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(71) Applicant *(for all designated States except US)*: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LI, Jianke** [CN/US]; 6 Kimball Court, Apartment 413, Woburn, Massachusetts 01801 (US). **ZHU, Guoxin** [US/CN]; 21F, 1 Corporate Avenue, Number 222, Hu Bin Road, Shanghai 200021 (CN).

(74) Agents: **WOOD, Dan, L.** et al.; Eli Lilly And Company, P. O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

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(54) **Title:** GLUCAGON RECEPTOR ANTAGONISTS, PREPARATION AND THERAPEUTIC USES

(57) **Abstract:** The present invention discloses novel compounds of Formula I, or pharmaceutically acceptable salts thereof, which have glucagon receptor antagonist or inverse agonist activity, as well as methods for preparing such compounds. In another embodiment, the invention discloses pharmaceutical compositions comprising compounds of Formula I as well as methods of using them to treat diabetic and other glucagon related metabolic disorders, and the like.

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GLUCAGON RECEPTOR ANTAGONISTS, PREPARATION AND THERAPEUTIC USES

This patent application claims the benefit of United States Provisional Patent Application No. 60/737,783 filed November 17, 2005.

This invention relates to compounds that are antagonists or inverse agonists of the glucagon receptor, and to pharmaceutical compositions thereof, and the uses of these compounds and compositions in the treatment of the human or animal body. The present compounds show a high affinity and selective binding for the glucagon receptor, and as such are useful in the treatment of disorders responsive to the modulation of glucagon receptors, such as diabetic and other glucagon related metabolic disorders, and the like.

Glucagon is a key hormonal agent that, in cooperation with insulin, mediates homeostatic regulation of the amount of glucose in the blood. Glucagon primarily acts by stimulating certain cells (important among these are liver cells) to release glucose when blood glucose levels fall. The action of glucagon is opposite to that of insulin, which stimulates cells to take up and store glucose whenever blood glucose levels rise. Both glucagon and insulin are peptide hormones. Glucagon is produced in the alpha islet cells of the pancreas and insulin is produced in the beta islet cells. Glucagon exerts its action by binding to and activating its receptor, which is a member of the Glucagon-Secretin branch of the 7-transmembrane G-protein coupled receptor family. The receptor functions by activating the adenylyl cyclase second messenger system resulting in an increase in cAMP levels. The glucagon receptor, or naturally occurring variants of the receptor, may possess intrinsic constitutive activity, in vitro, as well as in vivo (i.e. activity in the absence of an agonist). Compounds acting as inverse agonists can inhibit this activity.Diabetes mellitus is a common disorder of glucose metabolism. The disease is characterized by hyperglycemia and may be classified as type 1 diabetes, the insulin-dependent form, or type 2 diabetes, which is non-insulin-dependent in character. Subjects with type 1 diabetes are hyperglycemic and hypoinsulinemic, and the conventional treatment for this form of the disease is to provide insulin. However, in some patients with type 1 or type 2 diabetes, absolute or relative elevated glucagon levels have been shown to contribute to the hyperglycemic state. Both in healthy control animals as well as in animal models of type 1 and type 2 diabetes, removal of circulating glucagon with selective and specific antibodies has resulted in reduction of the glycemic level. Mice

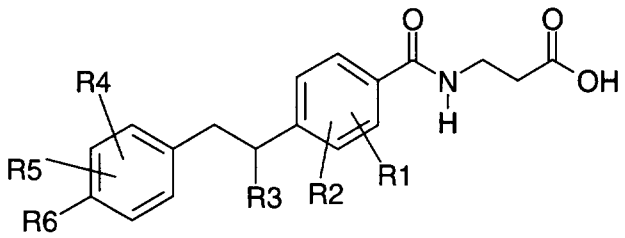
with a homozygous deletion of the glucagon receptor exhibit increased glucose tolerance. Also, inhibition of glucagon receptor expression using antisense oligonucleotides ameliorates diabetic syndrome in db/db mice. These studies suggest that glucagon suppression or an action that antagonizes glucagon could be a useful adjunct to conventional treatment of hyperglycemia in diabetic patients. The action of glucagon can be suppressed by providing an antagonist or an inverse agonist, i.e. substances that inhibit or prevent constituitive, or glucagon-induced, glucagon receptor mediated responses.

Several publications disclose peptides that are stated to act as glucagon antagonists. Peptide antagonists of peptide hormones are often potent; however they are generally known not to be orally available because of degradation by physiological enzymes and poor distribution in vivo. Therefore, orally available non-peptide antagonists of peptide hormones are generally preferred.

A number of publications have appeared in recent years reporting non-peptide agents that act at the glucagon receptor. For example, WO 03/048109, WO 2004/002480, and Kurukulasuriya et al., "Biaryl amide glucagon receptor antagonists" *Bioorganic & Medicinal Chemistry Letters*, vol. 14, no. 9, pages 2047-2050, 2004, each disclose non-peptide compounds allegedly having glucagon receptor antagonist activity. In spite of the number of treatments for diseases that involve glucagon, the current therapies suffer from one or more inadequacies, including poor or incomplete efficacy, unacceptable side effects, and contraindications for certain patient populations. Thus, there remains a need for an improved treatment using alternative or improved pharmaceutical agents that modulate glucagon receptor activity and treat the diseases that could benefit from glucagon receptor modulation. The present invention provides such a contribution to the art based on the finding that a novel class of compounds has a high affinity, selective, and potent inhibitory activity at the glucagon receptor. The present invention is distinct in the particular structures and their activities.

SUMMARY OF THE INVENTION

The present invention provides a compound structurally represented by Formula I:



(I)

or a pharmaceutically acceptable salt thereof wherein:

R1 and R2 are independently –H or -halogen;

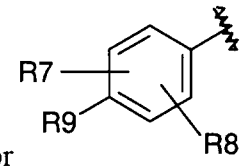
R3 is

-(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens), -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl, or -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R4 and R5 are independently

-H, -halogen, -hydroxy, hydroxymethyl, -CN, -(C_1-C_7) alkoxy, -(C_2-C_7)alkenyl, or -(C_1-C_6)alkyl (optionally substituted with 1 to 3 halogens);

R6 is

-H, -halogen, or 

, wherein the zig-zag mark shows the point of attachment to the parent molecule;

R7 and R8 are independently

-H, -halogen, -(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens), -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -C(O)R10, -COOR10, -OC(O)R10, -$OS(O)_2$R10, -SR10, -S(O)R10, -$S(O)_2$R10, or -O(C_2-C_7)alkenyl;

R9 is independently

-H, -halogen, -CN, -(C_3-C_7)cycloalkyl, -C(O)R10, -COOR10, -OC(O)R10, -$OS(O)_2$R10, -SR10, -S(O)R10, -$S(O)_2$R10, or -O(C_2-C_7)alkenyl, -(C_1-C_3)alkoxy(optionally substituted with 1 to 3 halogens), or -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens), and

R10 is independently at each occurrence

-hydrogen, or -(C_1-C_6) alkyl(optionally substituted with 1 to 3 halogens).

The present invention provides compounds that are useful as glucagon receptor antagonists or inverse agonists. The present invention further provides compounds that are selective antagonists or inverse agonists of the glucagon receptor over the GLP-1 receptor. The present invention further provides a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. The present invention further provides methods of using these compounds and compositions in the treatment of disorders responsive to the modulation of glucagon receptors, such as diabetic and other glucagon related metabolic disorders.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention provides compounds of Formula I as described in detail herein. While all of the compounds of the present invention are useful, certain of the compounds are particularly interesting and are preferred. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred embodiments as indicated herein.

In another embodiment the invention provides a compound of formula I wherein

R1 and R2 are –H;

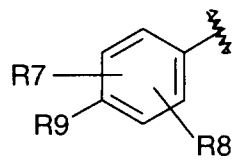
R3 is

-(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens), -(C_3-C_6)cycloalkyl, -(C_1-C_6)alkyl-(C_3-C_6)cycloalkyl, or -(C_3-C_6)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R4 and R5 are independently

-H, -halogen, or -(C_1-C_6)alkyl (optionally substituted with 1 to 3 halogens);

R6 is



, wherein the zig-zag mark shows the point of attachment to the parent molecule;

R7 and R8 are independently

-H, -halogen, -(C_1-C_3)alkyl(optionally substituted with 1 to 3 halogens), -(C_1-C_3)alkoxy; and

R9 is independently

-H, -halogen, or -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens).

In another embodiment the invention provides a compound of formula I wherein

R1 and R2 are –H;

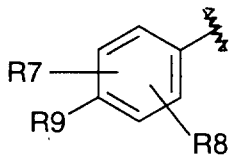
R3 is

-(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens), -(C_3-C_6)cycloalkyl, -(C_1-C_6)alkyl-(C_3-C_6)cycloalkyl, or -(C_3-C_6)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R4 and R5 are independently

-H, -halogen, or –CH_3 (optionally substituted with 1 to 3 halogens);

R6 is



, wherein the zig-zag mark shows the point of attachment to the parent molecule;

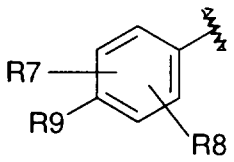
R7 and R8 are independently -H, or -halogen; and

R9 is independently -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens).

In another embodiment the invention provides a compound of formula I wherein R1 and R2 are –H; R3 is -(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens), -(C_3-C_6)cycloalkyl, -(C_1-C_6)alkyl-(C_3-C_6)cycloalkyl, or -(C_3-C_6)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R4 and R5 are –CH_3 (optionally substituted with 1 to 3 halogens) and each occupies a position adjacent to R6 on the phenyl ring to which R6 is attached;

R6 is



, wherein the zig-zag mark shows the point of attachment to the parent molecule;

R7 and R8 are -H; and R9 is independently -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens).

In another embodiment the invention provides a compound of Formula I wherein R1 and R2 are independently hydrogen or halogen; R3 is methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, 3,3-dimethylbutyl, 2-methylpropyl, 3-methyl-butyl, tertbutyl, 4-methylpentyl, 2,2-dimethylpropyl, 3-trifluoropropyl, 4-trifluorbutyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; R4 and R5 are independently hydrogen, methyl, ethyl, tertbutyl, cyclohexyl, pentyl, isopropoxy, chloro, fluoro, bromo, hydoxy, trifluoromethyl, -CN, methoxy, hydroxymethyl, 4-methylpentyloxy, or pentyloxy; R7 and R8 are independently hydrogen, fluoro, chloro, methyl, ethyl, pentyl, isopropyl, tertbutyl, trifluoromethyl, acetyl, 2-methylpropyl, methoxy, cyclohexyl, or trifluormethoxy; R9 is hydrogen, bromo, fluoro, methyl, tertbutyl, trifluoromethyl, or isopropyl.

Other embodiments of the invention are provided wherein each of the embodiments described herein above is further narrowed as described in the following preferences. Specifically, each of the preferences below is independently combined with each of the embodiments above, and the particular combination provides another embodiment in which the variable indicated in the preference is narrowed according to the preference.

Preferably R1 is –H. Preferably R1 is fluorine. Preferably R1 is chlorine. Preferably R2 is –H. Preferably R2 is fluorine. Preferably R2 is chlorine. Preferably R1 and R2 are –H. Preferably R1 is fluorine and R2 is fluorine.

Preferably R3 is -(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens). Preferably R3 is ethyl, propyl, isopropyl, butyl, tertbutyl, 3-methyl-butyl, pentyl, hexyl, heptyl, octyl, 3,3-dimethylbutyl, 2-methylpropyl, 4-methylpentyl, 2,2-dimethylpropyl, 3-trifluoropropyl, or 4-trifluorbutyl. Preferably R3 is isopropyl, butyl, tertbutyl, 3-methyl-butyl, pentyl, 3,3-dimethylbutyl, 2-methylpropyl, 4-methylpentyl, 2,2-dimethylpropyl, 3-trifluoropropyl, or 4-trifluorbutyl. Preferably R3 is isopropyl, 3-methyl-butyl, trifluoropropyl, or 4-trifluorbutyl.

Preferably R3 is -(C_3-C_7)cycloalkyl. Preferably R3 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Preferably R3 is cyclopropyl. Preferably R3 is cyclobutyl. Preferably R3 is cyclopentyl. Preferably R3 is cyclohexyl.

Preferably R3 is -(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl. Preferably R3 is -(C_1-C_3)alkyl-(C_3-C_6)cycloalkyl. Preferably R3 is -(C_1-C_3)alkyl-cyclopropyl. Preferably R3 is -(C_1-C_3)alkyl-cyclobutyl. Preferably R3 is -(C_1-C_3)alkyl-cyclopentyl. Preferably R3 is -(C_1-C_3)alkyl-cyclohexyl.

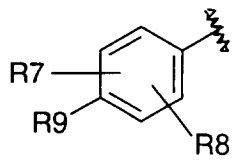
Preferably R3 is -(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens). Preferably R3 is -cyclopropyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens). Preferably R3 is -cyclobutyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens). Preferably R3 is -cyclopentyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens). Preferably R3 is -cyclohexyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens).

Preferably R4 is -H, -halogen, -hydroxy, hydroxymethyl, or -(C_1-C_6)alkyl (optionally substituted with 1 to 3 halogens). Preferably R4 is -H, -halogen, or -(C_1-C_3)alkyl (optionally substituted with 1 to 3 halogens). Preferably R4 is -H, -halogen, or -CH_3. Preferably R4 is –H. Preferably R4 is fluorine, clhorine, or bromine. Preferably R4 is -CH_3.

Preferably R5 is -H, -halogen, -hydroxy, hydroxymethyl, or -(C_1-C_6)alkyl (optionally substituted with 1 to 3 halogens). Preferably R5 is -H, -halogen, or -(C_1-C_3)alkyl (optionally substituted with 1 to 3 halogens). Preferably R5 is -H, -halogen, or -CH_3. Preferably R5 is –H. Preferably R5 is fluorine, chlorine, or bromine. Preferably R5 is -CH_3.

Preferably R4 and R5 are –H. Preferably R4 is halogen and R5 is –H. Preferably R4 is –H and R5 is -CH_3. Preferably R4 and R5 are -CH_3. Preferably R4 and R5 are -CH_3 and each occuppies a position adjacent to R6 on the phenyl ring to which R6 is attached.

Preferably R6 is –H. Preferably R6 is –halogen. Preferably R6 is

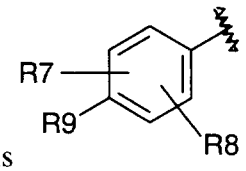


, wherein the zig-zag mark shows the point of attachment to the parent molecule.

Preferably R7 is -halogen, -(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens), -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -C(O)R10, -COOR10, -OC(O)R10, -$OS(O)_2$R10, -SR10, -S(O)R10, -$S(O)_2$R10, or -O(C_2-C_7)alkenyl. Preferably R7 is

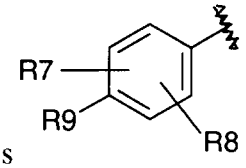
-halogen, -(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens), or -(C_1-C_6)alkoxy. Preferably R7 is -H or -halogen. Preferably R7 is -H.

Preferably R8 is -halogen, -(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens), -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -C(O)R10, -COOR10, -OC(O)R10, -OS(O)$_2$R10, -SR10, -S(O)R10, -S(O)$_2$R10, or -O(C_2-C_7)alkenyl. Preferably R8 is -halogen, -(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens), or -(C_1-C_6)alkoxy. Preferably R8 is -H or -halogen. Preferably R8 is -H. Preferably R7 is –H and R8 is –H.

Preferably R6 is 

, wherein the zig-zag mark shows the point of attachment to the parent molecule, and R7 is –H and R8 is –H.

Preferably R9 is -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens). Preferably R9 is methyl, ethyl, propyl, isopropyl, butyl, tertbutyl, trifluoromethyl, 3-methyl-butyl, pentyl, hexyl, 3,3-dimethylbutyl, 2-methylpropyl, 4-methylpentyl, 2,2-dimethylpropyl, 3-trifluoropropyl, or 4-trifluorbutyl. Preferably R9 is isopropyl, tertbutyl, or trifluoromethyl.

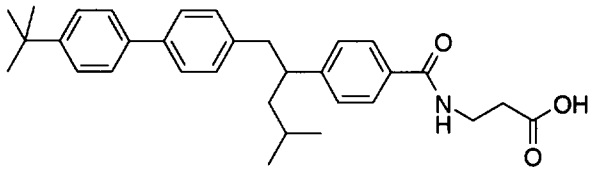
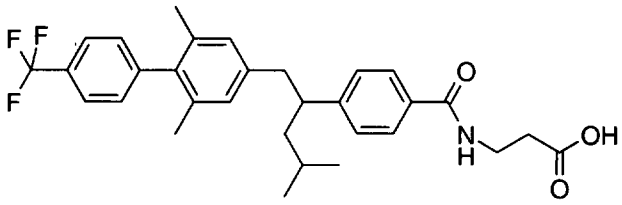
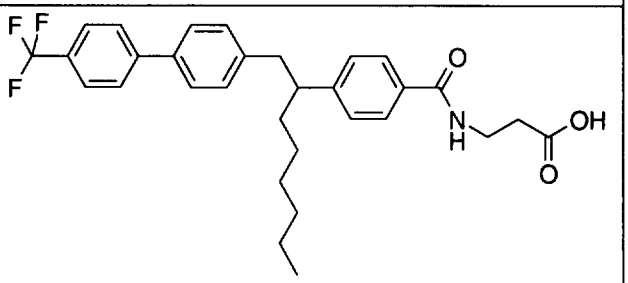
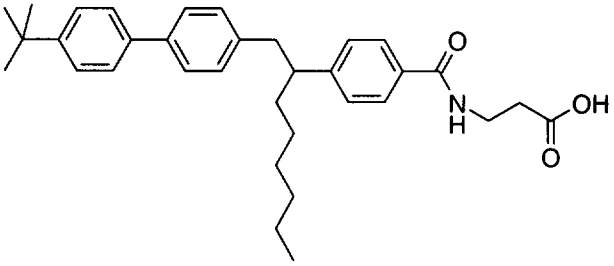
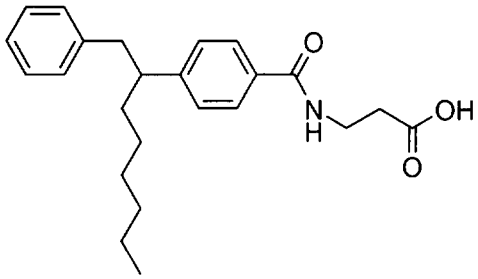
Preferably R6 is 

, wherein the zig-zag mark shows the point of attachment to the parent molecule, and R7 is –H and R8 is –H, and R9 is isopropyl, tertbutyl, or trifluoromethyl.

Preferably R10 is independently at each occurrence -(C_1-C_6) alkyl(optionally substituted with 1 to 3 halogens).

Further embodiments of the invention include the compounds of formulae X1 to X5. A further embodiment of the invention are any novel intermediate preparations described herein which are useful for preparing the glucagon receptor antagonists or inverse agonists of formulae I, or X1 to X5.

Table 1

Formula Number	Structure
X1	
X2	
X3	
X4	
X5	

Due to their interaction with the glucagon receptor, the present compounds are useful in the treatment of a wide range of conditions and disorders in which an interaction with the glucagon receptor is beneficial. These disorders and conditions are defined herein as "diabetic and other glucagon related metabolic disorders". One of skill in the art is able

to identify "diabetic and other glucagon related metabolic disorders" by the involvement of glucagon receptor mediated signaling either in the pathophysiology of the disorder, or in the homeostatic response to the disorder. Thus, the compounds may find use for example to prevent, treat, or alleviate, diseases or conditions or associated symptoms or sequelae, of the endocrinological system, the central nervous system, the peripheral nervous system, the cardiovascular system, the pulmonary system, and the gastrointestinal system, while reducing and or eliminating one or more of the unwanted side effects associated with the current treatments. "Diabetic and other glucagon related metabolic disorders" include, but are not limited to, diabetes, type 1 diabetes, type 2 diabetes, hyperglycemia, hyper insulinemia, beta-cell rest, improved beta-cell function by restoring first phase response, prandial hyperglycemia, preventing apoptosis, impaired fasting glucose (IFG), metabolic syndrome, hypoglycemia, hyper-/hypokalemia, normalizing glucagon levels, improved LDL/HDL ratio, reducing snacking, eating disorders, weight loss, polycystic ovarian syndrome (PCOS), obesity as a consequence of diabetes, latent autoimmune diabetes in adults (LADA), insulitis, islet transplantation, pediatric diabetes, gestational diabetes, diabetic late complications, micro-/macroalbuminuria, nephropathy, retinopathy, neuropathy, diabetic foot ulcers, reduced intestinal motility due to glucagon administration, short bowel syndrome, antidiarrheic, increasing gastric secretion, decreased blood flow, erectile dysfunction, glaucoma, post surgical stress, ameliorating organ tissue injury caused by reperfusion of blood flow after ischemia, ischemic heart damage, heart insufficiency, congestive heart failure, stroke, myocardial infarction, arrhythmia, premature death, anti-apoptosis, wound healing, impaired glucose tolerance (IGT), insulin resistance syndromes, syndrome X, hyperlipidemia, dyslipidemia, hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia, arteriosclerosis including atherosclerosis, glucagonomas, acute pancreatitis, cardiovascular diseases, hypertension, cardiac hypertrophy, gastrointestinal disorders, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, etc.

In addition, the present invention provides a compound of Formula I, or a pharmaceutical salt thereof, or a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient: for use in inhibiting the glucagon receptor; for use in inhibiting a glucagon receptor mediated cellular response in a mammal; for use in

reducing the glycemic level in a mammal; for use in treating a disease arising from excessive glucagon; for use in treating diabetic and other glucagon related metabolic disorders in a mammal; and for use in treating diabetes, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and wound healing. Thus, the methods of this invention encompass a prophylactic and therapeutic administration of a compound of Formula I.

The present invention further provides the use of a compound of Formula I, or a pharmaceutical salt thereof for the manufacture of a medicament for inhibiting the glucagon receptor; for the manufacture of a medicament for inhibiting a glucagon receptor mediated cellular response in a mammal; for the manufacture of a medicament for reducing the glycemic level in a mammal; for the manufacture of a medicament for treating a disease arising from excessive glucagon; for the manufacture of a medicament for treating diabetic and other glucagon related metabolic disorders in a mammal; and for the manufacture of a medicament for preventing or treating diabetes, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and improper wound healing.

The present invention further provides a method of treating conditions resulting from excessive glucagon in a mammal; a method of inhibiting the glucagon receptor in a mammal; a method of inhibiting a glucagon receptor mediated cellular response in a mammal; a method of reducing the glycemic level in a mammal; a method of treating diabetic and other glucagon related metabolic disorders in a mammal; a method of preventing or treating diabetes, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and improper wound healing; said methods comprising administering to a mammal in need of such treatment a glucagon receptor-inhibiting amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

In addition, the present invention provides a pharmaceutical composition which comprises a compound of Formula I, or a pharmaceutical salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient: adapted for use in inhibiting the glucagon receptor; adapted for use in inhibiting glucagon receptor mediated cellular

responses; adapted for use in reducing the glycemic level in a mammal; adapted for use in treating diabetic and other glucagon related metabolic disorders in a mammal; and adapted for use in preventing or treating diabetes, obesity, hyperglycemia, atherosclerosis, ischemic heart disease, stroke, neuropathy, and wound healing.

The compound or salt of the present invention further provides a diagnostic agent for identifying patients having a defect in the glucagon receptor, as a therapy to increase gastric acid secretions, and to reverse intestinal hypomobility due to glucagon administration. The invention also provides a method for the treatment of disorders or diseases, wherein a glucagon antagonistic action is beneficial, the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention. In another embodiment of the invention, the present compounds are used for the preparation of a medicament for the treatment of any glucagon-mediated conditions and diseases. In another embodiment of the invention, the present compounds are used for the preparation of a medicament for the treatment of hyperglycemia. In yet another embodiment of the invention, the present compounds are used for the preparation of a medicament for lowering blood glucose in a mammal. The present compounds are effective in lowering the blood glucose, both in the fasting and the postprandial stage. In still another embodiment of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment of IGT. In a further embodiment of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment of type 2 diabetes. In yet a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to type 2 diabetes. In yet another embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes. In a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment of type 1 diabetes. Such treatment is normally accompanied by insulin therapy. In yet a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment of obesity. In still a further embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for

the treatment of disorders of the lipid metabolism. In still another embodiment of the invention the present compounds are used for the preparation of a pharmaceutical composition for the treatment of an appetite regulation or energy expenditure disorder. In a further embodiment of the invention, treatment of a patient with the present compounds is combined with diet and/or exercise.

In a further aspect of the invention the present compounds are administered in combination with one or more further active substances in any suitable ratios. Such further active substances may for example be selected from antidiabetics, antiobesity agents, antihypertensive agents, agents for the treatment of complications resulting from or associated with diabetes and agents for the treatment of complications and disorders resulting from or associated with obesity. The following listing sets out several groups of combinations. It will be understood that each of the agents named may be combined with other agents named to create additional combinations.

Thus, in a further embodiment of the invention the present compounds may be administered in combination with one or more antidiabetics.

Suitable antidiabetic agents include insulin, insulin analogues and derivatives such as those disclosed in EP 792 290 (Novo Nordisk A/S), for example $N^{\varepsilon B29}$-tetradecanoyl des (B30) human insulin, EP 214 826 and EP 705 275 (Novo Nordisk A/S), for example Asp^{B28} human insulin, US 5,504,188 (Eli Lilly), for example Lys^{B28} Pro^{B29} human insulin, EP 368 187 (Aventis), for example Lantus®, which are all incorporated herein by reference, GLP-1 and GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), which is incorporated herein by reference, as well as orally active hypoglycemic agents.

The orally active hypoglycemic agents preferably comprise imidazolines, sulphonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, insulin sensitizers, insulin secretagogues, such as glimepiride, α-glucosidase inhibitors, agents acting on the ATP-dependent potassium channel of the β-cells for example potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S) which are incorporated herein by reference, or mitiglinide, or a potassium channel blocker, such as BTS-67582, nateglinide, GLP-1 antagonists, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase (protein tyrosine phosphatase) inhibitors, inhibitors of hepatic enzymes involved in stimulation of

gluconeogenesis and/or glycogenolysis, glucose uptake modulators, activators of glucokinase (GK) such as those disclosed in WO 00/58293, WO 01/44216, WO 01/83465, WO 01/83478, WO 01/85706, WO 01/85707, and WO 02/08209 (Hoffman-La Roche) or those disclosed in WO 03/00262, WO 03/00267 and WO 03/15774 (AstraZeneca), which are incorporated herein by reference, GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antilipidemic agents such as HMG CoA inhibitors (statins), compounds lowering food intake, PPAR (Peroxisome proliferator-activated receptor) ligands including the PPAR-alpha, PPAR-gamma and PPAR-delta substypes, and RXR (retinoid X receptor) agonists, such as ALRT-268, LG-1268 or LG-1069.

In another embodiment, the present compounds are administered in combination with insulin or an insulin analogue or derivative, such as $N^{\varepsilon B29}$-tetradecanoyl des (B30) human insulin, Asp^{B28} human insulin, Lys^{B28} Pro^{B29} human insulin, Lantus®, or a mix-preparation comprising one or more of these.

In a further embodiment of the invention the present compounds are administered in combination with a sulphonylurea such as glibenclamide, glipizide, tolbautamide, chloropamidem, tolazamide, glimepride, glicazide and glyburide.

In another embodiment of the invention the present compounds are administered in combination with a biguanide, for example, metformin.

In yet another embodiment of the invention the present compounds are administered in combination with a meglitinide, for example, repaglinide or nateglinide.

In still another embodiment of the invention the present compounds are administered in combination with a thiazolidinedione insulin sensitizer, for example, troglitazone, ciglitazone, piolitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037 or T 174 or the compounds disclosed in WO 97/41097, WO 97/41119, WO 97/41120, WO 00/41121 and WO 98/45292 (Dr. Reddy's Research Foundation), which are incorporated herein by reference.

In still another embodiment of the invention the present compounds may be administered in combination with an insulin sensitizer, for example, such as GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516 or the compounds disclosed in WO 99/19313, WO 00/50414, WO 00/63191, WO 00/63192, WO 00/63193 such as

ragaglitazar (NN 622 or (-)DRF 2725) (Dr. Reddy's Research Foundation) and WO 00/23425, WO 00/23415, WO 00/23451, WO 00/23445, WO 00/23417, WO 00/23416, WO 00/63153, WO 63196, WO 00/63209, WO 00/63190 and WO 00/63189 (Novo Nordisk A/S), which are incorporated herein by reference.

In a further embodiment of the invention the present compounds are administered in combination with an α-glucosidase inhibitor, for example, voglibose, emiglitate, miglitol or acarbose.

In another embodiment of the invention the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells, for example, tolbutamide, glibenclamide, glipizide, glicazide, BTS-67582 or repaglinide.

In yet another embodiment of the invention the present compounds may be administered in combination with nateglinide.

In still another embodiment of the invention the present compounds are administered in combination with an antilipidemic agent or antihyperlipidemic agent for example cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, pitavastatin, rosuvastatin, probucol, dextrothyroxine, fenofibrate or atorvastin.

In still another embodiment of the invention the present compounds are administered in combination with compounds lowering food intake.

In another embodiment of the invention, the present compounds are administered in combination with more than one of the above-mentioned compounds for example in combination with metformin and a sulphonylurea such as glyburide; a sulphonylurea and acarbose; nateglinide and metformin; repaglinide and metformin, acarbose and metformin; a sulfonylurea, metformin and troglitazone; insulin and a sulfonylurea; insulin and metformin; insulin, metformin and a sulfonylurea; insulin and troglitazone; insulin and lovastatin; etc.

In a further embodiment of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4

(melanocortin 4) agonists, MC3 (melanocortin 3) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 adrenergic agonists such as CL-316243, AJ-9677, GW-0604, LY362884, LY377267 or AZ-40140 MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors such as fluoxetine, seroxat or citalopram, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR (peroxisome proliferator-activated receptor) modulators, RXR (retinoid X receptor) modulators, TR β agonists, AGRP (Agouti related protein) inhibitors, H3 histamine antagonists, opioid antagonists (such as naltrexone), exendin-4, GLP-1 and ciliary neurotrophic factor (such as axokine), cannaboid receptor antagonist for example CB-1 (such as rimonabant). In another embodiment the antiobesity agent is dexamphetamine or amphetamine. In another embodiment the antiobesity agent is leptin. In another embodiment the antiobesity agent is fenfluramine or exfenfluramine. In still another embodiment the antiobesity agent is sibutramine. In a further embodiment the antiobesity agent is orlistat. In another embodiment the antiobesity agent is mazindol or phentermine. In still another embodiment the antiobesity agent is phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate or ecopipam.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, SCE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin.

The compounds of the present invention may be administered in combination with FAS inhibitors. The compounds of the present invention may also be administered in

combination with chemical uncouplers, hormone sensitive lipase inhibitor, imidazolines, 11-β-hydroxysteroid dehydrogenase inhibitors, lipoprotein lipase activator, AMPK activators, immunosuppressive drugs, nicotinamide, ASIS, anti-androgens or carboxypeptidase inhibitors.

It should be understood that any suitable combination of the compounds according to the invention with diet and/or exercise, one or more of the above-mentioned compounds and optionally one or more other active substances are considered to be within the scope of the present invention.

General terms used in the description of compounds, compositions, and methods herein described, bear their usual meanings. Throughout the instant application, the following terms have the indicated meanings:

"GLP-1" means glucagon-like peptide 1. The term "glucagon receptor" means one or more receptors that interact specifically with glucagon to result in a biological signal. The term "GLP-1 receptor" means one or more receptors that interact specifically with glucagon-like peptide 1 to result in a biological signal.

The term "glucagon receptor antagonist" means a compound of the present invention with the ability to block cAMP production in response glucagon. The term "glucagon receptor inverse agonist" means a compound of the present invention with the ability to inhibit the constitutive activity of glucagon receptor. The term "selective" antagonist or inverse agonist means a compound having greater affinity for the glucagon receptor as compared to the affinity for the GLP-1 receptor.

In the general formulae of the present document, the general chemical terms have their usual meanings. For example;

"Halogen" or "halo" means fluoro, chloro, bromo and iodo.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated configuration. As used herein, "(C_1-C_3) alkyl" are one to three carbon atoms, such as methyl, ethyl, propyl, n-propyl, isopropyl, and the like and branched or isomeric forms thereof, and optionally may be substituted with one to three halogens or a designated number of substituents as set forth in the embodiments recited herein. "(C_1-C_6) alkyl" are one to six carbon atoms such as methyl, ethyl, propyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, pentyl, isopentyl, hexyl, and the like, and branched or

isomeric forms thereof, and optionally may be substituted with one to three halogens or a designated number of substituents as set forth in the embodiments recited herein. "(C_1-C_8) alkyl" are one to eight carbon atoms, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and the like, and branched or isomeric forms thereof, and optionally may be substituted with one to three halogens as set forth in the embodiments recited herein.

The term "(C_3-C_7) cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 7 carbon atoms. Examples of (C_3-C_7) cycloalkyl include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "(C_1-C_6) alkoxy" represents an alkyl group of one to six carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. The term "(C_1-C_7) alkoxy" represents an alkyl group of one to seven carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like, and may be optionally substituted with three halogens as set forth in the embodiments recited herein.

The term "(C_2-C_7) alkenyl" means hydrocarbon chain of two to seven carbon atoms of either a straight or branched configuration having at least one carbon-carbon double bond which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl, 2-butenyl and the like, and may be optionally substituted with one to three halogens as set forth in the embodiments recited herein.

The term "optionally substituted," or "optional substituents," as used herein, means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent, the substituents may be the same or different. Furthermore, when using the terms "independently," "independently are," and "independently selected from" mean that the groups in question may be the same or different. Certain of the herein defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

The term "patient" includes human and non-human animals such as companion animals (dogs and cats and the like) and livestock animals. Livestock animals are animals raised for food production. Ruminants or "cud-chewing" animals such as cows, bulls, heifers, steers, sheep, buffalo, bison, goats and antelopes are examples of livestock.

Other examples of livestock include pigs and avians (poultry) such as chickens, ducks, turkeys and geese. Yet other examples of livestock include fish, shellfish and crustaceans raised in aquaculture. Also included are exotic animals used in food production such as alligators, water buffalo and ratites (e.g., emu, rheas or ostriches). The patient to be treated is preferably a mammal, in particular a human being.

The term "a glucagon receptor mediated cellular response" includes various responses by mammalian cells to glucagon stimulation or glucagon receptor activity. For example "glucagon receptor mediated cellular responses," include but are not limited to, release of glucose from liver, or other cells, in response to glucagon stimulation or glucagon receptor activity. One of ordinary skill in the art can readily identify other cellular responses mediated by glucagon receptor activity, for example by observing a change in the responsive cellular endpoint after contacting the cell with an effective dose of glucagon.

The terms "treatment", "treating" and "treat", as used herein, include their generally accepted meanings, i.e., the management and care of a patient for the purpose of preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, delaying, or reversing the progression or severity of a disease, disorder, or pathological condition, described herein, including the alleviation or relief of symptoms or complications, or the cure or elimination of the disease, disorder, or condition.

"Composition" means a pharmaceutical composition and is intended to encompass a pharmaceutical product comprising the active ingredient(s) including compound(s) of Formula I, and the inert ingredient(s) that make up the carrier. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which to effect the desired reaction.

The term "unit dosage form" means physically discrete units suitable as unitary dosages for human subjects and other non-human animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

The compounds of the present invention may be chiral, and it is intended that any enantiomers, whether pure, partially purified, or racemic mixtures, are included within the scope of the invention. Furthermore, when a double bond or a fully or partially saturated ring system or more than one center of asymmetry or a bond with restricted rotatability is present in the molecule diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention. Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention. The invention also includes tautomers, enantiomers and other stereoisomers of the compounds of Formula I. Such variations are contemplated to be within the scope of the invention.

The compounds of Formula I, when existing as a diastereomeric mixture, may be separated into diastereomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Alternatively, any enantiomer of a compound of Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration or through enantioselective synthesis.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee," which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 70:30 is achieved, the ee with respect to the first enantiomer is 40%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of

greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the specific stereoisomers and enantiomers of compounds of Formula I, can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, *et al.*, "Enantiomers, Racemates, and Resolutions," John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," Stereochemistry of Organic Compounds," (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998. Examples of resolutions include recrystallization techniques or chiral chromatography. Unless otherwise indicated, a compound indicated to be "isomer 1" will be the first isomer eluted from the chiral separation column and "isomer 2" will be the second.

In general, the term "pharmaceutical" when used as an adjective means substantially non-toxic to living organisms. For example, the term "pharmaceutical salt" as used herein, refers to salts of the compounds of Formula I, which are substantially non-toxic to living organisms. See, *e.g.*, Berge, S.M, Bighley, L.D., and Monkhouse, D.C., "Pharmaceutical Salts," *J. Pharm. Sci.*, 66:1, 1977. The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Pharmaceutically acceptable salts and common methodology for preparing them are well known in the art. *See e.g.*, P.Stahl, *et al.*, "Handbook Of Pharmaceutical Salts: Properties, Selection, and Use," (VCHA/Wiley-VCH, 2002); Berge, S.M, Bighley, L.D., and Monkhouse, D.C., "Pharmaceutical Salts," *J. Pharm. Sci.*, 66:1, 1977.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of present compounds, which are readily convertible *in vivo* into a compound of the present invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds of Formula I, can be prepared by one of ordinary skill in the art following a variety of procedures, some of which are illustrated in the procedures and schemes set forth below. The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound to being synthesized, the starting compound, and the relative liability of the substituted moieties. The reagents or starting materials are readily available to one of skill in the art, and to the extent not commercially available, are readily synthesized by one of ordinary skill in the art following standard procedures commonly employed in the art, along with the various procedures and schemes set forth below.

The following Schemes, Preparations, Examples and Procedures are provided to better elucidate the practice of the present invention and should not be interpreted in any way as to limit the scope of the same. Those skilled in the art will recognize that various modifications may be made while not departing from the spirit and scope of the invention. All publications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains.

The optimal time for performing the reactions of the Schemes, Preparations, Examples and Procedures can be determined by monitoring the progress of the reaction via conventional chromatographic techniques. Furthermore, it is preferred to conduct the reactions of the invention under an inert atmosphere, such as, for example, argon, or, particularly, nitrogen. Choice of solvent is generally not critical so long as the solvent employed is inert to the ongoing reaction and sufficiently solubilizes the reactants to effect the desired reaction. The compounds are preferably isolated and purified before their use in subsequent reactions. Some compounds may crystallize out of the reaction solution during their formation and then collected by filtration, or the reaction solvent may be removed by extraction, evaporation, or decantation. The intermediates and final products of Formula I may be further purified, if desired by common techniques such as recrystallization or chromatography over solid supports such as silica gel or alumina.

The skilled artisan will appreciate that not all substituents are compatible with all reaction conditions. These compounds may be protected or modified at a convenient point in the synthesis by methods well known in the art.

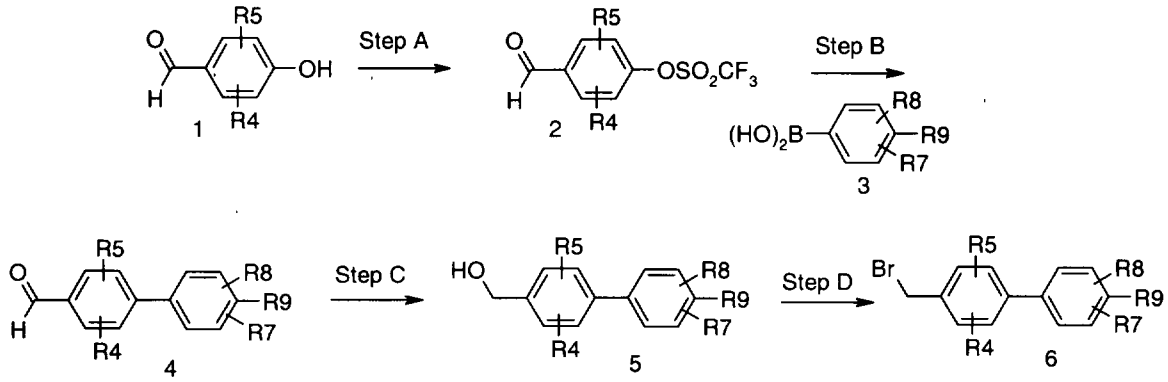
The terms and abbreviations used in the instant Schemes, Preparations, Examples and Procedures have their normal meanings unless otherwise designated. For example, as

used herein, the following terms have the meanings indicated: "min" refers to minutes; "h" or "hr" refers to hours; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ"refers to part per million down-field from tetramethylsilane; "MS" refers to mass spectrometry; "MS(ES)" refers to electron spray mass spectrometry, "UV" refers to ultraviolet spectrometry; "^{1}H NMR" refers to proton nuclear magnetic resonance spectrometry. In addition; "RT" refers to room temperature; "DEAD" refers to diethylazodicarboxylate; "PPh_3" refers to triphenylphosphine; "ADDP" refers to 1,1'-(azodicarbonyl)dipiperidine; "PBu_3" refers to tributylphosphine; "OTF" refers to triflate; "LAH" refers to lithium aluminum hydride; "DIBAL-H" refers to diisobutylaluminum hydride; "KOtBu" refers to potassoium t-butoxide; "THF" refers to tetrahydrofuran; "TBP" refers to tributylphosphine; "EDCI" refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiamide hydrochloride; "DMAP" refers to dimethylaminopyridine; "HNMe(OMe)" refers to N,N,dimethylhydroxyamine; "CDMT" refers to 2-chloro-4,6-dimethoxy-[1,3,5] triazine; "NMM" refers to *N*-methyl morpholine; "DCM" refers to dichloromethane; "DMSO" refers to dimethylsulfoxide; "ET_3N" refers to triethylamine; "DMF" refers to dimethylformamide; "Et" in a formula refers to ethyl, for example Et_2O refers to diethylether, and EtOAc refers to ethylacetate; "PyBOP" refers to bromo-tris-pyrrolidino-phosphonium hexafluorophosphate; "Me" refers to methyl as in MeOH which is methanol; "Pd/C" refers to 10% palladium on carbon. Unless otherwise indicated, isomer 1 refers to the first isomer to be eluted in a chiral separation and isomer 2 refers to the second isomer to be eluted in a chiral separation.

GENERAL SCHEMES

All of the compounds of the present invention can be chemically prepared, for example, by following the synthetic routes set forth in the Schemes and /or the Preparations and Examples below. However, the following discussion is not intended to be limiting to the scope of the present invention in any way. For example, the specific synthetic steps for each of the routes described may be combined in different ways, or in conjunction with steps from different schemes, to prepare additional compounds of Formula I.

Scheme I



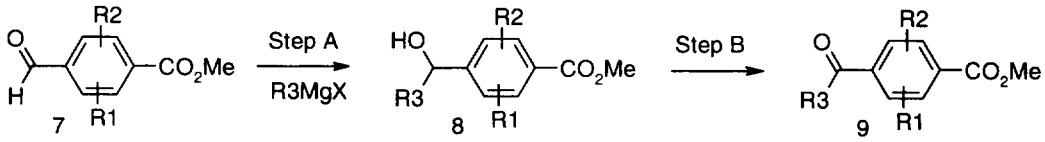
In Scheme I, Step A, a 4-hydroxy benzaldehyde of formula 1 is converted to a trifluoromethane sulfonic acid ester of formula 2. The hydroxyl benzaldehyde is treated with triflic anhydride in the presence of an organic base, such as pyridine at 0 °C to room temperature, for 1 to 20 hours, to obtain the triflate of formula 2.

In Scheme I, Step B, the triflate of formula 2 is coupled with a phenyl boronic acid of formula 3 using a Suzuki reaction to provide the biphenyl aldehyde of formula 4. It will be recognized by one skilled in the art that such Suzuki couplings using aryl triflates and phenyl boronic acids can be effected using a wide variety of reaction conditions. Preferred conditions use tetrakis(triphenylphosphine)palladium with lithium chloride and an inorganic base such as sodium carbonate or potassium carbonate under nitrogen. The reaction proceeds in an inert solvent such as toluene or benzene and water at a temperature of 40 °C to the reflux temperature of the reaction for about 4 to 48 hours.

In Scheme I, Step C, the biphenyl aldehyde of formula 4 is reduced to a biphenyl methanol of formula 5. Numerous methods for reducing aldehydes are well known to the skilled artisan and can be found in the text of R.C. Larock in "Comprehensive Organic Transformations", VCH Publishers, 1989, p. 528 - 536. The preferred method uses a metal hydride such as sodium borohydride in the presence of methanol at a temperature of 0 °C to room temperature. The reaction proceeds for about 15 minutes to 6 hours to provide the benzyl alcohol of formula 5 after an acidic workup.

In Scheme I, Step D, the benzyl alcohol of formula 5 is converted to the benzyl bromide of formula 6. The preferred method uses phosphorus tribromide in an inert solvent such as dioxane or tetrahydrofuran at 0 ° to 40 °C for about 1 to 24 h. Benzyl bromides of formula 6 are further elaborated as shown in Scheme III, wherein R6 is a phenyl substituted with R7, R8 and R9.

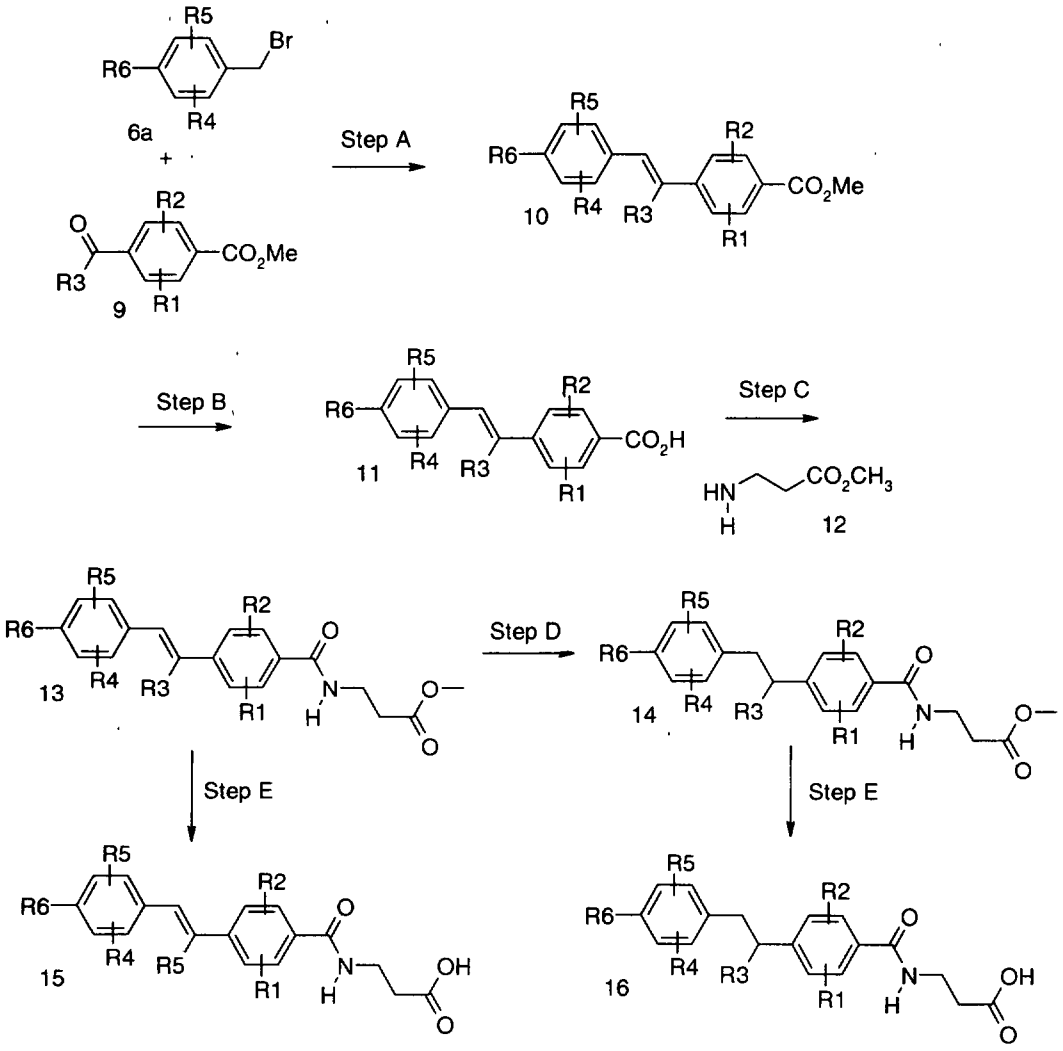
Scheme II



In Scheme II, Step A, a 4-formyl-benzoic acid methyl ester of formula 7 is reacted with a Grignard reagent such as hexylmagnesium bromide or isobutylmagnesium bromide to give a secondary alcohol of formula 8, wherein, for example, R3 = hexyl or isobutyl.

In Scheme II, Step B, the secondary alcohol of formula 8 is oxidized to the ketone of formula 9. There are numerous methods for oxidizing secondary alcohols which are recognized by one skilled in the art. Such methods include, but are not limited to, potassium permanganate, manganese (IV) oxide, ruthenium tetroxide, pyridium dichromate, Oxone®, *o*-iodobenzoic acid, Dess-Martin periodinane, tetrapropylammonium perruthenate (TPAP), and the like. The preferred conditions use pyridinium chlorochromate in an inert solvent such as dichloromethane at room temperature for about 2 to 48 hours.

Scheme III



In Scheme III, Step A, a benzyl bromide of formula 6a (wherein R6 is as previously defined, for example as Ph(R7)(R8)(R9) is converted to a benzyl trialkyl phosphonium bromide and combined in a Wittig reaction with a benzoyl of formula 9 to provide a styryl-benzoic acid methyl ester of formula 10. The Witting reagent can be formed with a triarylphosphine or trialkylphosphine, preferably tributylphosphine, in an inert solvent such as DMSO at a temperature of 50 to 100 °C for about 4 to 24 hours. The reaction is cooled to room temperature and treated with a strong base, such as potassium *t*-butoxide, potassium or sodium bis(trimethylsilylamide), or sodium hydride, with sodium hydride being preferred. A benzoyl of formula 9 is added and the reaction mixture stirred at room temperature for about 4 to 48 hours. The styryl-benzoic acid

methyl ester of formula 10 is isolated using common extractive techniques with an organic solvent and aqueous hydrochloric acid.

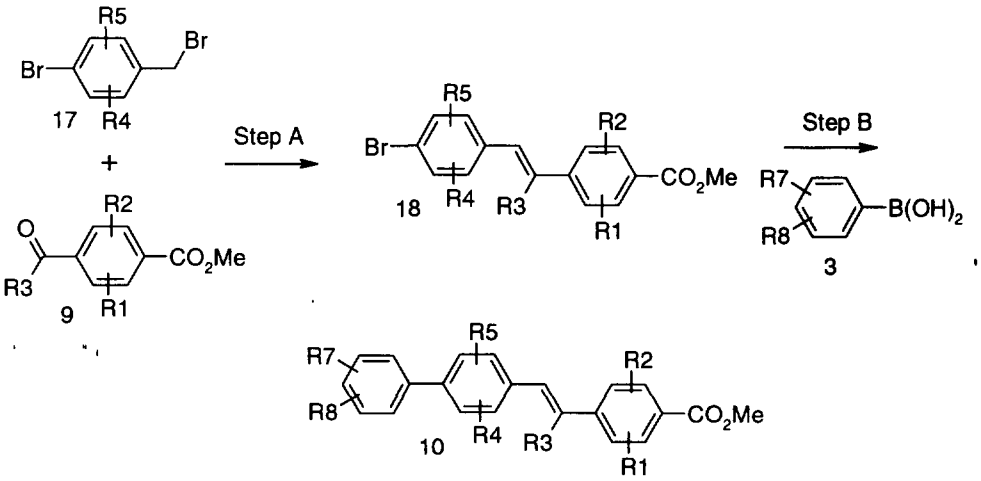
In Scheme III, Step B, a styryl-benzoic acid methyl ester of formula 10 is hydrolyzed to a styryl-benzoic acid of formula 11. The ester is hydrolyzed in an appropriate water soluable solvent such as ethanol, methanol, dioxane, or tetrahydrofuran, with tetrahydrofuran being preferred. The ester is treated with an inorganic base such as potassium or sodium hydroxide, with sodium hydroxide being preferred, at room temperature to the reflux temperature of the solvent for 2 to 48 hours. The styryl-benzoic acid of formula 11 is isolated by neutralization with hydrochloric acid followed by common extractive techniques.

In Scheme III, Step C, the benzoic acid of formula 11 is acylated to give the amide of formula 13. It will be recognized by one skilled in the art that there are numerous conditions for amide bond formation between a carboxylic acid and an amine. Such methods can be found in the text of R.C. Larock in "Comprehensive Organic Transformations", VCH Publishers, 1989, p. 972 - 976. The preferred conditions use a catalytic amount of 4-dimethylaminopyridine (DMAP), 1,[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and an organic base such as diisopropylethylamine or triethylamine in an inert solvent such as dichloromethane. The active ester is treated with an amine of formula 12 at 0 °C to the reflux temperature of the solvent, but preferably at room temperature, for about 4 to 48 hours.

In Scheme III, Step D, the olefin of formula 13 is reduced to the saturated alkane of formula 14. The olefin is reduced over 5 or 10% palladium on carbon in a solvent such as THF, ethyl acetate, methanol or ethanol, with ethanol being preferred. The reaction is placed under an atmosphere of hydrogen at room temperature for about 2 to 24 hours.

In Scheme III, Step E, the methyl ester of formula 13 or 14 is hydrolyzed to the acid of formula 15 or 16 in a manner similar to Scheme III, Step B, as described above.

Scheme IV



Alternatively, the intermediate styryl-benzoic acid methyl ester of formula 10 (where R6 = Ph(R7)(R8)) is obtained as shown in Scheme IV. In Scheme IV, Step A, a 4-bromo-benzylbromide of formula 17 is coupled with a benzoyl of formula 9 using a Wittig reaction as described for Scheme III, Step A.

In Scheme IV, Step B, a 4-bromostyrene of formula 18, is coupled with a phenyl boronic acid of formula 3 using a Suzuki reaction to provide a styryl-benzoic acid methyl ester of formula 10. It will be recognized by one skilled in the art that such Suzuki couplings using aryl bromides and phenyl boronic acids can be effected using a wide variety of reaction conditions. Preferred conditions use tetrakis(triphenylphosphine)palladium with potassium fluoride under nitrogen. The reaction proceeds in an inert solvent such as toluene or benzene and water at a temperature of 40 °C to the reflux temperature of the reaction for about 4 to 48 hours. The styryl-benzoic acid methyl ester of formula 10 is elaborated to final products as described for Scheme III, Steps B to E.

PREPARATIONS AND EXAMPLES

The Examples provided herein are illustrative of the invention claimed herein and are not intended to limit the scope of the claimed invention in any way. Names of the preparations and examples are derived using ChemDraw.

^{1}H NMR spectra are recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the (scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet), integration, coupling constant (Hz) and

assignment. ^{1}H-NMR indicates a satisfactory NMR spectrum was obtained for the compound described. Monoisotopic mass spectral data are obtained on an Agilent G1956B MSD single quadrapole instrument using electrospray ionization (ESI or ES). Analytical thin layer chromatography is performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization is accomplished with UV light. All examples are racemic unless indicated otherwise.

Preparation 1

4-Bromomethyl-2,6-dimethyl-4'-trifluoromethyl-biphenyl

Step A. Trifluoro-methanesulfonic acid 4-formyl-2,6-dimethyl-phenyl ester

To a solution of 4-hydroxy-3,5-dimethyl-benzaldehyde (4.5 g, 30 mmol) in pyridine (20 ml) at 0 °C is slowly added triflic anhydride (10 g, 36 mmol). The resulting mixture is stirred at 0 °C for 10 min and then allowed to warm to room temperature and stirred for 20 h. The resulting mixture is poured into water and extracted with ether. The organic portion is washed with water, 1N HCl, brine, dried over $MgSO_4$, and concentrated. The resulting residue is purified by silica gel column chromatography, eluting with EtOAc/hexanes to afford 4.4 g (52%) of the titled compound as a colorless oil. ^{1}H-NMR.

Step B. 2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-carbaldehyde

Trifluoro-methanesulfonic acid 4-formyl-2,6-dimethyl-phenyl ester (4 g, 14.2 mmol), 4-trifluoromethyl-phenylboronic acid (5.4 g, 28.4 mmol), tetrakis(triphenylphosphine)palladium (1.64 g, 1.42 mmol), LiCl (1.8 g, 42.6 mmol), and K_2CO_3 (5.9 g, 42.6 mmol) are placed in a flask. The system is purged with nitrogen, followed by the addition of toluene (20 ml) and water (5 ml). The resulting mixture is refluxed overnight, loaded on silica gel directly, and purified by silica gel column chromatography, eluting with EtOAc/hexanes to afford 3.8 g (96%) of the titled compound as a white solid. ^{1}H-NMR.

Step C. (2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-yl)-methanol

To the solution of 2,6-dimethyl-4'-trifluoromethyl-biphenyl-4-carbaldehyde (3.0 g, 10.8 mmol) in MeOH (20 ml) is added $NaBH_4$ (410 mg, 10.8 mmol). The mixture is stirred at room temperature for about 2 h, diluted with ethyl acetate, washed with 1N HCl, water, brine, dried over $MgSO_4$, and concentrated to afford 2.5 g of the titled compound as a white solid. ^{1}H-NMR.

Step D. 4-Bromomethyl-2,6-dimethyl-4'-trifluoromethyl-biphenyl

To a solution of (2,6-dimethyl-4'-trifluoromethyl-biphenyl-4-yl)-methanol (2.22 g, 7.9 mmol) in THF (30 ml) is added PBr_3 (3.22 g, 11.9 mmol) in THF (5 ml) and the reaction is allowed to stir at room temperature for about 2 h. The reaction is cooled to 0 °C and ice water is added slowly. The mixture is extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. The resulting residue is purified by silica gel column chromatography, eluting with EtOAc/hexanes to afford 2.2 g of the titled compound as a white solid. ^{1}H-NMR.

Preparation 2

4-(3-Methyl-butyryl)-benzoic acid methyl ester

Step A. Racemic 4-(1-Hydroxy-3-methyl-butyl)-benzoic acid methyl ester

A solution of 4-formyl-benzoic acid methyl ester (32.4 g, 147 mmol) in anhydrous THF (800 mL) is cooled to 0 °C while stirring under nitrogen. Isobutyl magnesium bromide (2.0M in diethyl ether, 110 mL, 221 mmol) is added slowly over 10 min. The reaction is allowed to stir at 0 °C for 1 h, and then allowed to warm to room temperature. The reaction is monitored by HPLC, and upon complete consumption of the aldehyde, the reaction is quenched carefully with 1N HCl. The reaction is diluted with diethyl ether and water, followed by extraction. The organic layer is washed with water and brine, followed by drying over anhydrous sodium sulfate. The solution is filtered and concentrated, then further purified using flash column chromatography using ethyl acetate/hexanes to provide 12 g (37%) of product.

Step B. 4-(3-Methyl-butyryl)-benzoic acid methyl ester

To a solution of 4-(1-hydroxy-3-methyl-butyl)-benzoic acid methyl ester (19.72 g, 88.78 mmol) in dichloromethane (300 mL) is added pyridinium chlorochromate (22.03 g, 97.65 mmol). The mixture is allowed to stir at room temperature, and the solution turns black over time. The reaction is monitored by HPLC. Upon complete conversion, the reaction is diluted with dichloromethane and silica gel (2% by wt) is added to the mixture. The mixture is purified by flash column chromatography using dichloromethane as mobile phase, producing 15.79 g (72%) of product. MS (ES): 221.3 (M^++1).

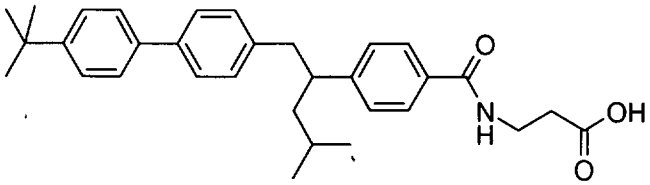
Preparation 3

4-Heptanoyl-benzoic acid methyl ester

The titled intermediate was prepared in a manner similar to Preparation 2, starting with 4-formyl-benzoic acid methyl ester and N-hexylmagnesium bromide. ^{1}H-NMR.

Example 1

3-{4-[1-(4'-*tert*-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid



Step A. 3-{4-[1-(4-Bromo-benzylidene)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester

To a solution of 1-bromo-4-bromomethyl-benzene (1.80 g, 7.2 mmol) in DMSO (15 ml) is added PBu_3 (2.18 g, 10.8 mmol). The resulting mixture is stirred at 60 °C for 23 h. The reaction solution is then cooled down to room temperature, and NaH (432 mg, 10.8 mmol) is added, followed by the addition of 4-(3-methyl-butyryl)-benzoic acid methyl ester (Preparation 2) (1.74 g, 7.92 mmol). The reaction mixture is stirred at room temperature for about 48 h, and then diluted with ethyl acetate. The organic portion is washed with 1N HCl, water, brine, dried over $MgSO_4$, and concentrated. The resulting residue is hydrolyzed in THF using 5N NaOH. The reaction is neutralized with 5N HCl, extracted with diethyl ether. The organic phase is washed with water, dried, filter and concentrated. The resulting residue is taken into dichloromethane (150 ml). To the solution is added triethyl amine (6.41 ml, 46 mmol), followed by the addition of DMAP (5 mg), 3-amino-propionic acid methyl ester hydrochloride (3.21 g, 23 mmol) and EDCI (8.83 g, 46 mmol). The reaction mixture is stirred at room temperature for 2 days. The reaction mixture is loaded on a silica gel column and eluted with a gradient from 0 - 100% ethyl acetate in hexanes to afford 2.60 g of the titled compound.

Step B. 3-{4-[1-(4'-*tert*-Butyl-biphenyl-4-ylmethylene)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester

3-{4-[1-(4-bromo-benzylidene)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester (2.6 g, 5.86 mmol), 4-*t*-butyl phenyl boronic acid (2.08 g, 12 mmol), potassium fluoride (1.02 g, 17.6 mmol) and tetrakis(triphenylphosphine)palladium (0.677 g, 0.59 mmol) are placed in a flask. The system is purged with nitrogen. Toluene (40 mL) and

water (10 ml) are added and the resulting mixture is refluxed overnight. The reaction is loaded directly onto silica gel and chromatographed using EtOAc/hexanes to yield the titled compound as a yellow oil (0.95 g).

Step C. 3-{4-[1-(4'-*tert*-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester

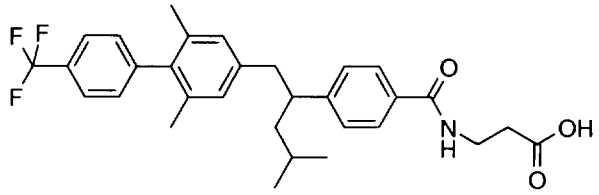
3-{4-[1-(4'-*tert*-Butyl-biphenyl-4-ylmethylene)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester (240 mg) is taken into ethanol (20 ml) and 10% Pd/C (20 mg) is added. The system is purged with nitrogen, followed by the introduction of hydrogen (30 psi). The mixture is stirred at room temperature for 4 h, filtered through Celite®, and concentrated. The resulting residue is purified by silica gel column chromatography, eluting with EtOAc/hexanes to afford 160 mg of the titled compound. MS (ES): 500.3 (M^++1).

Step D. 3-{4-[1-(4'-*tert*-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid

The methyl ester (30 mg) is dissolved in MeOH (20 mL) and treated with 5N NaOH (1 mL) at room temperature for 5 h. The reaction is concentrated followed by addition of ethyl acetate and acidification with 5N HCl. The aqueous portion is extracted with ethyl acetate. Combined organic portions are dried and concentrated to afford the titled compound (28 mg). MS (ES): 486.2 (M^++1).

Example 2

3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid



Step A. 3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethylene)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester

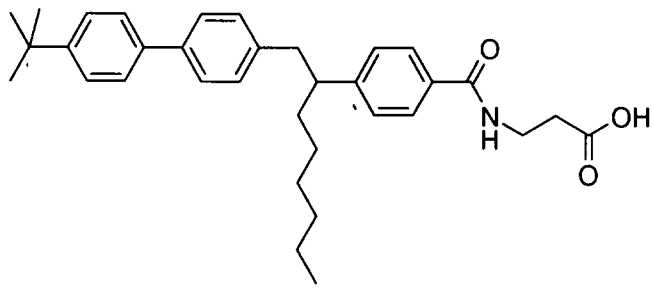
The titled compound is prepared in a manner similar to Example 1, Step A, starting with 4-bromomethyl-2,6-dimethyl-4'-trifluoromethyl-biphenyl (Preparation 1) in place of 1-bromo-4-bromomethyl-benzene to afford 330 mg. ^{1}H-NMR.

Step B. 3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid

The titled compound is prepared in a manner similar to Example 1, Step D to afford 45 mg. MS (ES): 526.2 (M^++1).

Example 3

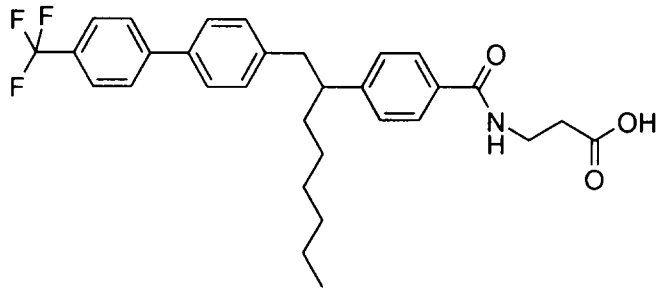
3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid



The titled compound is prepared in a manner similar to Example 1, starting with 4-heptanoyl-benzoic acid methyl ester (Preparation 3) in place of 4-(3-methyl-butyryl)-benzoic acid methyl ester. MS (ES): 514.5 (M^++1).

Example 4

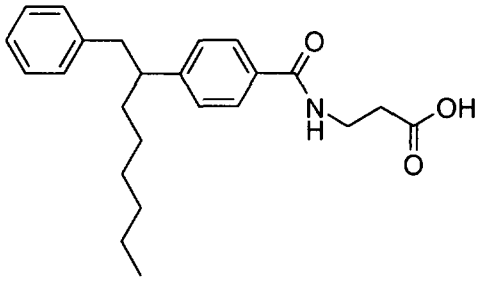
3-{4-[1-(4'-Trifluoromethyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid



The titled compound is prepared in a manner similar to Example 1 starting with 4-bromomethyl-2,6-dimethyl-4'-trifluoromethyl-biphenyl (Preparation 1) and 4-heptanoyl-benzoic acid methyl ester (Preparation 3). MS (ES): 526.2 (M^++1).

Example 5

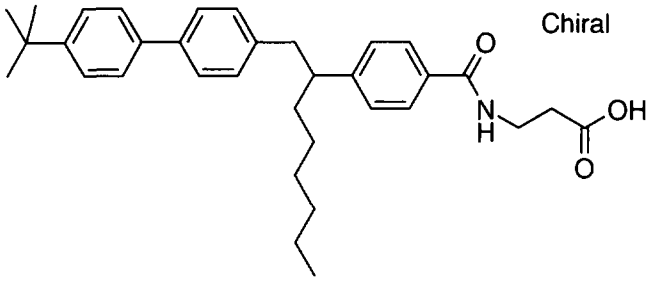
3-[4-(1-Benzyl-heptyl)-benzoylamino]-propionic acid



The titled compound is prepared in a manner similar to Example 1 starting with benzyl bromide and 4-heptanoyl-benzoic acid methyl ester (Preparation 3). MS (ES): 382.3 (M^++1).

Example 6

3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid, Isomer 1

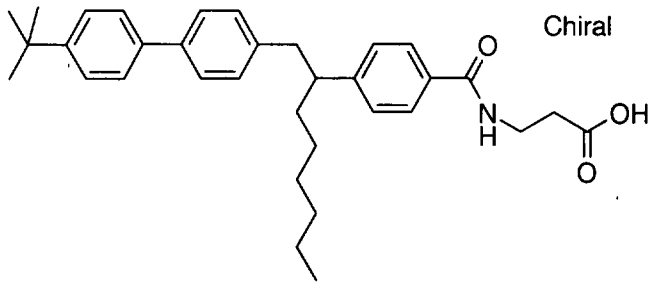


The racemic 3-{4-[1-(4'-*tert*-butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid methyl ester (obtained in preparation of Example 3) is resolved on a Chiralpak AD-H column (4.6 × 150 mm) by elution with propanol/acetonitrile (90/10). The appropriate fractions are concentrated to provide a pure enantiomer ester (isomer 1, 99.7 % ee). The enantiomer of the ester is hydrolyzed with 5N NaOH to provide the titled compound. MS (ES): 514.5 $[M+H]^+$.

The following enantiomerically pure compounds (Examples 7 to 11) were obtained by substantially similar chiral separations using a Chiralpak AD-H column (4.6 × 150 mm) or a Chiralcel OJ-H column (4.6 × 150 mm), followed by hydrolysis of the chiral ester.

Example 7

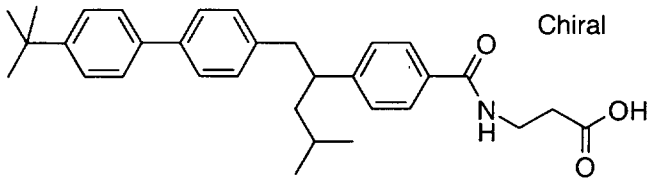
3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid, Isomer 2



The titled compound is obtained by resolving racemic 3-{4-[1-(4'-tert-butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid methyl ester on a Chiralpak AD-H column (4.6 × 150 mm), followed by hydrolysis with 5N NaOH. MS (ES): 514.5 (M^++1).

Example 8

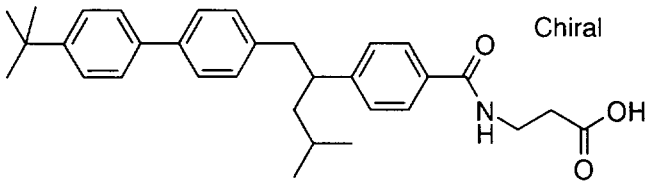
3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 1



The titled compound is obtained by resolving racemic 3-{4-[1-(4'-*tert*-butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester on Chiralcel OJ-H column (4.6 × 150 mm), followed by hydrolysis with 5N NaOH. MS (ES): 486.2 (M^++1).

Example 9

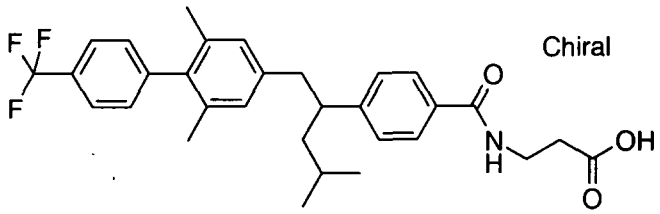
3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 2



The titled compound is obtained by resolving racemic 3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester on Chiralcel OJ-H column (4.6 × 150 mm), followed by hydrolysis with 5N NaOH. MS (ES): 486.2 (M^++1).

Example 10

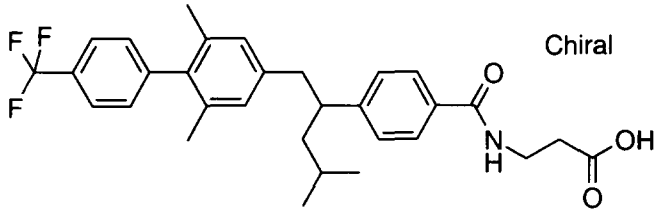
3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 1



The titled compound is obtained by resolving racemic 3-{4-[1-(2,6-dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester on a Chiralpak AD-H column (4.6 x 150 mm), followed by hydrolysis with 5N NaOH. MS (ES): 526.2 (M^++1).

Example 11

3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 2



The titled compound is obtained by resolving racemic 3-{4-[1-(2,6-dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid methyl ester on Chiralpak AD-H column (4.6 x 150 mm), followed by hydrolysis with 5N NaOH. MS (ES): 526.2 (M^++1).

Preferably the compound is administered orally. Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose. Therefore, another embodiment of the present invention is a pharmaceutical composition comprising a compound of Formula I and one or more pharmaceutically acceptable carriers, diluents or excipients. Such pharmaceutical compositions and processes for preparing same are well known in the art. *See, e.g.*, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, *et al.*,

eds., 19th ed., Mack Publishing Co., 1995). The particular dosage of a compound of formula (I) or a pharmaceutically acceptable salt thereof required to constitute an effective amount according to this invention will depend upon the particular circumstances of the conditions to be treated. Considerations such as dosage, route of administration, and frequency of dosing are best decided by the attending physician.

The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient. The compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e., glucagon antagonist activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 0.01 milligrams to about 1,000 milligrams, preferably from about 0.01 to about 950 milligrams, more preferably from about 0.01 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art. Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day.

There is increasing evidence that glucagon plays an important role in glucose homeostasis. Compounds of Formula I are effective as antagonists or inverse agonists of the glucagon receptor, and thus inhibit the activity of the glucagon receptor. More particularly, these compounds are selective antagonists or inverse agonists of the glucagon receptor. As selective antagonists or inverse agonists, the compounds of Formula I are useful in the treatment of diseases, disorders, or conditions responsive to the inactivation of the glucagon receptor, including but not limited to diabetic and other glucagon related disorders. It is expected that selective antagonists or inverse agonists of

the glucagon receptor will lower plasma glucose levels and thus prevent or treat diabetic and other glucagon related metabolic disorders.

PHARMACOLOGICAL METHODS

In the following section binding assays as well as functional assays useful for evaluating the efficiency of the compounds of the invention are described.

Binding of compounds to the glucagon receptor may be determined in a competition binding assay using the cloned human glucagon receptor, and selectivity against the hGlp1 receptor. Antagonism may be determined as the ability of the compounds to inhibit the amount of cAMP formed in the assay in the presence of 5 nM glucagon.

Glucagon Receptor (hGlucR) Binding Assay

The receptor binding assay uses cloned human glucagon receptor (Lok S, Kuijper JL, Jelinek LJ, Kramer JM, Whitmore TE, Sprecher CA, Mathews S, Grant FJ, Biggs SH, Rosenberg GB, et al.Gene 140 (2), 203-209 (1994)) isolated from 293HEK membranes. The hGlucR cDNA is subcloned into the expression plasmid phD (Trans-activated expression of fully gamma-carboxylated recombinant human protein C, an antithrombotic factor. Grinnell, B.W., Berg, D.T., Walls, J. and Yan, S.B. Bio/Technology 5: 1189-1192 (1987)). This plasmid DNA is transfected into 293 HEK cells and selected with 200 µg/mL Hygromycin.

Crude plasma membranes are prepared using cells from suspension culture. The cells are lysed on ice in hypotonic buffer containing 25 mM Tris HCL, pH 7.5, 1 mM $MgCl_2$, DNAse1, 20 u/mL, and Roche Complete Inhibitors-without EDTA. The cell suspension is homogenized with a glass dounce homogenizer using a Teflon pestle for 25 strokes. The homogenate is centrifuged at 4 degrees C at 1800 x g for 15 mins. The supernate is collected and the pellet is resuspended in hypotonic buffer and rehomogenized. The mixture is centrifuged at 1800 x g for 15 mins. The second supernate is combined with the first supernate. The combined supernates are recentrifuged at 1800 x g for 15 mins to clarify. The clarified supernate is transferred to high speed tubes and centrifuged at 25000 x g for 30 minutes at 4 degrees C. The membrane pellet is resuspended in homogenization buffer and stored as frozen aliquots at –80 degree C freezer until needed.

Glucagon is radioiodinated by I-125-lactoperoxidase procedure and purified by reversed phase HPLC at Perkin-Elmer/NEN (NEX207). The specific activity is 2200 Ci/mmol. Kd determination is performed by homologous competition instead of saturation binding due to high propanol content in the I-125 glucagon material. The Kd is estimated to be 3 nM and is used to calculate Ki values for all compounds tested.

The binding assays are carried out using a Scintillation Proximity Assay (Amersham) with WGA beads previously blocked with 1% fatty acid free BSA (ICN). The binding buffer contains 25 mM Hepes, pH 7.4, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% fatty acid free BSA, (ICN), 0.003% tween-20, and Roche Complete Inhibitors without EDTA. Glucagon is dissolved in 0.01 N HCl at 1 mg/mL and immediately frozen at –80 degrees C in 30 µl aliquots. The glucagon aliquot is diluted and used in binding assays within an hour. Test compounds are dissolved in DMSO and serially diluted in DMSO. 10 ul diluted compounds or DMSO is transferred into Corning 3632, opaque clear bottom assay plates containing 90 µl assay binding buffer or cold glucagon (NSB at 1 µM final). 50 µl of I-125 glucagon (0.15 nM final in reaction), 50 µl of membranes (300 µg/well), and 40 µl of WGA beads (150 mgs/well) are added, covered, and mixed end over end. Plates are read with a MicroBeta after 14 hours of settling time at room temp.

Results are calculated as a percent of specific I-125-glucagon binding in the presence of compound. The absolute EC50 dose of compound is derived by non-linear regression of percent specific binding of I-125-glucagon vs. the dose of compound added. The EC50 dose is converted to Ki using the Cheng-Prusoff equation (Cheng Y., Prusoff W. H., Biochem. Pharmacol. 22, 3099-3108, 1973).

Glucagon –Like – Peptide 1 (Glp1-R) Receptor Binding Assay

The receptor binding assay uses cloned human glucagon-like peptide 1 receptor (hGlp1-R) (Graziano MP, Hey PJ, Borkowski D, Chicchi GG, Strader CD, Biochem Biophys Res Commun. 1993 Oct 15;196(1):141-6) isolated from 293HEK membranes. The hGlp1-R cDNA is subcloned into the expression plasmid phD (Trans-activated expression of fully gamma-carboxylated recombinant human protein C, an antithrombotic factor. Grinnell, B.W., Berg, D.T., Walls, J. and Yan, S.B. Bio/Technology 5: 1189-1192 (1987)). This plasmid DNA is transfected into 293 HEK cells and selected with 200 µg/mL Hygromycin.

Crude plasma membrane is prepared using cells from suspension culture. The cells are lysed on ice in hypotonic buffer containing 25 mM Tris HCl, pH 7.5, 1 mM $MgCl_2$, DNAse, 20 µ/mL, and Roche Complete Inhibitors without EDTA. The cell suspension is homogenized with a glass dounce homogenizer using a Teflon pestle for 25 strokes. The homogenate is centrifuged at 4 degrees C at 1800 x g for 15 mins. The supernate is collected and the pellet is resuspended in hypotonic buffer and rehomogenized. The mixture is centrifuged at 1800 x g for 15 mins. The second supernate is combined with the first supernate. The combined supernates are recentrifuged at 1800 x g for 15 mins to clarify. The clarified supernate is transferred to high speed tubes and centrifuged at 25000 x g for 30 minutes at 4 degrees C. The membrane pellet is resuspended in homogenization buffer and stored as frozen aliquots in –80 degree C freezer until use.

Glucagaon-like peptide 1 (Glp-1) is radioiodinated by the I-125-lactoperoxidase procedure and purified by reversed phase HPLC at Perkin-Elmer/NEN (NEX308). The specific activity is 2200 Ci/mmol. Kd determination is performed by homologous competition instead of saturation binding due to high propanol content in the I-125 Glp-1 material. The Kd is estimated to be 3 nM and is used to calculate Ki values for all compounds tested.

The binding assays are carried out using a Scintillation Proximity Assay (Amersham) with wheat germ agglutinin (WGA) beads previously blocked with 1% fatty acid free BSA (ICN). The binding buffer contains 25 mM Hepes, pH 7.4, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% fatty acid free BSA, (ICN), 0.003% tween-20, and Roche Complete Inhibitors without EDTA. Glucagon-like peptide 1 is dissolved in PBS at 1 mg/mL and immediately frozen at –80 degrees C in 30 ul aliquots. The glucagon-like peptide aliquot is diluted and used in binding assays within an hour. Test compounds are dissolved in DMSO and serially diluted in DMSO. 10 µl diluted compounds or DMSO is transferred into Corning 3632, opaque clear bottom assay plates containing 90 µl assay binding buffer or cold glucagon-like peptide 1 (NSB at 1 µM final). 50 µl of I-125 glucagon-like peptide 1 (0.15 nM final in reaction), 50 µl of membranes (600 µg/well), and 40 µl of WGA beads (150 µgs/well) are added, covered, and mixed end over end. Plates are read with a MicroBeta after 14 hours of settling time at room temp.

Results are calculated as a percent of specific I-125-glucagon-like peptide 1 binding in the presence of compound. The absolute EC50 dose of compound is derived by non-linear regression of percent specific binding of I-125-glucagon-like peptide 1 vs. the dose of compound added. The EC50 dose is converted to Ki using the Cheng-Prusoff equation (Cheng Y., Prusoff W. H., Biochem. Pharmacol. 22, 3099-3108, 1973).

Glucagon-Stimulated cAMP Functional Antagonist Assay

The cAMP functional assay uses the same cloned human glucagon receptor cell line isolated for the hGlucR binding assay described above. Cells are stimulated with a mixture of an EC80 dose of glucagon in the presence of compound. The cAMP generated within the cell is quantitated using an Amplified Luminescent Proximity Homogeneous Assay, Alpha Screen, from Perkin Elmer (6760625R). Briefly, cAMP within the cell competes for binding of biotinylated cAMP from the kit to a coated anti-cAMP antibody Acceptor bead and a strepavidin coated Donor bead. As the cAMP level within the cell increases, a disruption of the Acceptor bead-biotinlyated cAMP –Donor bead complex occurs and decreases the signal.

Glucagon is dissolved in 0.01 N HCl at 1 mg/mL and immediately frozen at –80 degrees C in 30 ul aliquots. The glucagon aliquot is diluted and used in the functional assay within an hour. Cells are harvested from sub-confluent tissue culture dishes with Enzyme-Free Cell Dissociation Solution, (Specialty Media 5-004-B). The cells are pelleted at low speed and washed 3 times with assay buffer [25 mM Hepes in HBSS-with Mg and Ca (GIBCO, 14025-092) with 0.1% Fatty Acid Free BSA (ICN)] then diluted to a final concentration of 250,000 cells per mL. Compounds are serially diluted into DMSO then diluted into assay buffer with a 3X concentration of glucagon and 3% DMSO. The EC80 of glucagon is pre-determined from a full glucagon dose response and represents the dose at which glucagons produces an 80% of the maximal glucagon response. A mixture of biotinylated cAMP (1 unit/well final) from the Alpha Screen Kit and 3X IBMX (1500 μM) is prepared in Assay Buffer.

The functional assay is performed in 96 well, low-volume, white, poylstyrene Costar Plates (3688). The biotinylated cAMP/IBMX mixture, 0.02 mLs, is placed into each well, followed by addition of 0.02 mLs of glucagon dose response, cAMP standard curve, or compound/glucagon mixtures. The reaction is started by addition of 0.02 mLs of cells (5000/well final). After 60 minutes at room temperature, the reaction is stopped

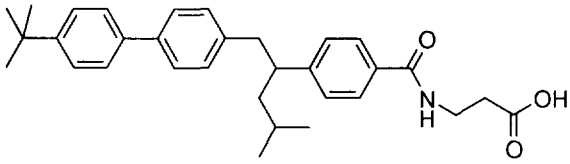
by the addition of 0.03 mLs of Lysis Buffer [10 mM Hepes, pH 7.4, 1% NP40, and 0.01% fatty acid free BSA (ICN) containing 1 unit each/well of Acceptor and Donor beads from the Alpha Screen Kit]. Lysis Buffer addition is performed under a green light to prevent bleaching of the detection beads. The plates are wrapped in foil and left to equilibrate overnight at room temperature. The plates are read on a Packard Fusion™-α Instrument.

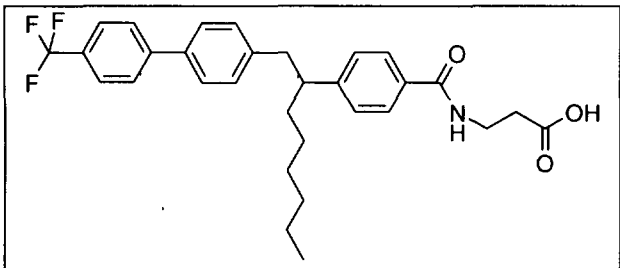
Alpha screen units are converted to pmoles cAMP generated per well based upon the cAMP standard curve. The pmoles cAMP produced in the presence of compound are converted to % of a maximal response with the EC80 dose of glucagon alone. With each experiment, the dose of glucagon needed to produce a 50% response of pmoles cAMP is determined. This EC50 dose is used to normalize results to a Kb using a modified Cheng-Prusoff equation (Cheng Y., Prusoff W. H., Biochem. Pharmacol. 22, 3099-3108, 1973), where Kb = (EC50 compound)/ [1 + (pM glucagon used/ EC50 in pM for glucagon dose response)].

The compounds according to the invention preferably have a Ki value of no greater than 50 μM as determined by the Glucagon Receptor (hGlucR) Binding Assay disclosed herein. More preferably, the compounds according to the invention have a Ki value of less than 5 μM, preferably of less than 500 nM and even more preferred of less than 100 nM as determined by the Glucagon Receptor (hGlucR) Binding Assay disclosed herein. Generally, the compounds according to the invention show a higher affinity for the glucagon receptor compared to the GLP-1 receptor, and preferably have a higher binding affinity to the glucagon receptor than to the GLP-1 receptor. All of the examples provided herein have a Ki value of less than 1 μM.

The results are given below for the indicated compound.

Table 1:

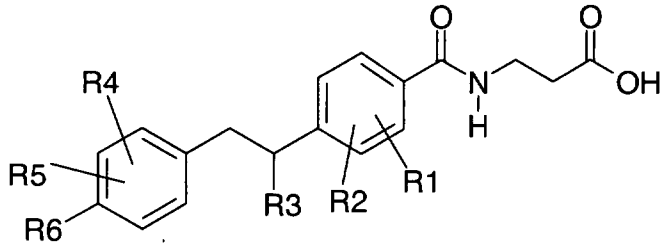
Example	Ki (nM)
	266

	232

From the above description, one skilled in the art can ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the claims.

WHAT IS CLAIMED:

1. A compound structurally represented by Formula I



(I)

or a pharmaceutically acceptable salt thereof wherein:

R1 and R2 are independently –H or -halogen;

R3 is

-(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens),

-(C_3-C_7)cycloalkyl,

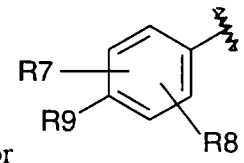
-(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl, or

-(C_3-C_7)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R4 and R5 are independently

-H, -halogen, -hydroxy, hydroxymethyl, -CN, -(C_1-C_7) alkoxy, -(C_2-C_7)alkenyl, or -(C_1-C_6)alkyl (optionally substituted with 1 to 3 halogens);

R6 is

-H, -halogen, or 

, wherein the zig-zag mark shows the point of attachment to the parent molecule;

R7 and R8 are independently

-H, -halogen, -(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens), -(C_1-C_6)alkoxy, -(C_3-C_7)cycloalkyl, -C(O)R10, -COOR10, -OC(O)R10, -$OS(O)_2$R10, -SR10, -S(O)R10, -$S(O)_2$R10, or -O(C_2-C_7)alkenyl;

R9 is independently

-H, -halogen, -CN, -(C_3-C_7)cycloalkyl, -C(O)R10, -COOR10, -OC(O)R10, -$OS(O)_2$R10, -SR10, -S(O)R10, -$S(O)_2$R10, or -O(C_2-C_7)alkenyl, -(C_1-C_3)alkoxy(optionally substituted with 1 to 3 halogens), or -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens), and

R10 is independently at each occurrence

-hydrogen, or -(C_1-C_6) alkyl(optionally substituted with 1 to 3 halogens).

2. A compound or salt of claim 1 wherein

R1 and R2 are –H;

R3 is

-(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens),

-(C_3-C_6)cycloalkyl,

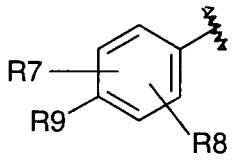
-(C_1-C_6)alkyl-(C_3-C_6)cycloalkyl, or

-(C_3-C_6)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R4 and R5 are independently

-H, -halogen, or -(C_1-C_6)alkyl (optionally substituted with 1 to 3 halogens);

R6 is



, wherein the zig-zag mark shows the point of attachment to the parent molecule;

R7 and R8 are independently

-H, -halogen, -(C_1-C_3)alkyl(optionally substituted with 1 to 3 halogens), -(C_1-C_3)alkoxy; and

R9 is independently

-H, -halogen, or -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens).

3. A compound or salt of claim 1 wherein

R1 and R2 are –H;

R3 is

-(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens),

-(C_3-C_6)cycloalkyl,

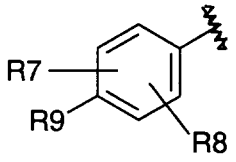
-(C_1-C_6)alkyl-(C_3-C_6)cycloalkyl, or

-(C_3-C_6)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens);

R4 and R5 are independently

-H, -halogen, or $-CH_3$ (optionally substituted with 1 to 3 halogens);

R6 is



, wherein the zig-zag mark shows the point of attachment to the parent molecule;

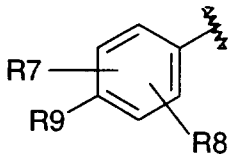
R7 and R8 are independently -H, or -halogen; and

R9 is independently -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens).

4. The compound or salt of claim 1 wherein

R1 and R2 are –H; R3 is -(C_1-C_8) alkyl(optionally substituted with 1 to 3 halogens), -(C_3-C_6)cycloalkyl, -(C_1-C_6)alkyl-(C_3-C_6)cycloalkyl, or -(C_3-C_6)cycloalkyl-(C_1-C_6)alkyl(optionally substituted with 1 to 3 halogens); R4 and R5 are $-CH_3$ (optionally substituted with 1 to 3 halogens) and each occupies a position adjacent to R6 on the phenyl ring to which R6 is attached;

R6 is



, wherein the zig-zag mark shows the point of attachment to the parent molecule;

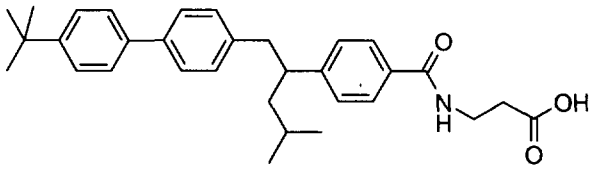
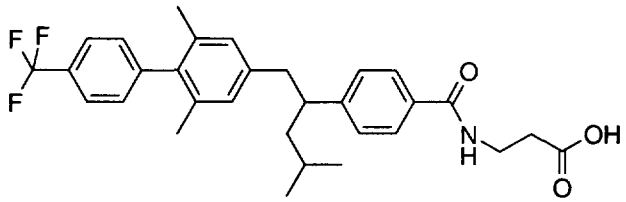
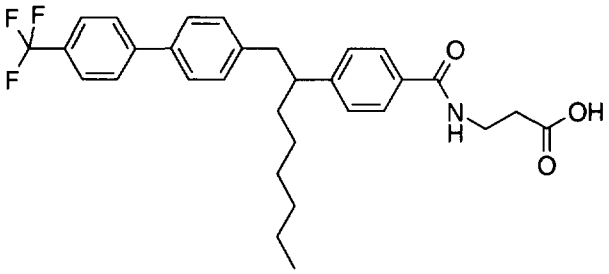
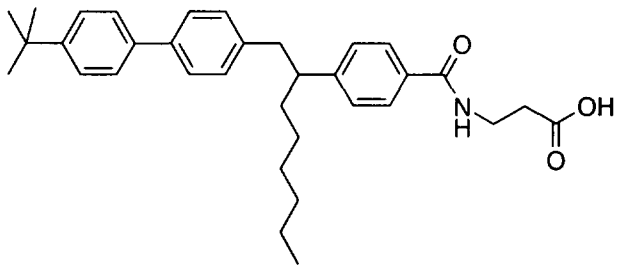
R7 and R8 are -H; and R9 is independently -(C_1-C_6) alkyl (optionally substituted with 1 to 3 halogens).

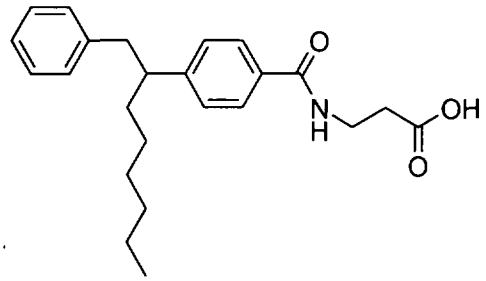
5. The compound or salt of claim 1 wherein

R1 and R2 are independently hydrogen or halogen; R3 is methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, 3,3-dimethylbutyl, 2-methylpropyl, 3-methyl-butyl, tertbutyl, 4-methylpentyl, 2,2-dimethylpropyl, 3-trifluoropropyl,

4-trifluorbutyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; R4 and R5 are independently hydrogen, methyl, ethyl, tertbutyl, cyclohexyl, pentyl, isopropoxy, chloro, fluoro, bromo, hydoxy, trifluoromethyl, -CN, methoxy, hydroxymethyl, 4-methylpentyloxy, or pentyloxy; R7 and R8 are independently hydrogen, fluoro, chloro, methyl, ethyl, pentyl, isopropyl, tertbutyl, trifluoromethyl, acetyl, 2-methylpropyl, methoxy,cyclohexyl, or trifluormethoxy; and R9 is hydrogen, bromo, fluoro, methyl, tertbutyl, trifluoromethyl, or isopropyl.

6. The compound of claim 1, selected from the group consisting of formulae X1 to X5;

Formula Number	Structure
X1	
X2	
X3	
X4	

Formula Number	Structure
X5	

or a pharmaceutically acceptable salt thereof.

7. A compound of claim 1 selected from the group consisting of:

3-{4-[1-(4'-*tert*-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid;

3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid;

3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid;

3-{4-[1-(4'-Trifluoromethyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid;

3-[4-(1-Benzyl-heptyl)-benzoylamino]-propionic acid;

3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid, Isomer 1;

3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-heptyl]-benzoylamino}-propionic acid, Isomer 2;

3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 1;

3-{4-[1-(4'-tert-Butyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 2;

3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 1; and

3-{4-[1-(2,6-Dimethyl-4'-trifluoromethyl-biphenyl-4-ylmethyl)-3-methyl-butyl]-benzoylamino}-propionic acid, Isomer 2;

or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition which comprises a compound or salt of any of claims 1-7 and a pharmaceutically acceptable carrier.

9. A method of inhibiting the glucagon receptor in a mammal comprising administering to a mammal in need thereof a glucagon receptor inhibiting dose of a compound of formula I, or a salt thereof, as described in any of claims 1-8.

10. A method of selectively reducing the glycemic level in a mammal comprising administering to a mammal in need thereof a glucagon receptor inhibiting dose of a compound of formula I, or a salt thereof, as described in any of claims 1-8.

11. A method for treatment of Type 2 diabetes which comprises administering to a mammal in need of such treatment or prevention an effective amount of a compound of any of claims 1-8.

12. A method for treatment of Type 2 diabetes which comprises administering to a mammal in need of such treatment or prevention an effective amount of a pharmaceutical composition of claim 8.

13. A compound of formula I, or a salt thereof, as claimed in any one of claims 1-7, for use in treating Type 2 diabetes.

14. The use of a compound of formula I, or a salt thereof, as claimed in any one of claims 1-8, for the manufacture of a medicament for treatment of Type 2 diabetes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/060857

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C233/83 A61K31/166 A61P3/10

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)
C07C 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, 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.
P,Y	WO 2005/118542 A (LILLY CO ELI [US]; CHAPPELL MARK DONALD [US]; CONNER SCOTT EUGENE [US]) 15 December 2005 (2005-12-15) example 94	1-14
P,Y	WO 2006/102067 A (MERCK & CO INC [US]; STELMACH JOHN E [US]; ROSAUER KEITH G [US]; PARME) 28 September 2006 (2006-09-28) claim 1	1-14
A	KURUKULASURIYA ET AL: "Biaryl amide glucagon receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 9, 2004, pages 2047-2050, XP002339903 ISSN: 0960-894X the whole document	1-14

☐ Further documents are listed in the continuation of Box C.

☒ 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" later 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2007	28/09/2007

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Pérez Carlón, Raquel

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/060857

Box 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.: 9-14
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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 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 fee, this Authority did not invite payment of any additional fee.

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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/060857

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005118542 A	15-12-2005	EP 1758859 A1	07-03-2007
WO 2006102067 A	28-09-2006	NONE	