Compounds of formula (I) or pharmaceutically acceptable salts thereof are GPCR agonists and are useful as for the treatment of obesity and diabetes.
PIPERIDINE GPCR AGONISTS

BACKGROUND OF THE INVENTION

The present invention is directed to G-protein coupled receptor (GPCR) agonists. In particular, the present invention is directed to GPCR agonists that are useful for the treatment of obesity, e.g. as regulators of satiety, metabolic syndrome and for the treatment of diabetes.

Obesity is characterized by an excessive adipose tissue mass relative to body size. Clinically, body fat mass is estimated by the body mass index (BMI; weight(kg)/height(m)^2), or waist circumference. Individuals are considered obese when the BMI is greater than 30 and there are established medical consequences of being overweight. It has been an accepted medical view for some time that an increased body weight, especially as a result of abdominal body fat, is associated with an increased risk for diabetes, hypertension, heart disease, and numerous other health complications, such as arthritis, stroke, gallbladder disease, muscular and respiratory problems, back pain and even certain cancers.

Pharmacological approaches to the treatment of obesity have been mainly concerned with reducing fat mass by altering the balance between energy intake and expenditure. Many studies have clearly established the link between adiposity and the brain circuitry involved in the regulation of energy homeostasis. Direct and indirect evidence suggest that serotonergic, dopaminergic, adrenergic, cholinergic, endocannabinoid, opioid, and histaminergic pathways in addition to many neuropeptide pathways (e.g. neuropeptide Y and melanocortins) are implicated in the central control of energy intake and expenditure. Hypothalamic centres are also able to sense peripheral hormones involved in the maintenance of body weight and degree of adiposity, such as insulin and leptin, and fat tissue derived peptides.

Drugs aimed at the pathophysiology associated with insulin dependent Type I diabetes and non-insulin dependent Type II diabetes have many potential side effects and do not adequately address the dyslipidaemia and hyperglycaemia in a high proportion of patients. Treatment is often focused at individual patient needs using diet, exercise, hypoglycaemic agents and insulin, but there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, metabolic syndrome (syndrome X) places people at high risk of coronary artery disease, and is characterized by a cluster of risk factors including central obesity (excessive fat tissue in the abdominal region), glucose intolerance, high triglycerides and low HDL cholesterol, and high blood pressure. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

GPR19 (previously referred to as GPR16) is a GPCR identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors, US 6,468,756 also discloses the mouse receptor (accession numbers: AAN95194 (human), AAN95195 (rat) and ANN95196 (mouse)).

In humans, GPR19 is expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR19 receptor indicates its potential utility as a target for the treatment of obesity and diabetes.
and WO2006/067532 disclose heterocyclic derivatives as GPR19 receptor agonists.
International patent applications PCT/GB2006/050176, PCT/GB2006/050177,
PCT/GB2006/050178 and PCT/GB2006/050182 (published after the priority date of the present
application) disclose further GPR19 receptor agonists.

The present invention relates to agonists of GPR19 which are useful for the treatment
of obesity e.g. as peripheral regulators of satiety, metabolic syndrome and for the treatment of
diabetes.

SUMMARY OF THE INVENTION

Compounds of formula (I):

![Chemical Structure](image)

or pharmaceutically acceptable salts thereof, are agonists of GPR19 and are useful for the
prophylactic or therapeutic treatment of obesity and diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I), or a pharmaceutically
acceptable salt thereof:

![Chemical Structure](image)

wherein one of X and Y is O and the other is N;
R¹ is SO₂R⁵, NR⁶R⁷, or CONR⁶R⁷;
R² is hydrogen or methyl;
R³ is hydrogen or methyl;
R⁴ is C₂₋₅ alkyl;
R⁵ is C₁₋₃ alkyl;
R⁶ and R⁷ are independently hydrogen, C₁₋₄ alkyl, which may optionally be substituted
by halo, hydroxy, C₁₋₄ alkoxy, aryloxy, arylC₁₋₄ alkoxy, C₁₋₄ alkylS(O)ᵢᵢᵢ, C₃₋₇ heterocyclyl,
N(R⁸)₂ or -C(O)OR⁸; or may be C₃₋₇ cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein the
cylic groups may be substituted with one or more substituents selected from halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl,
OR⁶, CN, SO₂CH₃, N(R⁸)₂ and NO₂; or taken together R⁶ and R⁷ may form a 5- or
6-membered heterocyclic ring optionally substituted by hydroxy, C₁₋₄ alkyl or C₁₋₄ hydroxyalkyl
and optionally containing a further heteroatom selected from O and NR⁸;
R^8 are independently hydrogen or C_1-4 alkyl; or a group N(R^8)_2 may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR^8:  

R^9 is hydrogen or C_1-4 alkyl; and  
m is 0, 1 or 2.  
In one embodiment of the invention X is O and in another Y is O.  
X is preferably O.  
Y is preferably N.  
When R^1 is CONHR^6, R^2 is preferably methyl.  
In one embodiment of the invention R^3 is hydrogen and in another R^3 is methyl. When R^3 is methyl, the stereocentre created preferably has the (R)-configuration.  
R^4 is preferably C_3-4 alkyl, particularly w-propyl, isopropyl, or tert-butyl, even more preferably C_3 alkyl, especially isopropyl.  
R^5 is preferably methyl.  
R^6 is preferably hydrogen, C_i_3 alkyl, or C_2-3 alkyl substituted by hydroxy and R^7 is preferably hydrogen.  
When R^6 is C_2-3 alkyl substituted by hydroxy, it may be substituted by one or more, e.g. 1 or 2, preferably 1, hydroxy group.  
R^6 is more preferably C_i_3 alkyl or C_2-3 alkyl substituted by hydroxy, more preferably C_2-3 alkyl substituted by hydroxy, e.g. 2-hydroxyethyl, 2-hydroxy-l-methylethyl, 2,3-dihydroxypropyl or 2-hydroxy-l-hydroxymethylethyl, preferably 2-hydroxyethyl or 2-hydroxy-l-methylethyl, even more preferably 2-hydroxy-l-methylethyl, especially (R)-2-hydroxy-l-methylethyl.  

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred and particularly listed groups.  
Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.  

As used herein, unless stated otherwise, "alkyl" means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl and pentyl.  
The term "halo" includes fluorine, chlorine, bromine, and iodine atoms, in particular fluorine or chlorine, especially fluorine.  

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in
using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, hydrochloric, methanesulfonic, sulfuric, p-toluenesulfonic acid and the like.

Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as described below. PG represents a protecting group, G is a substituted oxadiazole as defined above, and R₁, R₂, R³ and R⁴ are also as defined above.

Compounds of formula (II), where PG is a suitable protecting group can be readily prepared from known compounds (Scheme 1). For example, the ethyl ester of compound (II) where PG is Boc has been previously reported (US Patent 6,518,423). Hydrogenation under standard conditions will yield the racemic compound of formula (III). Chiral reduction of the alkene under suitable conditions such as a hydrogenation in the presence of a chiral catalyst yields compounds of formula (III) in high enantiomeric excess. An example of a suitable catalyst is [Rh(norbornadiene)₂]BF₄ and (5)-1-[(R)-2-(di-tert-butylphosphino)ferrocenyl]-ethylbis(2-methylphenyl)phosphine. Compounds of formula (IV) can then be obtained by reduction of the carboxylic acids of formula (III) under standard conditions, for example borane in a suitable solvent such as THF. Removal of the protecting group is then achieved under conditions well known to those with skill in the art.

![Scheme 1](image_url)

The compound of formula (V) where R₃= H is a known compound (Scheme 2, Siegel, M. G. et al. Tetrahedron 1999, 55, 11619-1 1639). Compounds of formula (VII) can be prepared from compounds of formula (V) under standard conditions. For example, treatment of compounds of formula (V) with cyanogen bromide followed by condensation of the resultant cyanamide (VI) with a compound of formula (IX) under standard conditions yields compounds of formula (VII) where X is O. Compounds of formula (IX) are either commercially available, or readily prepared from the corresponding carboxylic acids using well known techniques. Alternatively, synthesis of the regioisomeric oxadiazole, where Y is O, can be achieved by heating compounds of formula (VI) with hydroxylamine to give N-hydroxyguanidines of
formula (VIII) that may be condensed with a carboxylic acid of formula (X) under suitable conditions. Acids of formula (X) are commercially available.

Scheme 2


Scheme 3

Compounds of formula (I) where R^1 is either a sulfone or amide can be formed as outlined in Scheme 4. The compound where R^1 is methylsulfonyl and R^2 is hydrogen has been reported previously (WO 2005/063738). Combining compounds of formula (VIII) and formula (VII) using Mitsunobu conditions, for example in a suitable solvent such as THF, at between 0°C and room temperature, followed by the addition of triphenylphosphine and diisopropylazodicarboxylate yields compounds of formula (I). Compounds of formula (I) where R^1 is an amide can be synthesized starting from the commercially available compound of formula (VIII) where R^1 is cyano and R^2 is methyl using chemistry well known to those with skill in the art. For example, Mitsunobu condensation of this compound with the alcohol of formula (VII) would give a cyanopyridine that could be transformed into the corresponding acid by hydrolysis, then onto the desired amides by standard amide bond-forming techniques. Aminopyridines of formula (I) may be prepared from the corresponding sulfones of formula (I) by displacement of alkanesulfmate by the appropriate amine on heating at an elevated temperature.

Scheme 4
Other compounds of formula (I) may be prepared by methods analogous to those described above or by methods known per se.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000, compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

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Any novel intermediates, such as those defined above, may be of use in the synthesis of compounds of formula (I) and are therefore also included within the scope of the invention, as well as salts or protected derivatives thereof.

As indicated above the compounds of formula (I) are useful as GPR1 19 agonists, e.g. for the treatment and/or prophylaxis of obesity and diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), in combination with a pharmaceutically acceptable carrier.
Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by modulating GPRI 19, resulting in the prophylactic or therapeutic treatment of obesity, e.g. by regulating satiety, or for the treatment of diabetes, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like
may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable accessory machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.
In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I) may be used in the treatment of diseases or conditions in which GPRI 19 plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which GPRI 19 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. Diseases or conditions in which GPRI 19 plays a role include obesity and diabetes. In the context of the present application the treatment of obesity is intended to encompass the treatment of diseases or conditions such as obesity and other eating disorders associated with excessive food intake e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound and diabetes (including Type 1 and Type 2 diabetes, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts, cardiovascular complications and dyslipidaemia). And the treatment of patients who have an abnormal sensitivity to ingested fats leading to functional dyspepsia. The compounds of the invention may also be used for treating metabolic diseases such as metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and hypertension.

The compounds of the invention may offer advantages over compounds acting via different mechanisms for the treatment of the above mentioned disorders in that they may offer beta-cell protection, increased cAMP and insulin secretion and also slow gastric emptying.

The compounds of the invention may also be used for treating conditions characterised by low bone mass such as osteopenia, osteoporosis, rheumatoid arthritis, osteoarthritis, periodontal disease, alveolar bone loss, osteotomy bone loss, childhood idiopathic bone loss, Paget's disease, bone loss due to metastatic cancer, osteolytic lesions, curvature of the spine and loss of height.

The invention also provides a method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.
The invention also provides a method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of diabetes, including Type 1 and Type 2 diabetes, particularly type 2 diabetes, comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglycerideremia, hypercholesterolemia, low HDL levels or hypertension comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I) may exhibit advantageous properties compared to known GPR 119 agonists, for example, the compounds may exhibit improved potency or stability, or improved solubility thus improving absorption properties and bioavailability, or other advantageous properties for compounds to be used as pharmaceuticals.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I) or a different disease or condition. The therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of formula (I) may be administered with other active compounds for the treatment of obesity and/or diabetes, for example insulin and insulin analogs, gastric lipase inhibitors, pancreatic lipase inhibitors, sulfonyl ureas and analogs, biguanides, α2 agonists, glitazones, PPAR-γ agonists, mixed PPAR-α/γ agonists, RXR agonists, fatty acid oxidation inhibitors, α-glucosidase inhibitors, dipeptidyl peptidase IV inhibitors, GLP-I agonists e.g. GLP-I analogues and mimetics, β-agonists, phosphodiesterase inhibitors, lipid lowering agents, glycogen phosphorylase inhibitors, antiobesity agents e.g. pancreatic lipase inhibitors, MCH-I antagonists and CB-I antagonists (or inverse agonists), amylin antagonists, lipoxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTP1B inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, serotonergic/dopaminergic antiobesity drugs, reuptake inhibitors e.g. sibutramine, CRF antagonists, CRF binding proteins, thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-I inhibitors or sorbitol dehydrogenase inhibitors.
Combination therapy comprising the administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and at least one other antiobesity agent represents a further aspect of the invention.

The present invention also provides a method for the treatment of obesity in a mammal, such as a human, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent, to a mammal in need thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent for the treatment of obesity.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with another antiobesity agent, for the treatment of obesity.

The compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s) may be co-administered or administered sequentially or separately.

Co-administration includes administration of a formulation which includes both the compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s), or the simultaneous or separate administration of different formulations of each agent. Where the pharmacological profiles of the compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s) allow it, coadministration of the two agents may be preferred.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent in the manufacture of a medicament for the treatment of obesity.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent, and a pharmaceutically acceptable carrier. The invention also encompasses the use of such compositions in the methods described above.

GPRI 19 agonists are of particular use in combination with centrally acting antiobesity agents.


Other diseases or conditions in which GPRI 19 has been suggested to play a role include those described in WO 00/50562 and US 6,468,756, for example cardiovascular disorders,
hypertension, respiratory disorders, gestational abnormalities, gastrointestinal disorders, immune disorders, musculoskeletal disorders, depression, phobias, anxiety, mood disorders and Alzheimer's disease.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

Materials and methods

Column chromatography was carried out on Siθ₂ (40-63 mesh) unless specified otherwise. LCMS data were obtained as follows: Atlantis 3μ C18 column (3.0 X 20.0 mm, flow rate = 0.85 mL/min) eluting with a H₂O-CH₃CN solution containing 0.1% HCO₂H over 6 min with UV detection at 220 nm. Gradient information: 0.0-0.3 min 100% H₂O; 0.3-4.25 min: Ramp up to 10% H₂O-90% CH₃CN; 4.25-4.4 min: Ramp up to 100% CH₃CN; 4.4-4.9 min: Hold at 100% CH₃CN; 4.9-6.0 min: Return to 100% H₂O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES⁺) or negative (ES⁻) ion modes.

Abbreviations and acronyms; Ac: Acetyl; DIPEA: N,N-Diisopropylethylamine; EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Et: Ethyl; h: hour(s); HOBt: 1-Hydroxybenzotriazole; IH: Isohexane; /Pr: Isopropyl; Me: Methyl; RT: Retention time; THF: Tetrahydrofuran; TMEDA: N⁺, N⁺, N⁺, N⁺-Tetramethylethylenediamine.

The syntheses of the following compounds have been described elsewhere: N-Hydroxyisobutryramidine: J. Org. Chem. 2003, 68, 7316-7321; 3-Piperidin-4-ylpropan-l-ol: Tetrahedron 1999, 55, 11619-1 1639. All other compounds were available from commercial sources.

Preparation 1: 4-(3-Hydroxypropyl)piperidine-l-carbonitrile

![Image](attachment://attachment.png)

A slurry OfNaHCO₃ (35.2 g, 0.42 mol) in H₂O (70 mL) was added to a stirred solution of 3-piperidin-4-ylpropan-l-ol (20.0 g, 0.14 mol) in CH₂Cl₂ at 0°C. A solution of BrCN (17.8 g, 0.17 mol) in CH₂Cl₂ (19 mL) was added to the reaction over 1 min, then stirring was continued at 0°C for 0.5 h. The reaction was then stirred at 20°C for 2 h, before being washed with saturated aqueous NaHCO₃ and brine. The CH₂Cl₂ solution was dried (MgSO₃), filtered and concentrated in vacuo to furnish an oil that was dissolved in a small amount of CH₂Cl₂ before being filtered through a SiO₂ pad, eluting with EtOAc. The filtrate was concentrated under reduced pressure to afford the title compound: m/z (ES⁺) = 169.1 [M+ H]⁺.

Preparation 2: 3-[l-(3-Isopropyl[l,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-l-ol
ZnCl₂ (1M in Et₂O, 145 mL, 145 mmol) was added over 20 min to a stirred solution of 4-(3-hydroxypropyl)piperidine-1-carbonitrile (Preparation 1, 20.3 g, 121 mmol) and N-hydroxyisobutyramidine (14.8 g, 145 mmol) in EtOAc (290 mL) and THF (270 mL). After 2 h, the white precipitate that had formed was collected and washed with THF-EtOAc (1:1, 50 mL). This precipitate was dissolved in EtOH (550 mL) and 12M HCl (70 mL), then the solution was stirred with heating to 70°C for 16 h. The EtOH was removed in vacuo, the remainder was diluted with H₂O, then the pH was adjusted to 7 with solid NaHCO₃. The mixture was extracted with EtOAc (3x), then the combined extracts were washed with brine, before being dried (MgSO₄). Filtration and solvent removal furnished the title compound: m/z (ES⁺) = 254.1 [M + H]⁺.

Preparation 3: 5-{3-[l-(3-Isopropyl-[l,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}pyridine-2-carboxylic acid

A stirred solution of methyl 5-hydroxypyridine-2-carboxylate (726 mg, 4.7 mmol), 3-[l-(3-isopropyl][l,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol (Preparation 2, 1.00 g, 4.0 mmol), and triphenyl phosphine (1.24 g, 4.7 mmol) in THF was treated dropwise with diisopropyl azodicarboxylate (1.1 mL, 4.7 mmol). After 16 h, the reaction was concentrated, then the residue was dissolved in EtOAc. The solution was washed with 2M NaOH (2x) and brine, before being dried (MgSO₄), filtered and concentrated. The remainder was then stirred with a small amount of Et₂O at 0°C. After 40 min, the mixture was filtered, then the filtrate was concentrated and the residue purified by column chromatography (EtOAc-CH₂Cl₂, 3:7) to provide methyl 5-{3-[l-(3-isopropyl][l,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}pyridine-2-carboxylate: m/z (ES⁺) = 389.00 [M + H]⁺. A mixture of this ester (1.34 g, 3.5 mmol), LiOH-H₂O (1.45 g, 34.6 mmol), MeOH (26 mL), and H₂O (7 mL) were stirred at 20°C for 16 h. The MeOH was removed in vacuo, then more H₂O was added. The solution was washed with EtOAc (2x), before being acidified to pH 5 with 2M HCl. The precipitate formed was collected and vacuum-dried to afford the title compound: m/z (ES⁺) = 374.96 [M+ H]⁺.

Preparation 4: 5-{3-[l-(3-Isopropyl-[l,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-3-methylpyridine-2-carboxylic acid

Mitsunobu condensation of 5-hydroxy-3-methylpyridine-2-carbonitrile (1.00 g, 7.5 mmol) with 3-[l-(3-isopropyl][l,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol
(Preparation 2, 1.57 g, 6.2 mmol), by a procedure similar to that outlined in Preparation 3, provided 5-{3-[l-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy}-3-methylpyridine-2-carbonitrile: \( m/z \) (ES\(^+\)) = 370.01 \([M + H]^+\). A solution of this nitrile (500 mg, 1.4 mmol) in EtOH (8 mL) and 2M NaOH (4 mL, 8.0 mmol) was heated at 70°C for 7 h, before being stirred at ambient temperature for 16 h. The EtOH was removed under reduced pressure, then the remainder was diluted with \( \text{H}_2\text{O} \). The solution was washed with EtOAc (2x), before being acidified to pH5 with 2M HCl. The mixture was extracted with EtOAc (2x), then the combined extracts were dried (MgSO\(_4\)), filtered and concentrated. The residue was purified by column chromatography (MeOH-CH\(_2\)Cl\(_2\) (1:9) to yield the title compound: RT = 3.31 min; \( m/z \) (ES\(^+\)) = 389.02 \([M + H]^+\).

Preparation 5: 2-Bromo-5-{3-[l-(3-isopropyl-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propoxy} pyridine

Mitsunobu condensation of 2-bromo-5-hydroxypyridine with 3-[l-(3-isopropyl]-[1,2,4]oxadiazol-5-yl)piperidin-4-yl]propan-1-ol (Preparation 2), by a procedure similar to that outlined in Preparation 3, provided the title compound: RT = 4.01 min; \( m/z \) (ES\(^+\)) = 409.0 \([M+ H]^+\).

Example 1: 5-{3-[l-(3 -Isopropyl- [1,2,4]oxadiazol-5 -yl)piperidin-4-yl]propoxy} -3-methylpyridine-2-carboxylic acid ((R)-2-hydroxy-l-methylethyl)amide

A solution of 5-{3-[l-(3 -isopropyl- [1,2,4]oxadiazol-5 -yl)piperidin-4-yl]propoxy} -3-methylpyridine-2-carboxylic acid (Preparation 4, 178 mg, 459 \( \mu \)mol), EDCI (176 mg, 917 \( \mu \)mol), HOBt (141 mg, 917 \( \mu \)mol) and DIPEA (160 \( \mu \)L, 917 \( \mu \)mol) in anhydrous THF (8 mL) was stirred for 30 min. \((R)-2\)-Aminopropan-1-ol (108 \( \mu \)L, 1376 \( \mu \)mol) was added, then stirring was continued for 16 h. The solvents were removed under reduced pressure, then CH\(_2\)Cl\(_2\) was added. The solution was washed with \( \text{H}_2\text{O} \), 2M NaOH, \( \text{H}_2\text{O} \) and brine, before being dried (MgSO\(_4\)). Filtration, solvent evaporation and column chromatography (EtOAc) furnished the title compound: \( \delta_H (\text{CDCl}_3) \) 1.25-1.41 (m, HH), 1.47-1.62 (m, 3H), 1.81-1.96 (m, 4H), 2.77 (s, 3H), 2.93 (sept, IH), 3.02-3.13 (m, 2H), 3.63-3.71 (m, IH), 3.78-3.82 (m, IH), 4.02-4.10 (m, 2H), 4.15-4.28 (m, 3H), 4.45-4.55 (br, IH), 7.02 (d, IH), 8.05-8.15 (m, 2H); RT = 3.49 min; \( m/z \) (ES\(^+\)) = 446.00 \([M+ H]^+\).

Example 2: 5-{3-[l-(3 -Isopropyl- [1,2,4]oxadiazol-5 -yl)piperidin-4-yl]propoxy} pyridine-2-carboxylic acid ((R)-2-hydroxy-l-methylethyl)amide
Condensation of 5-\{3-\{\text{-isopropyl-}[1,2,4]oxadiazol-5-yl\}piperidin-4-yl\}propoxy\}-pyridine-2-carboxylic acid \textit{(Preparation 3)} with \((R)-2\text{-aminopropan-1-ol, employing a procedure similar to that used in Example 1, gave the title compound: } m/z (ES\textsuperscript{+}) = 432.03 [M + H]\textsuperscript{+}.

\textbf{Example 3:} 5-\{3-\{\text{-isopropyl-}[1,2,4]oxadiazol-5-yl\}piperidin-4-yl\}propoxy\}-3-methylpyridine-2-carboxylic acid amide

Condensation of 5-\{3-\{\text{-isopropyl-}[1,2,4]oxadiazol-5-yl\}piperidin-4-yl\}propoxy\}-3-methylpyridine-2-carboxylic acid \textit{(Preparation 4)} with ammonia, employing a procedure similar to that used in Example 1, gave the title compound: RT = 3.62 min; m/z (ES\textsuperscript{+}) = 388.02 [M + H]\textsuperscript{+}.

\textbf{Example 4:} 5\{-3\{-\text{-isopropyl-}[1,2,4]oxadiazol-5-yl\}piperidin-4-yl\}propoxy\}-2-methanesulfonlylpyridine

W-BuLi (322 µL of a 2.5 M solution in hexanes, 0.81 mmol) was added dropwise to a stirred solution of 2-bromo-5-\{3-\{\text{-isopropyl-}[1,2,4]oxadiazol-5-yl\}piperidin-4-yl\}propoxy\}pyridine \textit{(Preparation 5, 300 mg, 0.73 mmol)} in anhydrous THF \((4 \text{ mL)} \text{ at } -78^\circ\text{C. After 15 min, the reaction was treated with (MeS)}\textsubscript{2} (132 µL, 1.47 mmol), then stirring was continued at -78\textdegree \text{C for an additional 15 min. The reaction was then allowed to warm to } -50 \textdegree \text{C over 1 h, before finally being warmed up to room temperature. The mixture was partitioned between 1M HCl and EtOAc, then the organic phase was washed with 1M NaOH and brine, before being dried (MgSO\textsubscript{3}). Filtration, solvent evaporation and column chromatography (EtOAc-IH, 15% to 30%) afforded } 5-\{3-\{\text{-isopropyl-}[1,2,4]oxadiazol-5-yl\}piperidin-4-yl\}propoxy\}-2-methylthioether\textsuperscript{anlylpyridine. A stirred solution of this thioether (75 mg, 0.2 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) was treated with 3-chloroperbenzoic acid (99 mg of 70% pure, 0.4 mmol). After 40 min, the reaction was quenched with aqueous Na\textsubscript{2}C\textsubscript{3}O\textsubscript{4}, then the organic phase was separated and concentrated. The residue was purified by column chromatography (EtOAc-IH, 20% to 50%) to yield the title compound: RT = 3.55 min; m/z (ES\textsuperscript{+}) = 409.18 \{M+ H\}\textsuperscript{+}.

The following compound may also be made by the processes described above: 5\{-\{(R)-3-\{\text{-isopropyl-}[1,2,4]oxadiazol-5-yl\}piperidin-4-yl\}butoxy\}-2-methanesulfonlylpyridine

The biological activity of the compounds of the invention may be tested in the following assay systems:
Yeast Reporter Assay

The yeast cell-based reporter assays have previously been described in the literature (e.g. see Miret J. J. et al, 2002, J. Biol. Chem., 277:6881-6887; Campbell R.M. et al, 1999, Bioorg. Med. Chem. Lett, 9:2413-2418; King K. et al, 1990, Science, 250:121-123); WO 99/14344; WO 00/12704; and US 6,100,042). Briefly, yeast cells have been engineered such that the endogenous yeast G-alpha (GPAI) has been deleted and replaced with G-protein chimeras constructed using multiple techniques. Additionally, the endogenous yeast GPCR, Ste3 has been deleted to allow for heterologous expression of a mammalian GPCR of choice. In the yeast, elements of the pheromone signaling transduction pathway, which are conserved in eukaryotic cells (for example, the mitogen-activated protein kinase pathway), drive the expression of Fusl. By placing β-galactosidase (LacZ) under the control of the Fusl promoter (Fuslp), a system has been developed whereby receptor activation leads to an enzymatic read-out.

Yeast cells were transformed by an adaptation of the lithium acetate method described by Agatep et al, (Agatep, R. et al, 1998, Transformation of Saccharomyces cerevisiae by the lithium acetate/single-stranded carrier DNA/polyethylene glycol (LiAc/ss-DNA/PEG) protocol. Technical Tips Online, Trends Journals, Elsevier). Briefly, yeast cells were grown overnight on yeast tryptone plates (YT). Carrier single-stranded DNA (10µg), 2µg of each of two Fuslp-LacZ reporter plasmids (one with URA selection marker and one with TRP), 2µg of GPR1 19 (human or mouse receptor) in yeast expression vector (2µg origin of replication) and a lithium acetate/ polyethylene glycol/ TE buffer was pipetted into an Eppendorf tube. The yeast expression plasmid containing the receptor/ no receptor control has a LEU marker. Yeast cells were inoculated into this mixture and the reaction proceeds at 30°C for 60min. The yeast cells were then heat-shocked at 42°C for 15min. The cells were then washed and spread on selection plates. The selection plates are synthetic defined yeast media minus LEU, URA and TRP (SD-LUT). After incubating at 30°C for 2-3 days, colonies that grow on the selection plates were then tested in the LacZ assay.

In order to perform fluorimetric enzyme assays for β-galactosidase, yeast cells carrying the human or mouse GPR1 19 receptor were grown overnight in liquid SD-LUT medium to an unsaturated concentration (i.e. the cells were still dividing and had not yet reached stationary phase). They were diluted in fresh medium to an optimal assay concentration and 90µl of yeast cells added to 96-well black polystyrene plates (Costar). Compounds, dissolved in DMSO and diluted in a 10% DMSO solution to 10X concentration, were added to the plates and the plates placed at 30°C for 4h. After 4h, the substrate for the β-galactosidase was added to each well. In these experiments, Fluorescein di (β-D-galactopyranoside) was used (FDG), a substrate for the enzyme that releases fluorescein, allowing a fluorimetric read-out. 20µl per well of 500µM FDG/2.5% Triton X100 was added (the detergent was necessary to render the cells permeable). After incubation of the cells with the substrate for 60min, 20µl per well of 1M sodium carbonate was added to terminate the reaction and enhance the fluorescent signal. The plates were then read in a fluorimeter at 485/535nm.

The compounds of the invention give an increase in fluorescent signal of at least ~ 1.5-fold that of the background signal (i.e. the signal obtained in the presence of 1% DMSO without
compound). Compounds of the invention which give an increase of at least 5-fold may be preferred.

cAMP Assay

A stable cell line expressing recombinant human GPRI 19 was established and this cell line may be used to investigate the effect of compounds of the invention on intracellular levels of cyclic AMP (cAMP). The cell monolayers are washed with phosphate buffered saline and stimulated at 37°C for 30 min with various concentrations of compound in stimulation buffer plus 1% DMSO. Cells are then lysed and cAMP content determined using the Perkin Elmer AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) cAMP kit. Buffers and assay conditions are as described in the manufacturer’s protocol.

In vivo feeding study

The effect of compounds of the invention on body weight and food and water intake may be examined in freely-feeding male Sprague-Dawley rats maintained on reverse-phase lighting. Test compounds and reference compounds are dosed by appropriate routes of administration (e.g. intraperitoneally or orally) and measurements made over the following 24 h. Rats are individually housed in polypropylene cages with metal grid floors at a temperature of 21±4°C and 55±20% humidity. Polypropylene trays with cage pads are placed beneath each cage to detect any food spillage. Animals are maintained on a reverse phase light-dark cycle (lights off for 8 h from 09.30-17.30 h) during which time the room is illuminated by red light. Animals have free access to a standard powdered rat diet and tap water during a two week acclimatization period. The diet is contained in glass feeding jars with aluminum lids. Each lid has a 3-4 cm hole in it to allow access to the food. Animals, feeding jars and water bottles are weighed (to the nearest 0.1 g) at the onset of the dark period. The feeding jars and water bottles are subsequently measured 1, 2, 4, 6 and 24 h after animals are dosed with a compound of the invention and any significant differences between the treatment groups at baseline compared to vehicle-treated controls.

Anti-diabetic effects of compounds of the invention in an in-vitro model of pancreatic beta cells (HIT-T15)

Cell Culture

HIT-T15 cells (passage 60) were obtained from ATCC, and were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum and 30mM sodium selenite. All experiments were done with cells at less than passage 70, in accordance with the literature, which describes altered properties of this cell line at passage numbers above 81 (Zhang HJ, Walseth TF, Robertson RP. Insulin secretion and cAMP metabolism in HIT cells. Reciprocal and serial passage-dependent relationships. Diabetes. 1989 Jan;38(1):44-8).

cAMP assay

HIT-T15 cells were plated in standard culture medium in 96-well plates at 100,000 cells/ 0.1ml/ well and cultured for 24 hr and the medium was then discarded. Cells were incubated for 15 min at room temperature with 100µl stimulation buffer (Hanks buffered salt solution, 5mM HEPES, 0.5mM IBMX, 0.1% BSA, pH 7.4). This was discarded and replaced with compound dilutions over the range 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 µM in
stimulation buffer in the presence of 0.5% DMSO. Cells were incubated at room temperature for 30 min. Then 75 µl lysis buffer (5 mM HEPES, 0.3% Tween-20, 0.1% BSA, pH 7.4) was added per well and the plate was shaken at 900 rpm for 20 min. Particulate matter was removed by centrifugation at 3000 rpm for 5 min, then the samples were transferred in duplicate to 384-well plates, and processed following the Perkin Elmer AlphaScreen cAMP assay kit instructions. Briefly, 25 µl reactions were set up containing 8 µl sample, 5 µl acceptor bead mix and 12 µl detection mix, such that the concentration of the final reaction components is the same as stated in the kit instructions. Reactions were incubated at room temperature for 150 min, and the plate was read using a Packard Fusion instrument. Measurements for cAMP were compared to a standard curve of known cAMP amounts (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 nM) to convert the readings to absolute cAMP amounts. Data was analysed using XLfit 3 software.

Representative compounds of the invention were found to increase cAMP at an EC₅₀ of less than 10 µM. Compounds showing an EC₅₀ of less than 1 µM in the cAMP assay may be preferred.

**Insulin secretion assay**

HIT-T1 5 cells are plated in standard culture medium in 12-well plates at 106 cells/1 ml/well and cultured for 3 days and the medium is then discarded. Cells are washed ×2 with supplemented Krebs-Ringer buffer (KRB) containing 119 mM NaCl, 4.74 mM KCl, 2.54 mM CaCl₂, 1.19 mM MgSO₄, 1.19 mM KH₂PO₄, 25 mM NaHCO₃, 10 mM HEPES at pH 7.4 and 0.1% bovine serum albumin. Cells are incubated with 1 ml KRB at 37°C for 30 min which is then discarded. This is followed by a second incubation with KRB for 30 min, which is collected and used to measure basal insulin secretion levels for each well. Compound dilutions (0, 0.1, 0.3, 1, 3, 10 µM) are then added to duplicate wells in 1 ml KRB, supplemented with 5.6 mM glucose. After 30 min incubation at 37°C samples are removed for determination of insulin levels. Measurement of insulin is done using the Mercodia Rat insulin ELISA kit, following the manufacturers’ instructions, with a standard curve of known insulin concentrations. For each well insulin levels are corrected by subtraction of the basal secretion level from the pre-incubation in the absence of glucose. Data is analysed using XLfit 3 software.

**Oral Glucose Tolerance Tests**

The effects of compounds of the invention on oral glucose (Glc) tolerance were evaluated in male Sprague-Dawley rats. Food was withdrawn 16 h before administration of Glc and remained withdrawn throughout the study. Rats had free access to water during the study. A cut was made to the animals’ tails, then blood (1 drop) was removed for measurement of basal Glc levels 60 min before administration of the Glc load. Then, the rats were weighed and dosed orally with test compound or vehicle (20% aqueous hydroxypropyl-ß-cyclodextrin) 45 min before the removal of an additional blood sample and treatment with the Glc load (2 g kg⁻¹ p.o.). Blood samples were then taken from the cut tip of the tail 5, 15, 30, 60, 120, and 180 min after Glc administration. Blood glucose levels were measured just after collection using a commercially available glucose-meter (OneTouch® UltraTM from Lifescan). Representative compounds of the invention statistically reduced the Glc excursion at doses of <10 mg kg⁻¹.

The effects of compounds of the invention on oral glucose (Glc) tolerance may also be evaluated in male C57B1/6 or male ob/ob mice. Food is withdrawn 5 h before administration of
GIc and remains withdrawn throughout the study. Mice have free access to water during the study. A cut is made to the animals' tails, then blood (20 µL) is removed for measurement of basal Glc levels 45 min before administration of the Glc load. Then, the mice are weighed and dosed orally with test compound or vehicle (20% aqueous hydroxypropyl-β-cyclodextrin or 25% aqueous Gelucire 44/14) 30 min before the removal of an additional blood sample (20 µL) and treatment with the Glc load (2-5 g kg⁻¹ p.o.). Blood samples (20 µL) are then taken 25, 50, 80, 120, and 180 min after Glc administration. The 20 µL blood samples for measurement of Glc levels are taken from the cut tip of the tail into disposable micro-pipettes (Dade Diagnostics Inc., Puerto Rico) and the sample added to 480 µL of haemolysis reagent. Duplicate 20 µL aliquots of the diluted haemolysed blood are then added to 180 µL of Trinders glucose reagent (Sigma enzymatic (Trinder) colorimetric method) in a 96-well assay plate. After mixing, the samples are left at rt for 30 min before being read against Glc standards (Sigma glucose/urea nitrogen combined standard set).
WHAT IS CLAIMED IS:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

![Chemical Structure Image]

(I)

wherein one of X and Y is O and the other is N;

R² is hydrogen or methyl;

R³ is hydrogen or methyl;

R⁴ is C₂₋₅ alkyl;

R⁵ is C₃₋₅ alkyl;

R⁶ and R⁷ are independently hydrogen, C₁₋₅ alkyl, which may optionally be substituted by halo, hydroxy, C₁₋₃ alkoxy-, aryloxy-, arylicC₁₋₃ alkoxy-, Cl₂₋₅ alkylS(0)ₓ, C₃₋₇ heterocyclyl, N(R⁸)₂ or -C(O)OR⁹; or may be C₃₋₇ cycloalkyl, ary1, heterocyclyl or heteroaryl, wherein the cyclic groups may be substituted with one or more substituents selected from halo, C₁₋₅ alkyl, Cl₂₋₅ fluoroalkyl, OR⁶, CN, SO₂CH₃, N(R⁸)₂ and NO₂; or taken together R⁶ and R⁷ may form a 5- or 6-membered heterocyclic ring optionally substituted by hydroxy, C₁₋₅ alkyl or C₁₋₅ hydroxyalkyl and optionally containing a further heteroatom selected from O and NR⁸;

R⁸ are independently hydrogen or C₁₋₅ alkyl; or a group N(R⁸)₂ may form a 4- to 7-membered heterocyclic ring optionally containing a further heteroatom selected from O and NR⁸;

R⁹ is hydrogen or C₁₋₅ alkyl; and

m is 0, 1 or 2.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is O.

3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is O.

4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R¹ is SO₂R⁵.

5. A compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein R¹ is SO₂CH₃.

6. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R¹ is -CONR⁶R⁷.
7. A compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein R⁶ is hydrogen, C₃₋₃alkyl, or C⁷₋₃alkyl substituted by hydroxy and R⁷ is hydrogen.

8. A compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein R⁶ is C₄alkyl or C⁷₋₃alkyl substituted by hydroxy.

9. A compound according to claim 8, or a pharmaceutically acceptable salt thereof, wherein R⁶ is C₆₋₃alkyl substituted by hydroxy.

10. A compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein R⁶ is 2-hydroxyethyl or 2-hydroxy-l-methylethyl.

11. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen.

12. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R³ is methyl.

13. A compound according to claim 12, or a pharmaceutically acceptable salt thereof, wherein R³ is methyl and the sterocentre produced has the (R)-configuration.

14. A compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R⁴ is C₃₋₄alkyl.

15. A compound according to claim 14, or a pharmaceutically acceptable salt thereof, wherein R⁴ is isopropyl.

16. A compound of formula (I) as defined in any one of Examples 1 to 4, or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

18. A method for the treatment of a disease or condition in which GPRI 19 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof.

19. A method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof.

20. A method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof.
21. A method for the treatment of diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof.

22. A method for the treatment of metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or hypertension comprising a step of administering to a patient in need thereof an effective amount of a compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof.

23. A compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, for use as a medicament.

24. A compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment or prevention of a disease or condition as defined in any one of claims 18 to 22.

25. A compound according to any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a disease or condition as defined in any one of claims 17 to 21.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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<th>INV.</th>
<th>International application No.</th>
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<td>PCT/GB2008/050014</td>
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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)

C07D

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 practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>P,X</td>
<td>WO 2007/003962 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; FYFE MATTHEW CO...</td>
<td>1-25</td>
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<td></td>
<td>COLIN THO) 11 January 2007 (2007-01-11) cited in the application page 8; claims 1,21</td>
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<td>P,A</td>
<td>WO 2007/116229 A (PROSIDION LTD [GB]; BERTRAM LISA SARAH [GB]; FYFE MATTHEW CO...</td>
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<tr>
<td></td>
<td>COLIN THOR (;) 18 October 2007 (2007-10-18) claims 1,22</td>
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<td>X</td>
<td>WO 2006/067531 A (PROSIDION LTD [GB]; FYFE MATTHEW COLIN THOR [GB]; GARDNER LISA S...</td>
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<td></td>
<td>SARAH (;) 29 June 2006 (2006-06-29) cited in the application claims 1,17</td>
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D Further documents are listed in the continuation of Box C. X See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance.

E earlier document but published on or after the international filing date.

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).

O document referring to an oral disclosure, use, exhibition or other means.

P document published prior to the international filing date but later than the priority date claimed.

T document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.

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.

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family.

Date of the actual completion of the international search: 27 March 2008

Date of mailing of the international search report: 07/04/2008

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-0400, Tx: 31 651 epos nl, Fax: (+31-70) 340-3016

Authorized officer:

Gettins, Marc
**INTERNATIONAL SEARCH REPORT**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
   
   Although claims 18-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. **☐** Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- **☐** The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- **☐** No protest accompanied the payment of additional search fees.
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