sequence of the invention, the present compounds either do not display initial "spikes" or "bursts" in plasma concentration levels following subcutaneous administration or any

such “burst” is significantly reduced. This reduces the likelihood and/or severity of possible side effects associated with high circulating levels of the compounds.

Conditions

The invention also provides a compound, derivative or salt of the invention, or a composition comprising the compound, derivative or salt together with a pharmaceutically acceptable carrier and optionally a further therapeutic agent, for use as a medicament.

The invention also provides a method of treating or preventing a disease or disorder or other non-desired physiological state in a subject comprising administration of a therapeutically effective amount of a compound, derivative or salt of the invention, or of a composition comprising the compound, derivative or salt together with a pharmaceutically acceptable carrier and optionally a further therapeutic agent. Preferably the compound, derivative, salt or composition is administered subcutaneously.

According to certain embodiments, the disease or disorder or other non-desired physiological state is diabetes or obesity, and particularly diabetes (e.g. type II diabetes).

According to certain embodiments, the disease or disorder or other non-desired physiological state may be the physiological state of being overweight.

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

In addition, or alternatively, the subject may have, or may be at risk of having, a disorder in which obesity or being overweight is a risk factor. Such disorders include, but are not

limited to, heart disease, cardiovascular disease, for example hypertension, atherosclerosis, congestive heart failure, and dyslipidemia; stroke; gallbladder disease; osteoarthritis; sleep apnea; reproductive disorders for example, polycystic ovarian syndrome; cancers, for example breast, prostate, colon, endometrial, kidney, and esophagus cancer; varicose veins; acanthosis nigricans; eczema; exercise intolerance; insulin resistance; hypertension hypercholesterolemia; cholithiasis; osteoarthritis; orthopedic injury; insulin resistance, for example, type 2 diabetes and syndrome X; and thromboembolic disease (see Kopelman, *Nature* 404:635-43, 2000; Rissanen *et al.*, *British Med. J.* 301, 835, 1990).

Other disorders associated with obesity include depression, anxiety, panic attacks, migraine headaches, PMS, chronic pain states, fibromyalgia, insomnia, impulsivity, obsessive compulsive disorder, and myoclonus. Certain neurological disorders and certain firms of neurological degeneration are also associated with obesity. Furthermore, obesity is a recognized risk factor for increased incidence of complications of general anesthesia (see e. g., Kopelman, *Nature* 404:635-43, 2000). In general, obesity reduces life span and carries a serious risk of co-morbidities such as those listed above.

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

odours, clothing difficulties, low back pain; musculoskeletal disease; pseudotumor cerebri (or benign intracranial hypertension), and sliding hiatal hernia.

In some embodiments, the disease or disorder may be non-alcoholic fatty liver disease.

According to certain embodiments the disease or disorder or other non-desired physiological state may be being of a non-desired weight despite not being obese or overweight. The subject may be of normal weight (this includes but is not limited to subjects who were previously overweight or obese and who wish to prevent a return to an unhealthy weight). A subject may be a subject who desires weight loss, for example female and/or male subjects who desire a change in their appearance. In some cases where the subject is of a normal weight, aspects of the invention may relate to cosmetic treatment rather than to therapeutic treatment.

The invention also provides a method of reducing appetite in a subject, reducing food intake in a subject, reducing calorie intake in a subject, improving insulin release in a subject, improving carbohydrate metabolism in a subject, and/or improving carbohydrate tolerance in a subject, comprising administration of a therapeutically effective amount of a compound, derivative, salt or composition of the invention. Such methods may relate to treating subjects having a pre-diabetic state such as insulin insensitivity or pre-diabetes.

The invention also provides a method for improving a lipid profile in a subject comprising administration of a therapeutically effective amount of a compound, derivative, salt or composition of the invention. The invention also provides a method for alleviating a condition or disorder that can be alleviated by reducing nutrient availability comprising administration of a therapeutically effective amount of a compound, derivative, salt or composition of the invention.

A compound, derivative, salt or composition of the invention may be used for weight control and treatment, for example reduction or prevention of obesity, in particular any one or more of the following: preventing and reducing weight gain; inducing and promoting weight loss; and reducing obesity as measured by the Body Mass Index. A

compound, derivative, salt or composition of the invention may be used in maintaining any one or more of a desired body weight, a desired Body Mass Index, a desired appearance and good health.

The present invention may also be used in treating, prevention, ameliorating or alleviating conditions or disorders caused by, complicated by, or aggravated by a relatively high nutrient availability. The term "condition or disorder which can be alleviated by reducing caloric (or nutrient) availability" is used herein to denote any condition or disorder in a subject that is either caused by, complicated by, or aggravated by a relatively high nutrient availability, or that can be alleviated by reducing nutrient availability, for example by decreasing food intake. Subjects who are insulin resistant, glucose intolerant, or have any form of diabetes mellitus, for example, type 1, 2 or gestational diabetes, can also benefit from methods in accordance with the present invention.

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

J. Cereb. Blood Flow Metab. 2011 Apr 13 (Teramoto S *et al.*) discusses the use of both GLP-1 and exendin-4 to confer cardioprotection after myocardial infarction and demonstrates that exendin-4 may be used to provide neuroprotection against cerebral ischemia-reperfusion injury. The study showed that mice receiving a transvenous injection of exendin-4, after a 60-minute focal cerebral ischemia showed significantly reduced infarct volume and improved functional deficit as well as suppressed oxidative stress, inflammatory response, and cell death after reperfusion. The study provided evidence that the protective effect of exendin-4 is mediated through increased intracellular cAMP levels and suggested that exendin-4 is potentially useful in the treatment of acute ischemic stroke.

Accordingly, the invention also provides a method of providing cytoprotection in a subject, such as providing cardiac protection, providing neuroprotection and/or treating or preventing neurodegeneration, comprising administration of a therapeutically effective amount of a compound, derivative, salt or composition of the invention.

In certain embodiments the disease or disorder or other non-desired physiological state which the compound, derivative, salt or composition of the invention may be used to treat or prevent is neurodegeneration. Such neurodegeneration may be caused by apoptosis, necrosis or loss of function of neuronal cells, preferably in the CNS. Neurodegeneration treated or prevented may be that following a brain injury (for example following physical trauma or following a non-traumatic injury such a stroke, tumor, hypoxia, poisoning, infection, ischemia, encephalopathy or substance abuse). Alternatively or additionally, neurodegeneration may be prevented or treated in a subject having (or diagnosed as having a predisposition to) a neurodegenerative disease such as Alzheimer's disease, Parkinson's disease, Gehrig's disease (Amyotrophic Lateral Sclerosis), Huntington's disease, Multiple Sclerosis, other demyelination related disorders, senile dementia, subcortical dementia, arteriosclerotic dementia, AIDS-associated dementia, other dementias, cerebral vasculitis, epilepsy, Tourette's syndrome, Guillain Barre Syndrome, Wilson's disease, Pick's disease, neuroinflammatory disorders, encephalitis, encephalomyelitis, meningitis, other central nervous system infections, prion diseases, cerebellar ataxias, cerebellar degeneration, spinocerebellar degeneration syndromes, Friedrich's ataxia, ataxia teangiectasia, spinal dysmyotrophy, progressive supranuclear palsy, dystonia, muscle spasticity, tremor, retinitis pigmentosa, striatonigral degeneration, mitochondrial encephalomyopathies, neuronal ceroid lipofuscinosis. Preferably, the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Gehrig's disease (Amyotrophic Lateral Sclerosis) and Huntington's disease. In such circumstances the treatment would be regarded as neuroprotective. According to certain preferred embodiments, the treatment is neuroprotective following cerebral ischemia or neuroprotective in a subject having a neurodegenerative disease or diagnosed as having a predisposition to a neurodegenerative disease.

According to other embodiments the disease or disorder or other non-desired physiological state is cardiac degeneration (in particular myocardial degeneration by apoptosis, necrosis or loss of function of myocardial cells), in which case the compound, derivative, salt or composition according to the invention provides cardiac protection.

According to certain preferred embodiments that treatment is protective of myocardial function following myocardiac infarction.

The invention also provides a compound, derivative, salt or composition of the invention, for use in the treatment of obesity or diabetes.

The invention also provides a compound, derivative, salt or composition of the invention, for use in increasing energy expenditure of a subject, improving insulin release in a subject, improving carbohydrate tolerance in a subject and/or improving carbohydrate metabolism in a subject. Such use may relate to treating subjects having a pre-diabetic state such as insulin insensitivity or pre-diabetes.

The invention also provides a compound, derivative, salt or composition of the invention, for use in the reduction of appetite in a subject, use in the reduction of food intake in a subject, use in the reduction of calorie intake in a subject, use in improving insulin release in a subject, and/or use in improving carbohydrate tolerance in a subject. Such use may relate to treating subjects having a pre-diabetic state such as insulin insensitivity or pre-diabetes.

The invention also provides a compound, derivative, salt or composition of the invention, for use as a cytoprotective agent (e.g. in treating or preventing neurodegeneration, providing neuroprotection and/or providing cardiac protection). For example, the compound, derivative, salt or composition may be for use in myocardial protection in a subject following myocardial infarction, or for use in neuroprotection in a subject following cerebral ischemia or stroke, or for use in neuroprotection in a subject having a chronic neurodegenerative disease. Various features of neuroprotective or cardioprotective use of the compound, derivative, salt or composition may be as outlined above in relation to methods of the invention.

In the case of neuroprotection, the subject may have experienced previously a brain injury, stroke or other event causing cerebral ischemia. Alternatively, the subject may have or have been diagnosed with a predisposition to develop a chronic neurodegenerative disease. In the case of cardioprotection the subject may have experienced previously an event causing myocardial ischemia such as a myocardial

infarction and angina. According to some embodiments a compound, derivative, salt or composition of the invention may be administered as soon as possible after the subject has experienced a suspected myocardial infarction. According to certain embodiments a compound, derivative, salt or composition of the invention may be administered as soon as possible after the subject has experienced as suspected stroke.

The invention also provides use of a compound, derivative, salt or composition of the invention for the manufacture of a medicament for the treatment of obesity or diabetes, of a subject, who may be as described above in reference to other aspects of the invention.

The invention also provides use of a compound, derivative or salt of the invention for the manufacture of a medicament for improving insulin release in a subject, for improving carbohydrate tolerance in a subject and/or improving carbohydrate metabolism in a subject. Such use may relate to treating subjects with a pre-diabetic state such as insulin insensitivity or pre-diabetes.

The invention also provides use of a compound, derivative or salt of the invention for the manufacture of a medicament for the reduction of appetite in a subject, reducing food intake in a subject, reducing calorie intake in a subject, improving insulin release in a subject, and/or use in improving carbohydrate tolerance in a subject.

The invention also provides use of a compound, derivative or salt of the invention for the manufacture of a medicament for providing cytoprotection (e.g. preventing or treating neurodegeneration, providing neuroprotection and/or providing cardiac protection) of a subject, who may be as described above in reference to other aspects of the invention.

According to certain embodiments the compound, derivative, salt or composition of the invention is to be administered parentally. According to other embodiments the compound, derivative, salt or composition of the invention is administered subcutaneously, intravenously, intramuscularly, intranasally, transdermally or sublingually. According to other embodiments the compound, derivative, salt or composition of the invention is administered orally. In one preferred embodiment

compound, derivative, salt or composition of the invention is administered subcutaneously.

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

Compositions

It is preferable for the compound of formula (I), or the derivative and/or the salt thereof, to be present in a pharmaceutical formulation or composition. Accordingly, the invention provides a composition comprising a compound, derivative or salt of the invention together with a pharmaceutically acceptable excipient and optionally another therapeutic ingredient. Compositions comprising the compound, derivative or salt are suitable for pharmaceutical use. According to certain preferred embodiments the composition is present in a syringe or other administration device for subcutaneous administration to humans. According to certain preferred embodiments the composition has a pH of less than 5. Compositions of the invention may take the form of a pharmaceutical formulation as described below.

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

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include

the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Various pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, e.g., *Remington's Pharmaceutical Sciences* by E. W. Martin. See also Wang, Y. J. and Hanson, M. A., *Journal of Parenteral Science and Technology*, Technical Report No. 10, Supp. 42:2S, 1988, the contents of which are incorporated herein by reference.

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

Preferably, compositions according to the invention are suitable for subcutaneous administration, for example by injection. According to certain embodiments the

composition may contain metal ions, for example copper, iron, aluminium, zinc, nickel or cobalt ions. The presence of such ions may limit solubility and thus delay absorption into the circulatory system from the site of subcutaneous administration. .

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

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

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

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

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art. Conveniently in compositions for nasal aerosol or inhalation administration the compound of the invention is delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoro-methane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator can be formulated to contain a powder mix of the compound and a suitable

powder base, for example lactose or starch. In one specific, non-limiting example, a compound of the invention is administered as an aerosol from a metered dose valve, through an aerosol adapter also known as an actuator. Optionally, a stabilizer is also included, and/or porous particles for deep lung delivery are included (e.g., see U.S. Patent No. 6,447,743).

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

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

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

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

The compounds, derivatives and salts of the invention may also be suitably administered as sustained-release systems. Suitable examples of sustained-release systems of the invention include suitable polymeric materials, for example semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules; suitable hydrophobic materials, for example as an emulsion in an acceptable oil; or ion exchange resins; and sparingly soluble derivatives of the compound of the invention, for example, a sparingly soluble salt. Sustained-release systems may be administered orally; rectally; parenterally; intracisternally;

intravaginally; intraperitoneally; topically, for example as a powder, ointment, gel, drop or transdermal patch; bucally; or as an oral or nasal spray.

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

The use of a controlled release composition is preferred for indications such as the treatment of obesity and/or diabetes, where maximising the time period between injections is desirable. However, for indications such as providing neuroprotection or cardiac protection (e.g. following suspected myocardial infarction or stroke), where it is desired to achieve a therapeutic plasma concentration of the active agent in as short a time period as possible, an immediate release formulation will be preferred. In such cases, a dosage regime comprising administration of a dose of an immediate release formulation of the active agent (i.e. as soon as possible after suspected myocardial infarction or stroke) and subsequent administration of a dose of a controlled release formulation of the active agent may be preferred.

A compound, derivative or salt of the invention may be 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 a continuous subcutaneous infusion, 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) which is incorporated herein by reference. In another aspect of the

disclosure compounds of the invention are delivered by way of an implanted pump, described, for example, in U.S. Patent No. 6,436,091; U.S. Patent No. 5,939,380; U.S. Patent No. 5,993,414, the contents of which are incorporated herein by reference.

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

A therapeutically effective amount of the active agent of the invention may be administered as a single pulse dose, as a bolus dose, or as pulse doses administered over time. Thus, in pulse doses, a bolus administration of the active agent is provided, followed by a time period wherein no active agent is administered to the subject, followed by a second bolus administration. In specific, non-limiting examples, pulse doses are administered during the course of a day, during the course of a week, or during the course of a month.

Combination treatments

In certain embodiments, a therapeutically effective amount of a compound, derivative, salt or composition of the invention is administered with a therapeutically effective amount of a further agent or agents. The compound, derivative or salt may for example be administered simultaneously with one or more further therapeutic agent(s), or it may be administered sequentially or separately. Accordingly, the invention provides a compound, derivative or salt of the invention for use as a medicament, wherein the compound, derivative or salt is for use with a therapeutically effective amount of a further therapeutic agent or agents (e.g. for administration simultaneously, sequentially

or separately). In certain embodiments, the active agent of the invention is formulated and administered with a further therapeutic agent or agents as a single dose.

In certain embodiments, the further therapeutic agent or agents is/are an additional anti-diabetic, appetite suppressant, a food-intake-reducing, plasma glucose-lowering or plasma lipid-altering agent. Specific, non-limiting examples of an additional appetite suppressant include amfepramone (diethylpropion), phentermine, mazindol and phenylpropanolamine, fenfluramine, dexfenfluramine, phendimetrazine, benzphetamine, sibutramine, rimonabant, topiramate, fluoxetine, bupropion, zonisamide, naltrexone, orlistat and cetilistat. Specific, non-limiting examples of an additional anti- diabetic agent include metformin, phenformin, rosiglitazone, pioglitazone, troglitazone, repaglinide, nateglinide, tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide, fibroblast growth factor 21, miglitol, acarbose, exenatide, pramlintide, vildagliptin and sitagliptin.

In alternative embodiments, the further therapeutic agent or agents is/are an additional cardioprotective or neuroprotective agent. Specific, non-limiting, examples of additional cardioprotective agents include aspirin, N-acetylcysteine, phenethylamines, coenzyme Q10, vitamin E, vitamin C, L-carnitine, carvedilol and dexrazoxane. Specific, non-limiting examples of neuroprotective agents include statins such as simvastatin, steroids such as progesterone, minocycline, resveratrol and vitamin E. Examples of agents used for the treatment of Parkinson's disease include anticholinergics, pramipexole, bromocriptine, levodopa, carbidopa, rasagiline, amantadine and ropinirole.

Dosages

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

The therapeutically effective amount of the active agent of the invention will be dependent on the molecule utilized, the subject being treated, the severity and type of the affliction, and the manner and route of administration. For example, a therapeutically effective amount of a compound of the invention may vary from about 0.01 µg per kilogram (kg) body weight to about 1 g per kg body weight, for example about 0.1 µg to about 20 mg per kg body weight, for example about 1 µg to about 5 mg per kg body weight, or about 5 µg to about 1 mg per kg body weight.

In one embodiment of the invention, a compound, derivative or salt of the invention may be administered to a subject at from 0.5 to 1,333 nmol per kg bodyweight, for example 1 to 1,333nmol/kg bodyweight, for example 2 to 1,000 nmol per kg bodyweight, for example 4 to 1,333 nmol per kg bodyweight, for example from 5 to 1,000 nmol per kg bodyweight, for example at from 10 to 750 nmol per kg bodyweight, for example at from 20 to 500 nmol per kg bodyweight, in particular at from 30 to 240 nmol per kg bodyweight. In a preferred embodiment, a high activity compound of the invention is administered to a subject at from 0.2 to 10 nmol per kg bodyweight, for example 0.5 to 5.0 nmol/kg bodyweight, for example 1.0 to 2.0 nmol per kg bodyweight, for example 1.5 nmol per kg bodyweight., For a 75 kg subject, such doses correspond to dosages of from 37.5 nmol to 100 µmol, for example from 75 nmol to 100 µmol, for example from 150 nmol to 100 µmol, for example from 300 nmol to 100 µmol, for example from 375 nmol to 75 µmol, for example from 750 nmol to 56.25 µmol, for example from 1.5 to 37.5 µmol, in particular from 2.25 to 18 µmol. In a preferred embodiment for a high activity compound of the invention, for a 75 kg subject, such doses correspond to dosages of from 15 to 750 nmol, for example 37.5 to 375.0 nmol, for example 75 to 150 nmol, for example 112.5 nmol. The invention also contemplates dosages ranges bounded by any of the specific dosages mentioned herein.

The exact dose is readily determined by one of skill in the art based on the potency of the specific compound utilized, the route of delivery of the compound and the age, weight, sex and physiological condition of the subject.

For a compound with a long blood half-life, the doses discussed above may be given, for example, once or twice per month, or once, twice, three-times or four-times per

week. For a preferred compound, a dose may be given no more frequently than once a week. Alternatively, for a compound with a shorter half-life in the blood, the doses discussed above may be given, for example, once, twice, three-times or four-times a day or once or twice a week. In some embodiments, a dose may be given once every 2, 3 or 4 days. According to certain embodiments they may be administered once shortly before each meal to be taken.

Examples

The invention is further described with reference to the following non-limiting examples.

Materials and Methods

Peptide Synthesis

Peptide synthesis was carried out on a tricyclic amide linker resin. Amino acids were attached using the Fmoc strategy. For the portion of the molecule from Xaa1 to Xaa42, each amino acid was added sequentially from the C- to the N-termini. Peptide couplings were mediated using reagents such as HBTU. Peptide cleavage from the resin was achieved with trifluoracetic acid in the presence of scavengers. In a second stage, the lysine 42 residue was functionalised at its ε-amino group following deprotection of the ε-amino group. The chain on the lysine 42 residue was then constructed sequentially using the same amino acid attachment chemistry.

Peptides were purified by reverse phase HPLC. Quality control was performed on all purified peptides and peptides were shown in most cases to be greater than 90% pure by HPLC in two buffer systems. MALDI-MS showed the expected molecular ion.

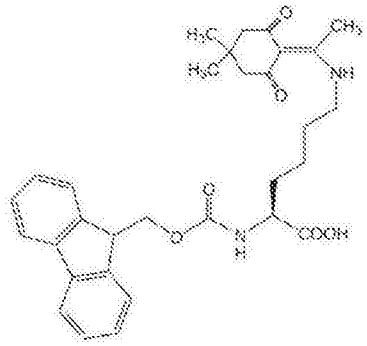
Example Synthesis

Example compound 193 (G Ref 6699) was prepared as follows using standard Fmoc chemistry:

1. Resin preparation: To 2Cl-Trt Resin (0.25 mmol, 1.00 eq) was added FMOC-LYS(DDE)-OH (133.15 mg, 250.00 µmol, 1.00 eq) and DIEA (193.85 mg, 1.50 mmol, 261.97 µL, 6.00 eq) in DCM (8.0 mL). The mixture was agitated with N_2 for 2 h at 20°C, then added MeOH (0.25 mL) and agitated with N_2 for another 30 min. The resin was washed with DMF (12.0 mL * 3). Then 20% piperidine in DMF (5.00 mL) was added and the mixture was agitated with N_2 for 30 min at 20°C. Then the mixture was filtered to get the resin. The resin was washed with DMF (12.0 mL * 5)

and filtered to get the resin.

FMOC-LYS(DDE)-OH has the structure:



The free acid is attached to the resin and the piperidine deprotection creates a free amino end group for the next coupling.

2. Coupling: a solution of FMOC-LYS(BOC)-OH (351.37 mg, 750.00 µmol, 3.00 eq), DIEA (193.85 mg, 1.50 mmol, 261.97 µL, 6.00 eq) and HBTU (270.20 mg, 712.50 µmol, 2.85 eq) in DMF (3.00 mL) was added to the resin and agitated with N_2 for 30 min at 20°C. The resin was then washed with DMF (12.0 mL * 3).

3. Deprotection: 20% piperidine in DMF (5.00 mL) was added to the resin and the mixture was agitated with N_2 for 30 min at 20°C. The resin was washed with DMF (12.0 mL * 5) and filtered to get the resin.

4. Steps 2–3 were repeated using the reagents in Table 1 until the last amino acid had been added (reaction iteration #1 in Table 1 is the first added Lys residue, as set out in steps 2 and 3 above).

Table 1:

#	Materials	Coupling reagents
1	FMOC-PRO-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
2	FMOC-PRO-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
3	FMOC-PRO-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
4	FMOC-LYS(BOC)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)

5	FMOC-GLY-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
6	FMOC-SER(TBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
7	FMOC-SER(TBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
8	FMOC-PRO-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
9	FMOC-GLY-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
10	FMOC-GLY-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
11	FMOC-ALA-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
12	FMOC-LYS(BOC)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
13	FMOC-LEU-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
14	FMOC-TRP(BOC)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
15	FMOC-GLU(OTBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
16	FMOC-ILE-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
17	FMOC-PHE-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
18	FMOC-LEU-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
19	FMOC-ARG(PBF)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
20	FMOC-VAL-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
21	FMOC-ARG(PBF)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
22	FMOC-GLU(OTBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
23	FMOC-GLU(OTBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
24	FMOC-GLU(OTBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
25	FMOC-LEU-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
26	FMOC-GLN(TRT)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
27	FMOC-LYS(BOC)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
28	FMOC-SER(TBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
29	FMOC-TYR(TBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
30	FMOC-ASP(OTBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
31	FMOC-SER(TBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
32	FMOC-THR(TBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
33	FMOC-PHE-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
34	FMOC-THR(TBU)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)

35	FMOC-GLY-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
36	FMOC-HIS(TRT)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
37	FMOC-AIB-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)
38	BOC-HIS(TRT)-OH (3.00 eq)	HBTU (2.85 eq) and DIPEA (6.00 eq)

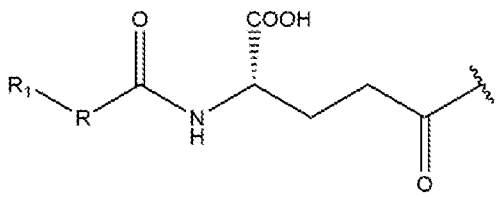
5. After the coupling of BOC-HIS(TRT)-OH in iteration #38, 3% $H_2N{\cdot}NH_2$/DMF was added and reacted for 30 min to remove Dde, and then repeated. The mixture was then drained and washed with DMF (15.0 mL) 5 times. After removal of the Dde group, the compound has a free amino end group at the ε-amino group of the lysine from step 1 and that is available for the next coupling.

6. The reactions of steps 2–3 were then carried out using the reagents in Table 2 until the last reagent has been added (reaction iteration #40 in Table).

Table 2:

#	**Materials**	**Coupling reagents**
39	FMOC-GLU-OTBU (3.00 eq)*	HBTU (2.85 eq) and DIEA (6.00 eq)
40	20-(tert-butoxy)-20-oxooctadecanoic acid (3.00 eq)	HBTU (2.85 eq) and DIEA (6.00 eq)

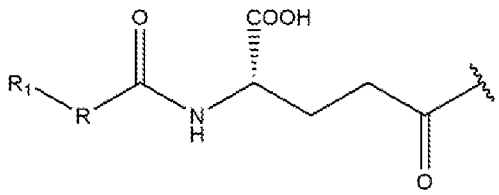
* As the protected glutamic acid reagent 39 has its C-1 acid group protected with TBU, it reacts at its C-5 acid with the ε-amino group of lysine 40. It is the FMOC-GLU-OTBU reagent that provides the glutamic acid residue portion in the Z part of the compound:



7. Peptide Cleavage and Purification:
The resin was washed with MeOH (20.0 mL * 2) and dried under vacuum to provide 2.0 g peptide resin. Then 22.0 mL of cleavage buffer (92.5% TFA/2.5% Mpr/2.5% TIS/2.5% H_2O) was added to the flask containing the side chain protected peptide resin at 20°C and the mixture was stirred for 2.5 h. The peptide was precipitated with cold tert-butyl methylether (250 mL) and centrifuged (2 min at 3000 rpm). The peptide precipitate was washed with tert-butyl methyl ether twice more (100 mL). The crude peptide was dried and the identity confirmed by LCMS.

The residue was purified by prep-HPLC (TFA condition; 30°C, A: 0.075% TFA/H_2O, B: CH_3CN) to give the title compound (202.4 mg, 40.66 μmol, 15.32% yield, 91.03% purity, TFA) as a white solid, the identity of which was confirmed by LCMS).

Equivalent methods were employed for all of the other peptides described herein. The sequences and other structural features of the exemplified peptides are shown in Figure 1. In the figure, the Lysine residue at position 42 is substituted on its ε amino group with a group Y and Y is Z-Xaa43-Xaa44- (blank in the column in question means that the residue is absent), and Z is group a having the structure:



wherein R is a C_{16}-C_{18} straight chain alkylene or alkenylene group; and

R^1 is CO_2H.

The number of carbon atoms in the alkylene or alkenylene group of R (n, n = 16–18) is indicated in the column headed "n (R = Cn)" in Figure 1. In the examples shown, n is 16 or 18.

Certain of the example compounds in Figure 1 are duplicate preparations of compounds listed elsewhere in the Figure and they are indicated as such as "dupl" in the column headed 'Notes'.

Receptor potency of peptides at the human GLP-1 receptor, overexpressed in CHO cells

Biological activity was assessed by potency of peptides to stimulate cAMP production in Chinese Hamster Ovary (CHO) cell lines overexpressing the human GLP receptor. Cells were plated at a density of $8x10^{-5}$ cells/mL in serum-free media, into 96 well half area plates, on the day of the assay. A commercial cAMP kit (Cisbio) was used to quantify cAMP in the cell via HTRF (Homogeneous Time-Resolved Fluorescence) technology after 30 mins of peptide stimulation and a further 1h lysis. Plates were read on a SpectraMax i3x Multi-Mode Detection Platform plate reader and concentration response curves drawn with Graph Pad Prism 7.0 (or higher). EC_{50} values were generated for each peptide and compared to the controls for the day.

***In vivo* efficacy study: single dose feeding studies in male rats**

Male rats (Charles River Ltd, Margate, UK) were used for animal experiments. Ad libitum fed rats were individually housed in IVC cages. Animals were randomised into treatment groups, with stratification by body weight. All peptide solutions were prepared freshly immediately prior to administration. The control animals were dosed water 5% v/v water and 95% NaCl (0.9% w/v) whilst peptides (either 1.5, 2, 3 or 6 nmol/kg body weight) were resuspended in water for injection. Peptide and vehicle were administered in the early light phase (0900-1000) by subcutaneous injection and animals provided a known amount of food. Animals were given free access to food and water during the

study period. Animal body weight and remaining food were weighed throughout the study, typically 24, 48, 72 and 96, and in some examples 168h post dosing. The results presented are the figures for 4 (96h) or 7 days (168h) post dosing.

The results for Example compounds 1 to 527 are shown in Figure 1. The rats were dosed with a single subcutaneous injection of peptide. The dose was generally 1.5–6 nmol/kg body weight. In the Table in Figure 1, column 'n' shows the number of times the compound in question was tested. Each test generally involved the compound being given to a group of 5 animals. The compounds were assessed for their propensity to inhibit food intake and their ability to bring about body weight change. The summation of their actions is reported as a single value, called "potency" in Figure 1. The compounds were compared with semaglutide/Ozempic. For "potency", a score of 8 means that the compound causes the same effect as Ozempic. A score above 8 indicates that there is greater inhibition of food intake and reduction in body weight and/or reduction in body weight gain than achieved by the same dose of Ozempic, or a similar effect to Ozempic but achieved with a lower dose of the test compounds. These high activity levels allow a compound to be administered at a lower dose than for semaglutide/Ozempic. In some cases, the dose can be 1/6th, 1/8^{th}, 1/10^{th} or even 1/12^{th} of the level of semaglutide/Ozempic.

PK measurements for half-life assessment

Male large white pigs receive a single subcutaneous injection of the test compound at the start of study (0 hours). Repeated blood samples were taken from the pig over the proceeding 168 hours and plasma separated and stored at -20 to -80°C. Plasma concentration of the test compound was quantified using mass spectrum analysis. Time taken from t_{max} to half of C_{max} was calculated and represents the half-life ($t_{1/2}$) of the compound. Typically, the presented $t_{1/2}$ is the mean of four separate animals.

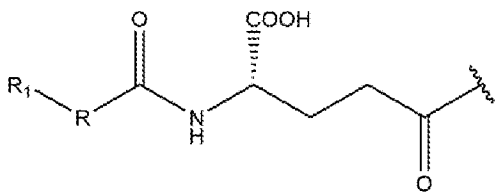
Results

Figure 1 is a table providing amino acid sequences and other structural information for the example compounds of the invention. For example, the amino acid sequence of example compound no. 1 is as follows [SEQ ID NO: 1]:

His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys
Gln	Leu	Glu	Glu	Glu	Ala	Val	Arg	Leu	Phe	Ile	Glu
Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro
Pro	Pro	Lys									

And the Lys residue at position 42 carries on its ε-amino group a group Z, where

Z is a group of formula:



wherein R is a C_{18} straight chain alkylene group; and

R^1 is CO_2H.

The figure also summarises the results of the *in vivo* feeding efficacy studies with the example peptides of the invention as discussed above.

To the right of the columns showing the feeding scores, the figure shows receptor potency data for example peptides at the GLP-1 receptor, overexpressed in Chinese hamster ovary (CHO) cells. Biological activity was assessed by the potency of peptides to stimulate cAMP production in the CHO cells as described above.

As can be seen from the Figure, rats which were given free access to food and which were administered example peptides of the invention, achieved reduced weight gain or achieved weight loss compared with rats which were administered saline. This supports

that the compounds of the invention are particularly effective at improving metabolism, and that they find use in the therapy of disorders such as obesity. However, the amount of food consumed by rats which were administered the example peptides was similar to or greater than the amount of food consumed by rats which were administered saline. The absence of, or only minimal, effect on amount of food ingested supports that the compounds have reduced side effects relating to nausea. As discussed above, rodents are not able to vomit, but those experiencing nausea are likely to be put off from consuming food. With the peptides of the invention, there was no observed evidence of the animals being put off consuming food.

Half-life:

The half-life of a selection of compounds of the invention was measured. The results, in hours, are shown in the column labelled t½ at the far right of the table in Figure 1.

Where in the foregoing description, integers or elements are mentioned which have known, obvious or foreseeable equivalents, then such equivalents are herein incorporated as if individually set forth. Reference should be made to the claims for determining the true scope of the present invention, which should be construed so as to encompass any such equivalents. It will also be appreciated by the reader that integers or features of the invention that are described as preferable, advantageous, convenient or the like are optional and do not limit the scope of the independent claims. Moreover, it is to be understood that such optional integers or features, whilst of possible benefit in some embodiments of the invention, may not be desirable, and may therefore be absent, in other embodiments.

Claims

1. A compound having an amino acid sequence of Formula (I):

Xaa1- AIB2- Xaa3-Gly4-Thr5-Phe6-Thr7-Ser8-Asp9-Xaa10-Ser11- Lys12- Gln13-Leu14- Glu15- Glu16-Xaa17-Xaa18-Val19-Xaa20-Xaa21-Phe22- Ile23- Glu24-Trp25-Leu26- Lys27-Xaa28-Xaa29-Gly30-Pro31-Ser32-Xaa33-Gly34-Xaa35-Xaa36- Pro37-Pro38-Xaa39-Xaa40-Xaa41-Lys42; (I) [SEQ ID NO: 528]

wherein

Xaa1 is His, Tyr or Phe;

Xaa3 is His, Gln or Glu;

Xaa10 is Leu, Tyr or Val;

Xaa17 is Glu or Lys;

Xaa18 is Ala or Arg;

Xaa20 is Arg, Gln, Lys or His;

Xaa21 is Leu, Ala, Arg, Lys or Glu;

Xaa28 is Ala, Asn, Gln, His;

Xaa29 is Gly or Ala;

Xaa33 is Ser, His or Gln;

Xaa35 is Lys, Pro, His, Arg, Asn, Gln, Glu, Ser or Ala;

Xaa36 is Phe, His, Gln, Glu, Lys, Ser, Arg or absent

Xaa39 is Pro or Gly;

Xaa40 is Gly or absent;

Xaa41 is Lys or absent;

and the lysine residue at position 42 is substituted at its ε-amino group with a group Y and Y is:

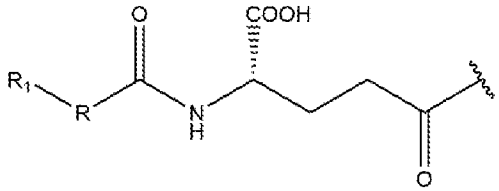
Z-Xaa43-Xaa44-

wherein:

Xaa43 is Asn or absent;

Xaa44 is His or absent;

and Z is a group of formula:



wherein R is a C_{16}-C_{18} alkylene or alkenylene group; and

R^1 is CO_2H;

or a derivative of the compound; or a salt or solvate of the compound or the derivative.

2. A compound, derivative, salt or solvate as claimed in claim 1 wherein:

Xaa17 is Lys;

Xaa20 is Arg or His;

Xaa21 is Leu or Glu;

Xaa28 is Ala, Gln or His;

Xaa29 is Gly;

Xaa33 is Ser

Xaa35 is Lys, Glu, His, Gln or Asn;

Xaa36 is absent;

Xaa39 is Pro;

Xaa41 is Lys;

Xaa43 is absent;

Xaa44 is absent; and

R is a C_{18} alkylene group

3. A compound, derivative, salt or solvate as claimed in claim 2 wherein:
Xaa1 is His or Phe;

Xaa3 is His or Glu;

Xaa10 is Tyr or Val;

Xaa17 is Lys;

Xaa18 is Ala or Arg;

Xaa20 is Arg or His;

Xaa21 is Glu;

Xaa28 is Ala or Gln;

Xaa35 is Lys; and

Xaa40 is Gly.

4. A compound, derivative, salt or solvate as claimed in claim 1, which has an amino acid sequence corresponding to any one of the amino acid sequences listed in the Table of Figure 1.

5. A derivative of a compound as claimed in any of claims 1 to 4, or a salt or solvate of such a derivative, which comprises one or more derivatisations selected from amidation, glycosylation, carbamylation, acylation, sulfation, phosphorylation, cyclization, lipidization, pegylation and fusion to another peptide or protein to form a fusion protein.

6. A compound, derivative, salt or solvate as claimed in any of claims 1 to 5 together with a further therapeutic agent, for simultaneous, sequential or separate administration.

7. A composition comprising a compound, derivative, salt or solvate as claimed in any of claims 1 to 6 together with a pharmaceutically acceptable carrier and optionally a further therapeutic agent.

8. A composition as claimed in claim 7, present in a syringe or other administration device for subcutaneous administration to humans.

9. A compound, derivative, salt or solvate as claimed in any of claims 1 to 6, or a composition as claimed in claim 7 or claim 8 for use as a medicament.

10. A method of treating or preventing a disease or disorder or other non-desired physiological state in a subject comprising administration of a therapeutically effective amount of a compound, derivative, salt or solvate as claimed in any of claims 1 to 6, or of a composition as claimed in claim 7 or claim 8.

11. A compound, derivative, salt or solvate as claimed in any of claims 1 to 6, or a pharmaceutical composition as claimed in claim 7 or claim 8, for use in the prevention or treatment of diabetes, obesity, heart disease, stroke and non-alcoholic fatty liver disease, improving insulin release in a subject, improving carbohydrate metabolism in a subject, improving the lipid profile of a subject, reducing appetite, reducing food intake, reducing calorie intake, improving carbohydrate tolerance in a subject, and/or for use as a cytoprotective agent.

12. A compound, derivative, salt or solvate or composition for use as a cytoprotective agent as claimed in claim 11, wherein the compound, derivative, salt or composition is

for use in the prevention or treatment of neurodegeneration, providing neuroprotection and/or providing cardiac protection.

13. A compound, derivative, salt or solvate or composition for use as a cytoprotective agent as claimed in claim 12, wherein the compound, derivative, salt or composition is for providing cardiac protection in a subject following a myocardial infarction.

14. A compound, derivative, salt or solvate or composition for use as a cytoprotective agent as claimed in claim 12, wherein the compound, derivative, salt or composition is for providing neuroprotection in a subject having or diagnosed as being at risk of a chronic neurodegenerative disease.

15. A compound, derivative, salt or solvate or composition for use as claimed in claim 14, wherein the chronic neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, Gehrig's disease (Amyotrophic Lateral Sclerosis), Huntington's disease, Multiple Sclerosis, other demyelination related disorders, senile dementia, subcortical dementia, arteriosclerotic dementia, AIDS-associated dementia, other dementias, cerebral vasculitis, epilepsy, Tourette's syndrome, Guillain Barre Syndrome, Wilson's disease, Pick's disease, neuroinflammatory disorders, encephalitis, encephalomyelitis, meningitis, other central nervous system infections, prion diseases, cerebellar ataxias, cerebellar degeneration, spinocerebellar degeneration syndromes, Friedrich's ataxia, ataxia teangiectasia, spinal dysmyotrophy, progressive supranuclear palsy, dystonia, muscle spasticity, tremor, retinitis pigmentosa, striatonigral degeneration, mitochondrial encephalomyopathies and neuronal ceroid lipofuscinosis.

16. A method of treating or preventing diabetes, obesity, heart disease, stroke or non-alcoholic fatty liver disease in a subject, improving insulin release in a subject, improving carbohydrate metabolism in a subject, improving the lipid profile of a subject, improving carbohydrate tolerance in a subject, reducing appetite, reducing food intake,

reducing calorie intake, and/or providing cytoprotection in a subject, comprising administration of a therapeutically effective amount of a compound, derivative, salt or solvate as claimed in any one of claims 1 to 6, or of a composition as claimed in claim 7 or claim 8.

17. Use of a compound, derivative, salt or solvate as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the prevention or treatment of diabetes, obesity, heart disease, stroke and non-alcoholic fatty liver disease, improving insulin release in a subject, improving carbohydrate metabolism in a subject, improving the lipid profile of a subject, improving carbohydrate tolerance in a subject, reducing appetite, reducing food intake, reducing calorie intake, and/or for use as a cytoprotective agent.

18. A method of causing weight loss or preventing weight gain in a subject for cosmetic purposes comprising administration of an effective amount of a compound, derivative, salt or solvate as claimed in any one of claims 1 to 6, or of a composition as claimed in claim 7 or claim 8.

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	5883	1	dupl 6149	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
2	6033	2		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
3	6036	3		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
4	6037	4		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
5	6038	5		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
6	6039	6		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
7	6040	7		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
8	6041	8		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
9	6043	9		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
10	6044	10		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
11	6060	11		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
12	6061	12		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
13	6063	13		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
14	6082	14		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
15	6083	15		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
16	6084	16		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
17	6087	17		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
18	6088	18		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
19	6089	19		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
20	6094	20		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
21	6095	21		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
22	6149	22	dupl 5883	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
23	6155	23		Phe	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
24	6157	24		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		His
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	His	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro			Lys	Asn	His

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
16	1	4	14	7	1.8	1	30
16	2	2	12	4	1.4		
18	3	1	4	2	11.5		
18	4	1	7	2	15.9		
18	5	1	6	2	13.9		
18	6	3	13	7	3.7		
18	7	1	5	2	6.6		
18	8	4	15	6	3.3		
18	9	1	4	3	6.8		
18	10	1	10	2	4.5		
18	11	1	6	2	5		
18	12	1	4	2	6		
18	13	1	3	2	6.7		
18	14	2	15	6	3.7		
18	15	7	13	8	3	3	77
18	16	1	10	5	3		
18	17	1	10	2	4.1		
18	18	1	10	4	4	1	57
18	19	1	11	2	3.5		
18	20	1	15	2	4.7		
18	21	4	15	4	2.8		
16	22			3	2		
16	23			1	59		
16	24	1	15	5	1.3	1	31

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
25	6158	25		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
26	6159	26		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
27	6160	27		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
28	6161	28		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
29	6162	29		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
30	6163	30		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
31	6168	31		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
32	6170	32		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
33	6173	33		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
34	6191	34	dupl 6341 + 6366 + 6458	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
35	6199	35		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
36	6205	36	dupl 6406 + 6470	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
37	6207	37		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
38	6211	38		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
39	6225	39		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
40	6226	40		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
41	6227	41		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
42	6237	42	dupl 6342	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
43	6238	43		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
44	6239	44	dupl 6578	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
45	6240	45		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
46	6243	46		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
47	6245	47		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
48	6249	48		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys	Asn	His
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys	Asn	
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys	Asn	
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys	Asn	
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys	Asn	
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys	Asn	
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
16	25	1	15	5	1	1	22
16	26	1	15				
16	27						
16	28						
16	29						
16	30	1	4	2	0.6		
18	31	1	7				
18	32	1	10				
16	33			2	2.6		
18	34	6	19	7	2.7	1	44
18	35	5	17	6	2.4	1	44
16	36	5	18	6	0.8		
16	37	1	13	2	1.3		
18	38	3	16	2	3		
18	39	3	14	6	2.8		
18	40	2	15	5	1.8		
18	41	2	17	3	1.5	1	43
18	42	5	18	12	1.5	1	30
18	43	1	7	2	1.8		
18	44	4	18	10	4.2	1	54
18	45	1	15	2	2.3		
18	46	1	15	2	1.9		
18	47	1	16	2	1.7	1	22
18	48	3	19	5	2.9	1	38

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
49	6250	49	dupl 6367	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
50	6252	50		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
51	6277	51		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
52	6299	52	dupl 6407	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
53	6321	53		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
54	6341	54	dupl 6191 + 6366 + 6458	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
55	6342	55	dupl 6237	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
56	6366	56	dupl 6191 + 6341 + 6458	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
57	6367	57	dupl 6250	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
58	6400	58		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
59	6401	59		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
60	6406	60	dupl 6205 + 6470	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
61	6407	61	dupl 6299	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
62	6458	62	dupl 6191 + 6341 + 6366	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
63	6470	63	dupl 6205 + 6406	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
64	6495	64		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
65	6496	65		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
66	6505	66		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
67	6506	67		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
68	6509	68		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
69	6510	69		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
70	6538	70		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
71	6539	71		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
72	6540	72		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Pro		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	49	3	18	9	3.3	3	48
18	50	1	16	4	3	1	55
18	51	1	12	2	5.6		
16	52	2	18	6	0.7		
18	53	1	7	2	5.6		
18	54	4	19	6	2.7	2	36
18	55	2	18	5	3.1		
18	56			2	4.8		
18	57	2	15	2	3.8		
16	58	3	14	2	1.2	1	76
18	59	1	5	2	3.5		
16	60			2	1.1		
16	61			3	0.9		
18	62			3	3.1		
16	63			3	0.8		
16	64	1	18	4	0.51	1	28
16	65	1	18	4	1.4	1	10
18	66	1	12	4	2.7	1	32
18	67	1	16	4	4.3	1	44
18	68	1	19	3	2.8	1	35
18	69	1	17	4	3	1	58
16	70	3	14	5	1.2	1	37
18	71	1	7	2	3.8		
16	72	1	10	2	0.8	1	67

0

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
73	6541	73		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
74	6545	74		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
75	6548	75		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
76	6549	76		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
77	6552	77		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
78	6553	78		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
79	6554	79		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
80	6555	80		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
81	6556	81		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
82	6557	82		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
83	6558	83		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
84	6559	84		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
85	6560	85		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
86	6561	86		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
87	6568	87		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
88	6569	88		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
89	6570	89		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
90	6571	90		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
91	6572	91		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
92	6573	92		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
93	6574	93		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
94	6575	94		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
95	6576	95		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
96	6577	96		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	73	1	8	3	3.2	1	54
18	74	1	6	2	1.8		
18	75	1	10	3	3.6	1	60
18	76	1	10	3	1.6	1	70
18	77	1	6	3	2.3		
18	78	1	6	3	3.3		
16	79	1	11	3	0.9		
18	80	1	5	3	2.5		
16	81	2	16	4	1	1	37
18	82	1	9	3	2.5		
16	83	2	15	3	0.6	1	68
18	84	1	6	3	1.7		
18	85	1	5	3	2.3		
18	86	1	7	2	2.6		
18	87	1	11	2	3.1	1	64
18	88	1	9	2	3.7		
18	89	1	7	2	4.5		
18	90	1	3	2	5.2		
16	91	1	14	2	0.6		
16	92	1	13	3	1.2	1	35
18	93	1	10	3	3	1	70
18	94	1	10	2	4.6		
18	95	1	12	2	4		
18	96	1	3	2	3.5		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
97	6578	97	dupl 6239	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
98	6579	98		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
99	6580	99		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
100	6581	100		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
101	6582	101		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
102	6583	102		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
103	6584	103	dupl 6935	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
104	6585	104		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
105	6587	105		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
106	6595	106		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
107	6597	107		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
108	6600	108		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
109	6601	109		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
110	6602	110		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
111	6603	111		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
112	6604	112		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
113	6605	113		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
114	6606	114	dupl 6608	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
115	6607	115		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
116	6608	116	dupl 6606	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
117	6609	117	dupl 6867	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
118	6610	118		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
119	6611	119		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
120	6612	120		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Gln	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys	Asn	His
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys	Asn	His
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys	Asn	His

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	97			2	5.1		
18	98	2	12	2	3.3	1	65
18	99	1	7	2	2.5		
18	100	1	7	2	2.6		
18	101	2	9	3	2.6	1	78
18	102	2	6	2	5.3	1	90
18	103	3	9	3	2.8	3	67
18	104	2	12	3	3.6	2	85
18	105	1	2	2	2.8		
18	106	1	12	4	4.7	1	37
18	107	2	9	4	3	2	68
18	108	1	8	2	3.8		
18	109	1	11	3	5.3		
16	110	2	16	5	1	1	46
18	111	2	15	4	1.6	2	67
18	112	3	16	6	2.2	2	56
18	113	2	10	4	2.9	2	47
18	114	1	12	2	2.6		
18	115	2	11	2	3.9	2	72
18	116	1	14	2	2.8	1	70
18	117	2	13	4	3.9	2	84
16	118	1	14	2	0.8		
16	119	1	17	2	0.9	1	62
16	120	1	16	3	1.2		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
121	6613	121		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
122	6614	122		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
123	6615	123		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
124	6616	124		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
125	6617	125		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
126	6618	126		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
127	6619	127		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
128	6620	128		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
129	6621	129		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
130	6622	130		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
131	6623	131		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
132	6624	132		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
133	6625	133		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
134	6626	134		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
135	6627	135		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
136	6628	136		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
137	6629	137	dupl 6873	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
138	6630	138		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
139	6633	139	dupl 6870	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
140	6634	140		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
141	6635	141		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
142	6636	142		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
143	6637	143		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
144	6638	144		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
16	121	1	13	2	0.9		
18	122	1	11	3	3.7	1	60
18	123	1	7	2	3.1		
18	124	1	10	2	3.3	1	71
16	125	1	16	2	0.9		
16	126	2	15	4	1	1	56
16	127	2	13	3	0.9	1	42
16	128	2	15	3	0.7		
16	129	2	15	4	0.9	1	35
16	130	1	13	2	0.6		
16	131	2	15	3	0.8		
16	132	2	16	3	0.7		
16	133	2	12	4	0.9	1	24
18	134	3	10	4	3.1	1	65
18	135	3	5	2	2.7	1	80
18	136	1	3	2	3		
18	137	2	7	5	3.3	2	97
18	138	1	5	2	3.7		
18	139	2	8	5	3.7	3	98
16	140	1	11	2	1		
18	141	1	6	2	3		
16	142	2	16	2	0.6	1	70
18	143	2	10	4	1.8	1	85
16	144	1	12	2	0.43		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
145	6639	145		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
146	6640	146		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
147	6641	147		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
148	6642	148		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
149	6643	149		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
150	6644	150		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
151	6645	151		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
152	6646	152		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
153	6647	153		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
154	6648	154		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
155	6649	155		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
156	6653	156		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
157	6655	157		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
158	6656	158		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
159	6657	159		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
160	6658	160		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
161	6659	161		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
162	6660	162		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
163	6661	163		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
164	6662	164		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
165	6663	165		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
166	6665	166		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
167	6666	167		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
168	6667	168		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu

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Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Gly			Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Arg		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Arg		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys	Asn	His

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	145	1	8	2	4.6		
18	146	1	13	2	3		
18	147	1	4	2	2.8		
16	148	1	9	3	1.5		
18	149	1	1	2	2.3		
18	150	1	12	2	2.2		
18	151	1	12	2	2.5	1	65
16	152	1	8	2	0.8		
18	153	2	10	2	2.2	1	61
16	154	1	9	2	0.7		
16	155	1	12	2	1.1		
18	156	1	3	2	3.5		
18	157	1	8	2	3.7		
16	158	1	12	3	1		
18	159	1	2	2	1.7		
18	160	1	7	2	2.6	1	57
16	161	1	10	3	0.9		
18	162	2	11	2	2.5	1	81
16	163	1	12	4	0.56		
18	164	2	7	2	2.4	1	64
18	165	1	5	2	2.6		
16	166	1	8	3	0.6		
18	167	1	4	2	2		
16	168	1	9	3	0.6		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
169	6668	169		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
170	6669	170		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
171	6670	171		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
172	6671	172		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
173	6672	173		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
174	6673	174		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
175	6677	175		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
176	6680	176		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
177	6681	177		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
178	6682	178		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
179	6683	179		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
180	6684	180		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
181	6685	181		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
182	6686	182		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
183	6688	183		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
184	6690	184		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
185	6691	185		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
186	6692	186		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
187	6693	187		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
188	6694	188		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
189	6695	189		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
190	6696	190		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
191	6697	191		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
192	6698	192		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

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Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ser		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys	Asn	His
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	169	1	2	2	1.8		
18	170	1	0	3	2.3		
18	171	1	5	2	2		
18	172	1	9	2	1.7		
16	173	1	11	2	0.7		
16	174	1	9	2	0.8		
18	175	1	5	3	3.5		
18	176	1	7	3	4.1		
16	177	1	7	2	1.7		
16	178	1	6	2	0.9		
16	179	1	13	2	0.55		
16	180	1	8	2	0.49		
16	181	1	8	2	0.52		
16	182	1	8	2	0.33		
16	183	1	10	2	0.51		
16	184	1	9	2	0.61		
16	185	1	6	2	0.6		
16	186	1	9	2	0.6		
18	187	1	8	2	2.3		
18	188	2	9	2	1.9	1	72
16	189	1	10	2	0.6		
18	190	2	7	4	2.2	1	100
16	191	1	11	2	0.6		
16	192	1	15	2	0.5		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
193	6699	193	dupl 6868	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
194	6700	194		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
195	6701	195		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
196	6702	196	dupl 6913	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
197	6703	197		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
198	6704	198		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
199	6705	199		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
200	6706	200		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
201	6707	201		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
202	6708	202		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
203	6709	203		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
204	6710	204		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
205	6711	205		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
206	6712	206		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
207	6713	207		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
208	6714	208		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
209	6715	209		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
210	6716	210		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
211	6717	211		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
212	6718	212		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
213	6719	213		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
214	6720	214		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
215	6721	215		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
216	6723	216		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro			Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	193	4	9	6	3.2	2	122
16	194	1	2	2	1.7		
16	195			2	1.4		
18	196	2	10	4	1.5	2	55
16	197	1	13	2	0.6		
16	198			2	0.8		
18	199	2	4	2	1.6	1	73
18	200	1	8	2	2.4		
18	201	2	8	2	2.1		
18	202	1	6	2	3.7		
18	203	1	6	2	2.9		
18	204	1	3	2	2.9		
16	205			2	0.7		
16	206			2	1.5		
18	207	2	6	2	2	1	89
16	208	1	4	2	0.7		
18	209	1	6	2	2.5		
18	210	1	8	2	2		
18	211	2	6	2	1.7		
18	212	1	0	2	1.7		
18	213	1	9	2	1.7		
18	214	1	-3	2	1.9		
18	215	1	0	2	2.4		
18	216	1	2	2	3.8		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
217	6724	217		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
218	6725	218		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
219	6726	219		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
220	6727	220		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
221	6728	221		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
222	6729	222		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
223	6730	223		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
224	6731	224	dupl 6920	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
225	6732	225	dupl 6872	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
226	6733	226		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
227	6734	227		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
228	6735	228	dupl 6869	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
229	6736	229		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
230	6737	230	dupl 6915	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
231	6738	231		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
232	6739	232		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
233	6740	233		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
234	6741	234		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
235	6742	235		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
236	6743	236		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
237	6744	237		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
238	6745	238		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
239	6746	239		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
240	6747	240		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly		Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
16	217			2	1.2		
16	218			2	0.9		
16	219			2	1.1		
16	220			2	1.3		
16	221	1	-1	2	0.9		
18	222	2	5	2	1.6	1	60
18	223	1	2	2	2.2		
18	224	1	5	2	2.5		
18	225	2	4	4	2.3	1	100
18	226	2	6	2	2.6		
18	227	2	10	2	3	1	74
18	228	2	5	6	2.6	1	106
18	229	1	1	2	2.1		
18	230	1	4	2	3.4		
18	231	1	5	5	2.3	1	101
18	232	1	2	2	1.8		
18	233	1	4	2	2.4		
18	234	2	6	2	2.8	1	89
18	235	1	6	2	1.2		
18	236	1	5	2	2.5		
18	237	1	4	2	2.1		
18	238	1	6	2	2.2	1	90
18	239	2	13	2	1.9	1	55
18	240	1	11	2	1.9	1	60

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
241	6748	241		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
242	6749	242		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
243	6750	243		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
244	6751	244		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
245	6752	245		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
246	6753	246		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
247	6754	247		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
248	6755	248		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
249	6756	249		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
250	6757	250		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
251	6758	251		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
252	6759	252		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
253	6760	253		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
254	6761	254		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
255	6762	255		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
256	6763	256		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
257	6764	257		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
258	6765	258		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
259	6766	259		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
260	6767	260		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
261	6768	261	dupl 6861	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
262	6769	262		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
263	6770	263		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
264	6771	264		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu

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Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Ser	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln	Ser	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His	Ser	Pro	Pro	Pro	Gly	Lys	Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	241	2	11	2	1.7	1	60
18	242	2	9	2	1.5	1	39
18	243	2	12	2	1.5	1	55
18	244	2	13	3	2.5	1	80
18	245	1	5	2	2		
18	246	2	12	3	1.7	1	32
18	247	2	9	2	1.1	1	59
18	248	2	10	2	2.6	1	48
18	249	2	10	2	1.2	1	60
18	250	1	8	2	1.5		
18	251	2	10	6	1.7	1	105
18	252	1	6	3	2.5		
18	253	2	5	3	2		
18	254	1	3	2	2.3		
18	255	1	3	2	2.2		
18	256	1	2	2	3.9		
18	257	1	1	2	2.9		
18	258	2	10	2	1.6		
18	259	2	11	2	2.4		
18	260	1	9	2	2.7	1	72
18	261	3	12	5	2.3	2	93
18	262	1	2	2	2.7		
18	263	1	2	2	2.1		
18	264	1	0	2	2.7		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
265	6774	265		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
266	6775	266		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
267	6776	267		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
268	6777	268		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
269	6778	269		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
270	6779	270		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
271	6780	271		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
272	6781	272		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
273	6782	273		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
274	6783	274		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
275	6787	275		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
276	6788	276		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
277	6790	277		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
278	6795	278		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
279	6796	279		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
280	6797	280		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
281	6798	281		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
282	6799	282		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
283	6800	283		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
284	6801	284		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
285	6802	285		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
286	6803	286		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
287	6804	287		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
288	6805	288		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Lys	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Gln	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Lys	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Lys	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His	His	Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	265	1	7	2	1.5		
18	266	1	3	2	1.6		
18	267	1	7	2	1.1		
18	268	1	11	2	2.5	1	40
18	269	2	15	4	2.6	1	99
18	270	1	11	6	2.1	1	93
18	271	2	10	2	1.8		
18	272	2	5	2	1.5		
18	273	2	10	2	2.5		
18	274	2	14	2	1.8	1	44
18	275	2	11	3	2.3		
18	276	2	5	2	1.2		
18	277	2	11	2	1.5		
18	278	2	7	3	2.9		
18	279	2	5	3	3.4		
18	280	2	9	3	3.9		
18	281	1	7	2	2.1		
18	282	1	11	2	2.7		
18	283	1	13	2	2.4	1	58
18	284	1	13	2	2.2	1	50
18	285	2	15	2	2.5	1	55
18	286	1	13	2	2.6	1	80
18	287	1	13	2	4.1	1	74
18	288	1	8	2	2.5		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
289	6806	289		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
290	6807	290		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
291	6808	291		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
292	6809	292		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
293	6810	293		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
294	6811	294		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
295	6812	295	dupl 6865	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
296	6813	296		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
297	6814	297		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
298	6815	298		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
299	6816	299	dupl 7074	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
300	6817	300		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
301	6818	301	dupl 7034	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
302	6819	302		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
303	6820	303		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
304	6821	304		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
305	6822	305		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
306	6823	306		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
307	6824	307		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
308	6825	308		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
309	6826	309		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
310	6827	310		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
311	6828	311		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
312	6829	312		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

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Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Ala		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	289	2	12	2	4.1	1	85
18	290	1	9	2	4.3		
18	291	1	2	2	2.8		
18	292	1	1	2	5.1		
18	293	1	2	2	3.5		
18	294	1	5	2	2.7		
18	295	2	11	2	3.4	1	85
18	296	2	10	4	3.5	2	82
18	297	2	12	2	4.7		
18	298	1	12	2	3.3	1	90
18	299	2	8	3	2.8	1	110
18	300	1	12	2	3.7		
18	301	8	15	11	1.9	3	120
18	302	1	8	2	4.3		
18	303	2	11	4	3.6	2	97
18	304	2	13	2	3		
18	305	1	13	2	2.7	1	73
18	306	1	18	4	2.3	2	93
18	307	1	17	2	2.4	1	59
18	308	3	14	6	1.9	2	97
18	309	2	13	6	2.3	2	98
18	310	1	11	2	2.7	1	100
18	311	6	14	6	1.4	5	137
18	312	1	12	2	4.2	1	40

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
313	6830	313		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
314	6831	314		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
315	6833	315		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
316	6834	316		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
317	6835	317		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
318	6836	318		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
319	6837	319		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
320	6838	320		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
321	6839	321		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
322	6840	322		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
323	6841	323		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
324	6860	324		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
325	6861	325	dupl 6768	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
326	6862	326		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
327	6863	327		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
328	6864	328		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
329	6865	329	dupl 6812	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
330	6867	330	dupl 6609	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
331	6868	331	dupl 6699	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
332	6869	332	dupl 6735	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
333	6870	333	dupl 6633	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
334	6872	334	dupl 6732	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
335	6873	335	dupl 6629	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
336	6887	336		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	His	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Lys	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	313	1	3	2	3.8		
18	314	1	4	2	3		
18	315	1	7	2	3.6		
18	316	1	7	2	5.5		
18	317	1	7	2	3		
18	318	1	7	2	2.3		
18	319	1	5	2	2		
18	320	1	6	2	2.9		
18	321	1	7	2	2.1		
18	322	1	8	2	2.3		
18	323	1	10	2	2.5		
18	324	1	14	6	1.9	1	83
18	325	2	12	6	2.2	1	93
18	326	1	10	2	2.4		
18	327	1	8	2	2.2		
18	328	1	9	2	2		
18	329	1	10	2	1.9		
18	330	1	15	6	4.2		
18	331	1	9	2	4		
18	332	1	4	2	3		
18	333	1	7	2	5.1		
18	334	1	5	2	3.5		
18	335	1	11	2	5		
18	336	1	10	2	4		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
337	6888	337		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
338	6889	338		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
339	6890	339		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
340	6891	340		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
341	6895	341		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
342	6897	342		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
343	6898	343		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
344	6901	344		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
345	6902	345		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
346	6903	346		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
347	6904	347		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
348	6906	348		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
349	6910	349		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
350	6911	350		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
351	6912	351		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
352	6913	352	dupl 6702	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
353	6914	353		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
354	6915	354	dupl 6737	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
355	6916	355		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
356	6917	356		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
357	6918	357		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
358	6919	358		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
359	6920	359	dupl 6731	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
360	6921	360		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Lys	His	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His	His	Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His	Lys	Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	His	Glu	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Lys	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Lys	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	337	1	6	2	6.3		
18	338	1	5	2	4.5		
18	339	1	6	2	8		
18	340	1	5	2	5.3		
18	341	1	13	2	3.7		
18	342	2	14	2	3.5	1	85
18	343	1	6	2	6.9		
18	344	1	2	2	4		
18	345	1	7	2	5.4		
18	346	1	3	2	5.3		
18	347	1	12	2	2.7		
18	348	1	11	2	3.3		
18	349	1	9	2	5.7		
18	350	1	13	2	7.7	1	65
18	351	2	12	4	3.9	1	105
18	352	2	10	2	2		
18	353	2	11	2	3.6	1	79
18	354	1	6	2	3.6		
18	355	1	3	2	4.5		
18	356	1	11	2	3.8	1	71
18	357	1	8	2	3.9		
18	358	1	12	2	5.2	1	69
18	359	1	9	2	2.7		
18	360	1	11	2	4		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
361	6922	361		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
362	6923	362		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Glu
363	6924	363		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
364	6925	364		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
365	6926	365		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
366	6927	366		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
367	6929	367		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
368	6930	368		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
369	6931	369		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
370	6932	370		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
371	6934	371		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
372	6935	372	dupl 6584	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
373	6937	373		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
374	6938	374		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
375	6940	375		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
376	6941	376		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
377	6943	377		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
378	6944	378		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
379	6945	379		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
380	6946	380		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
381	6947	381		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
382	6949	382		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
383	6950	383		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
384	6951	384		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys	Asn	His
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys	Asn	His
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro		Lys	Lys		
Arg	Val	His	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly		Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	361	1	14	2	5.3	1	50
18	362	1	10	2	4.7		
18	363	2	13	2	3.9	1	49
18	364	1	11	2	5.1		
18	365	1	11	2	5.6		
18	366	1	13	2	5.3	1	72
18	367	1	8	2	4.7		
18	368	1	10	2	3.6		
18	369	1	10	2	5.3		
18	370	1	4	2	3.8		
18	371	1	7	2	5		
18	372	1	11	2	3.9		
18	373	2	14	2	2.9	1	80
18	374	2	15	6	2.1	1	112
18	375	2	16	4	2.1	1	105
18	376	2	14	6	2.1	1	100
18	377	2	15	2	1.9		
18	378	2	12	2	1.9		
18	379	2	12	2	1.6	1	55
18	380	1	12	2	1.5		
18	381	2	18	2	1.5	1	78
18	382	1	10	2	1.9		
18	383	1	10	2	1.8		
18	384	1	11	2	1.5		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
385	6952	385		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
386	6953	386		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
387	6955	387		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
388	6956	388		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
389	6957	389		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
390	6958	390		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
391	6959	391		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
392	6960	392		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
393	6961	393		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
394	6962	394		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
395	6964	395		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
396	6965	396		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
397	6966	397		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
398	6967	398	dupl 7022	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
399	6968	399		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
400	6969	400		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
401	6970	401		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
402	6971	402		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
403	6972	403		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
404	6973	404		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
405	6974	405		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
406	6976	406		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
407	6977	407		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
408	6978	408		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Ala	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys	Asn	His
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys	Asn	His
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys	Asn	His
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys	Asn	His
Arg	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	His	Gly	Lys		Pro	Pro	Pro		Lys	Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	385	1	16	2	2	1	83
18	386	1	16	3	1.7	1	99
18	387	1	10	2	6.3		
18	388	2	14	6	3.2	1	70
18	389	1	6	2	2.9		
18	390	2	16	2	4.7	1	61
18	391	2	15	6	3		
18	392	2	11	2	2.8		
18	393	1	11	2	2.7		
18	394	1	8	2	2.5		
18	395	1	1	2	3.3		
18	396	1	0	2	2.4		
18	397	1	2	2	2.4		
18	398	4	18	6	2.7	3	110
18	399	3	11	3	2.5	1	110
18	400	1	5	2	2.9		
18	401	1	12	2	2.9		
16	402	1	8	2	0.7		
16	403	1	18	2	1.1	1	58
18	404	1	8	2	3.8		
18	405	1	8	2	6.1		
18	406	1	8	2	5.5		
18	407	1	2	2	5.3		
18	408	1	7	2	6.8		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
409	6979	409		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
410	6980	410		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
411	6981	411		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Glu
412	6982	412		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
413	6983	413		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
414	6984	414		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
415	6985	415		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
416	6986	416		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
417	6988	417		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
418	6989	418		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
419	6990	419		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
420	6991	420		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
421	6992	421		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
422	6993	422		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
423	6995	423		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
424	6997	424		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
425	6999	425		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
426	7000	426		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
427	7001	427		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
428	7002	428		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
429	7003	429		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
430	7004	430		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Glu
431	7005	431		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
432	7006	432		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Leu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro		Lys	Lys		
Arg	Val	Lys	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly		Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His	Gln	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln	His	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Gln	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln	Gln	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu	Phe	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Phe	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Phe	Pro	Pro	Gly		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Gln	Pro	Pro	Gly		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Pro	Ser	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Ser	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Gln	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		

WO 2022/123271 PCT/GB2021/053249

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	409	1	5	2	3.8		
18	410	1	5	2	4.5		
18	411	1	1	2	4.9		
18	412	1	3	2	2.9		
18	413	1	10	2	2.6		
18	414	1	11	3	3.8		
18	415	1	7	3	3.6		
18	416	1	7	3	2.7		
18	417	1	7	3	2.8		
18	418	1	6	2	3.5		
18	419	1	10	2	2.8		
18	420	2	13	2	2.6		
18	421	1	9	2	3.4		
18	422	1	8	2	3		
18	423	1	13	3	3		
18	424	1	12	2	3.8		
18	425	1	5	3	5.4		
18	426	1	9	3	3.8		
18	427	1	6	3	1.9		
18	428	3	18	6	2.9		
18	429	4	18	6	2.5	2	120
18	430	1	12	3	2.3		
18	431	3	21	6	2.4	2	78
18	432	2	15	6	2.1	2	96

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
433	7007	433		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Glu
434	7008	434		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
435	7009	435		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
436	7010	436		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
437	7011	437		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
438	7012	438		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
439	7013	439		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
440	7014	440		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
441	7016	441		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
442	7017	442		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
443	7018	443		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
444	7019	444		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
445	7020	445		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
446	7022	446	dupl 6967	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
447	7023	447		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
448	7024	448		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
449	7025	449		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
450	7026	450		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
451	7030	451	dupl 7032	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
452	7031	452		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
453	7032	453	dupl 7030	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
454	7033	454	dupl 7073	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
455	7034	455	dupl 6818	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
456	7036	456		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Gly		Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Arg	Pro	Pro	Gly		Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Arg	Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Arg		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Glu	Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Asn	Ala	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		

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Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	433	1	12	3	1.9		
18	434	3	15	6	1.9		
18	435	2	15	6	2.1	1	48
18	436	5	16	5	2.5	1	90
18	437	1	10	2	2.6		
18	438	1	10	2	2.4		
18	439	1	13	2	4.5		
18	440	2	16	3	2.1	1	91
18	441	1	13	2	2.5	1	68
18	442	1	11	2	2.5		
18	443	1	13	2	3	1	92
18	444	1	12	2	4.9		
18	445	1	8	2	2.5		
18	446	3	13	5	2	1	106
18	447	1	12	2	2.3		
18	448	1	9	2	3.1		
18	449	2	13	3	2.7	1	100
18	450	1	13	2	2.9		
18	451	3	19	6	2.9	2	115
18	452	4	19	2	2.9	1	62
18	453	3	19	7	3.2		
18	454	7	21	6	2.5	3	101
18	455	5	19	6	2		
18	456	2	17	2	3.7	1	100

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
457	7037	457		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
458	7038	458		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
459	7039	459		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
460	7040	460		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
461	7041	461		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
462	7042	462		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
463	7043	463		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
464	7044	464		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
465	7045	465		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
466	7046	466		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
467	7047	467		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
468	7048	468		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
469	7049	469		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
470	7050	470		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
471	7051	471		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
472	7052	472		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
473	7053	473		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
474	7054	474		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
475	7055	475		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
476	7056	476		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
477	7057	477		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
478	7062	478		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
479	7063	479		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
480	7064	480		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys

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Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	His	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Asn		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	His		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	His	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	457	1	14	3	3.2		
18	458	2	17	2	3.6	1	86
18	459	1	12	2	3.6		
18	460	2	13	2	3.3		
18	461	3	14	2	3.6	1	130
18	462	1	13	2	4.2		
18	463	1	15	2	2.9		
18	464	1	12	2	3.5		
18	465	4	17	4	2.2	2	106
18	466	2	13	2	3.9		
18	467	2	10	2	3.6		
18	468	2	16	2	2.9		
18	469	2	16	2	2.9		
18	470	3	18	2	2.3	1	73
18	471	1	14	2	2.5		
18	472	2	18	3	2		
18	473	2	16	2	3		
18	474	1	8	2	3.6		
18	475	1	6	2	2.6		
18	476	1	9	2	3.2		
18	477	1	11	2	2.5		
18	478	2	17	3	2.6	1	85
18	479	1	13	2	2.1		
18	480	1	12	2	2.9		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
481	7065	481		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
482	7066	482		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
483	7067	483		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
484	7068	484		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
485	7069	485		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
486	7070	486		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
487	7071	487		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
488	7072	488		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
489	7073	489	dupl 7033	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
490	7074	490	dupl 6816	His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
491	7075	491		Tyr	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
492	7076	492		Phe	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
493	7077	493		Tyr	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
494	7078	494		Tyr	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
495	7079	495		Phe	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
496	7080	496		Tyr	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
497	7092	497		His	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
498	7093	498		Tyr	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
499	7094	499		Phe	AIB	His	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
500	7095	500		Tyr	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
501	7096	501		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
502	7097	502		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
503	7098	503		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
504	7099	504		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Gly		Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Gly		Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Gly		Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Gly		Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Gly		Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	481	2	18	4	2	1	80
18	482	4	18	5	2.9	1	88
18	483	1	6	2	4		
18	484	1	11	2	4.2		
18	485	2	13	2	4.3	1	87
18	486	3	17	7	4.4		
18	487	1	13	2	3.9		
18	488	1	14	2	4.9		
18	489	2	24	4	1.8		
18	490	2	18	2	2.2		
18	491	1	3	2	6.9		
18	492	1	4	2	3.9		
18	493	7	16	6	5.1	3	112
18	494			2	39.3		
18	495			2	13.6		
18	496			3	9.2		
18	497	3	14	5	1.6	1	97
18	498			2	60.5		
18	499			2	25.1		
18	500	1	4	2	52.2		
18	501	1	9	4	14.4		
18	502	7	15	9	5.7	6	125
18	503	1	10	2	22.8		
18	504	1	6	2	12.2		

Figure 1

Ex	G ref	SEQ ID	Note	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
505	7100	505		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
506	7101	506		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
507	7102	507		His	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
508	7103	508		His	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
509	7104	509		His	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
510	7105	510		His	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ser	Lys	Gln	Leu	Glu	Glu	Lys
511	7107	511		His	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Leu	Ser	Lys	Gln	Leu	Glu	Glu	Lys
512	7122	512		Phe	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
513	7123	513		Phe	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
514	7124	514		His	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
515	7125	515		His	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
516	7130	516		Tyr	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
517	7131	517		Tyr	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
518	7134	518		Tyr	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
519	7135	519		His	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
520	7136	520		His	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
521	7137	521		His	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
522	7138	522		His	AIB	Gln	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
523	7145	523		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
524	7146	524		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
525	7147	525		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
526	7148	526		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys
527	7150	527		Phe	AIB	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Lys	Gln	Leu	Glu	Glu	Lys

Figure 1

18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Pro	Gly	Lys	Lys		
Ala	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys	Lys	Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Ala	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Glu		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Gln		Pro	Pro	Pro	Gly	Lys	Lys		
Arg	Val	Arg	Glu	Phe	Ile	Glu	Trp	Leu	Lys	Gln	Gly	Gly	Pro	Ser	Ser	Gly	Lys		Pro	Pro	Pro	Gly	Lys	Lys		

Figure 1

n (R = Cn)	Ex	Feeding study scores		Receptor binding results		Half life	
		n	potency	n	human GLP1R cAMP CHO cells	n	t1/2 (h)
18	505	1	13	2	6	1	88
18	506	6	14	4	8.5	3	102
18	507	6	15	4	2.1	5	118
18	508	2	17	2	2.5	1	107
18	509	4	18	3	2.4	1	62
18	510	3	16	4	2.5	2	110
18	511	3	19	4	1.6	2	111
18	512	2	22	4	6.1	1	88
18	513	1	7	2	10		
18	514	6	20	7	6.6	6	121
18	515	2	15	2	2.1		
18	516	3	17	4	4.6		
18	517	3	16	5	6.3	2	134
18	518	1	14	2	4.3		
18	519	3	19	2	5	1	94
18	520	2	19	2	6.7	1	63
18	521	1	18	2	12.7		
18	522	1	15	2	10		
18	523	3	18	7	3.3	1	97
18	524	2	16	2	4.3	1	98
18	525	2	14	2	4.7		
18	526	2	12	2	5.5		
18	527						

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2021/053249

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/605 A61P3/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/081418 A1 (COVX TECHNOLOGIES IRELAND LTD [IE]; BRADSHAW CURT [US] ET AL.) 10 July 2008 (2008-07-10) the whole document, in particular SEQ ID NOs: 14,173	1-18
X	CN 104 211 801 A (HANGZHOU SINOPEP PHARMACEUTICAL INC) 17 December 2014 (2014-12-17) the whole document	1-18
X	WO 2005/021022 A2 (NOVO NORDISK AS [DK]; SCHLEIN MORTEN [DK]; LUDVIGSEN SVEND [DK]) 10 March 2005 (2005-03-10) the whole document, in particular p.8, l.22-23 and claims, especially claim 26	1-18

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2022	22/03/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bassias, Ioannis

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2021/053249

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

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      [ ] in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).

      [ ] on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2021/053249

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No
PCT/GB2021/053249

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