The compound of the invention is useful as therapeutical agents for various ACC-related diseases.
TITLE OF THE INVENTION
SUBSTITUTED SPIROCHROMANONE DERIVATIVES

BACKGROUND OF THE INVENTION

Acetyl CoA carboxylase (hereinafter this may be abbreviated to ACC) is an enzyme that carboxylates acetyl CoA to produce malonyl CoA, and mammals have two isozymes of ACC1 and ACC2 in their own bodies. Malonyl CoA produced by ACC may be a starting material for long-chain fatty acids or neutral fats, and in addition, it may negatively control carnitine palmitoyl transferase-1 (CPT-I) that participates in oxidative decomposition of fatty acids. Of the above isozymes, ACC1 exists in cytoplasm and is considered as a rate-limiting enzyme in biosynthesis of long-chain fatty acids, while, ACC2 exists predominantly on mitochondria and is said to participate principally in oxidation of fatty acids. Accordingly, compounds capable of inhibiting ACC1 and/or ACC2 are expected not only to inhibit synthesis of fatty acids but also to reduce accumulated fats. In fact, it is shown that, as compared with normal mice, ACC2-knocked out mice hardly get fat (see Proceedings of the National Academy of Sciences of the United States of America, 100 (18), pp. 10207-10212, 2003).

An excess of accumulated fats may cause, for example, insulin resistance, diabetes, hypertension, hyperlipemia and obesity, and it is known that a plurality of those factors, as combined, lead to an extremely higher risk of arteriosclerosis, and the symptom is referred to as a metabolic syndrome. Further, it is known that hypertriglyceridemia or obesity leads to a higher risk of, for example, pancreatitis, liver dysfunction, cancers such as breast cancer, uterine cancer, ovarian cancer, colon cancer and prostate cancer, emmeniopathy, arthritis, gout, cholecystitis, gastroesophageal reflux, pickwickian syndrome, sleep apnea syndrome. It is well known that diabetes often causes, for example, cardiac angina, heart failure, stroke, claudication, retinopathy, eyesight failure, renal failure, neuropathy, skin ulcer, infectious diseases (see The Merck Manual of Medical Information, second home edition, Merck & Co., 2003). Accordingly, ACC inhibitors are useful for the treatment and/or prevention of such disorders.

ACC exists also in plants, parasites, bacteria and fungi, and it is known that it participates in the growth of cells. For example, aryloxyphenoxypyropionic acid-type herbicides represented by diclofop, and cyclohexanedione-type herbicides represented by setoxydim exert their activity by inhibiting ACC in plants (see Biochemical Society of Transaction, 22(3), p. 616 (1994)), and the aryloxyphenoxypyropionic acids also exhibit a growth-inhibiting effect on parasites (see Journal of Biological Chemistry, 277 (26), pp. 23208-23215 (2002)). In addition, sorafen and moiramide B known as ACC inhibitors exhibit an antibacterial effect and an antifungal effect (see Current Genetics, 25 (2), pp. 95-100 (1994); Journal of Biological Chemistry, 279 (25), pp. 26066-26073 (2004)).
Tumor cells generally show an increased synthesis of fatty acids, and it is reported that some fatty acid synthesis inhibitors exhibit a cell growth-inhibiting effect.

Based on the above-mentioned information, ACC inhibitors are expected to be useful for the treatment and/or prevention of disorders such as hyperlipemia, fatty liver, dyslipidemia, hepatic dysfunction, obesity, diabetes, insulin resistance, metabolic syndrome, arteriosclerosis, hypertension, cardiac angina, heart failure, cardiac infarction, stroke, claudication, retinopathy, eyesight failure, renal failure, electrolyte metabolism disorder, neuropathy, skin ulcer, bulimia, pancreatitis, emmeniopathy, arthritis, gout, cholecystitis, gastroesophageal reflux, pickwickian syndrome, sleep apnea syndrome, neoplasm, infectious diseases, such as parasite infection, bacterial infection, viral infection and fungal infection, and also as herbicides.

Up to the present, for example, those described in a pamphlet of WO 2003/094912, a pamphlet of WO 2003/072197, a pamphlet of WO 2003/059886, a pamphlet of WO 2003/059871 are known as compounds capable of inhibiting ACC, but the compounds described in these references are totally different from the compounds of the present invention in point of their structures.

On the other hand, various compounds having the same spirochromanone skeleton as that of the compounds of the present invention are disclosed in a pamphlet of WO 95/30642, EP 431973A or a pamphlet of WO 2004/092179. However, these references do neither disclose nor suggest the ACC-inhibiting effect of those compounds or the compounds of the present invention.

SUMMARY OF THE INVENTION

The present invention is useful in the field of medicines. More precisely, substituted spirochromanone derivatives of the invention are acetyl CoA carboxylase inhibitors useful as therapeutical agents for various vascular diseases, nervous system diseases, metabolic diseases, genital diseases, digestive system diseases, respiratory diseases, neoplasm and infectious diseases. In addition, they are also useful as herbicides.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of the following general formula (I), and salts and esters thereof, which have a strong ACC-inhibiting effect:
wherein ArI represents a group formed from an aromatic ring selected from a group consisting of indole, benzimidazole and 1,2-benzisoxazole, having R3 and R4, and optionally having a substituent selected from a group consisting of a halogen atom, a hydroxyl group, a C1-C6 alkyl group, a halo-C1-C6 alkyl group, a hydroxy-C1-C6 alkyl group, a cyclo-C3-C6 alkyl group, a C1-C6 alkoxy group, a halo-C1-C6 alkoxy group and carbamoyl group; R1 represents a phenyl group optionally substituted with a carboxyl group, a tetrazolyl group optionally substituted with a C2-C7 alkanoyloxy-C1-C6 alkyl group, a pyridyl group optionally substituted with a C1-C6 alkyl group or a carboxyl group, a dihydro-1,2,4-triazolyl group optionally substituted with an oxo group, or a dihydro-1,2,4-oxadiazolyl group optionally substituted with an oxo group; R2 represents a hydrogen atom, a halogen atom, a C1-C6 alkyl group, or a C1-C6 alkoxy group; and R3 and R4 each independently represent a hydrogen atom, a halogen atom, nitro group, a cyclo-C3-C6 alkyl group, a carbamoyl group optionally substituted with a C1-C6 alkyl or cyclo-C3-C6 alkyl group, a C1-C6 alkoxy group optionally substituted with a hydroxyl group, or a C1-C6 alkyl group optionally substituted with a hydroxyl group.

The compounds (I) of the invention have an ACC-inhibiting effect and are useful as therapeutical agents for various ACC-related disorders, for example, vascular diseases such as hypertension, cardiac angina, heart failure, cardiac infarction, stroke, claudication, diabetic nephropathy, diabetic retinopathy, eyesight failure, electrolyte metabolism disorder, arteriosclerosis; nervous system diseases such as bulimia, diabetic neuropathy; metabolic diseases such as metabolic syndrome, obesity, diabetes, insulin resistance, hyperlipemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, nonalcoholic fatty liver, hormone secretion failure, gout, and hepatic steatosis; genital diseases such as emmeniopathy, sexual dysfunction; digestive system diseases such as liver dysfunction, pancreatitis, cholecystitis, gastroesophageal reflux; respiratory diseases such as obesity-hypoventilation syndrome (pickwickian syndrome), sleep apnea syndrome; infectious diseases caused by bacteria, fungi or parasites; malignant neoplasm; and inflammatory diseases such as arthritis and skin ulcer. The compounds are also useful as herbicides.

In particular, the compounds (I) of the invention are useful as therapeutical agents, for example, for metabolic syndrome, fatty liver, hyperlipemia, obesity, diabetes, bulimia, malignant neoplasm and infectious diseases.
The invention relates to the compounds of formula (I), and their pharmaceutically
acceptable salts and esters, and to their production and use.

The meanings of the terms used herein are mentioned below, and the invention is
described in more detail hereinunder.

"Halogen atom" includes a fluorine atom, a chlorine atom, a bromine atom, and an iodine
atom.

"C1-C6 alkyl group" means a linear or branched alkyl group having from 1 to 6 carbon
atoms, and it includes, for example, a methyl group, an ethyl group, a propyl group, an isopropyl
group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an
isopentyl group, a hexyl group, and an isohexyl group.

"Halo-C1-C6 alkyl group" means the above-mentioned C1-C6 alkyl group which is
substituted with the above-mentioned halogen atom(s) of the same type or different types and
which has one or two or more, but preferably from 1 to 3 unlimited substitutable positions, and it
includes, for example, a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a
2-fluoroethyl group, a 1,2-difluoroethyl group, a chloromethyl group, a 2-chloroethyl group, a
1,2-dichloroethyl group, a bromomethyl group, and an iodomethyl group.

"Hydroxy-C1-C6 alkyl group" means the above-mentioned C1-C6 alkyl group which is
substituted with hydroxyl group(s) and which has one or two or more, but preferably one or two
unlimited substitutable positions, and it includes, for example, a hydroxymethyl group, a 2-
hydroxyethyl group, a 1-hydroxy-1-methylethyl group, a 1,2-dihydroxyethyl group, and a 3-
hydroxypropyl group.

"Cyclo-C3-C6 alkyl group" means a cycloalkyl group having from 3 to 6 carbon atoms,
and it includes a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, and a cyclohexyl
group.

"C1-C6 alkoxy group" means a linear or branched alkoxy group having from 1 to 6
carbon atoms, and it includes, for example, a methoxy group, an ethoxy group, a propoxy group,
an isoproxy group, a butoxy group, a sec-butoxy group, an isobutoxy group, a tert-butoxy
group, a pentyloxy group, an isopentyloxy group, a hexyloxy group, and an isohexyloxy group.

"Halo-C1-C6 alkoxy group" means the above-mentioned C1-C6 alkoxy group which is
substituted with the above-mentioned halogen atom(s) of the same type or different types and
which has one or two or more, but preferably from 1 to 3 unlimited substitutable positions, and it
includes, for example, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy
group, a 2-fluorothoxy group, a 1,2-difluorothoxy group, a 2,2,2-trifluorothoxy group, a
chloromethoxy group, a 2-chlorothoxy group, a 1,2-dichlorothoxy group, a bromomethoxy
group, and an iodomethoxy group.

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"C2-C7 alkanoyl group" means an alkanoyl group having the above-mentioned C1-C6 alkyl group, or that is, an alkanoyl group having from 2 to 7 carbon atoms, and it includes, for example, an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a valeryl group, an isovaleryl group, and a pivaloyl group.

"C2-C7 alkoxyacyl group" means an alkoxyacyl group having the above-mentioned C1-C6 alkoxy group, or that is, an alkoxyacyl group having from 2 to 7 carbon atoms, and it includes, for example, a methoxyacyl group, an ethoxyacyl group, a propoxycarbonyl group, an isopropanoyl group, a butyroyl group, an isobutyroyl group, a tert-butoxyacyl group, and a pentyloxyacyl group.

"C2-C7 alkanoyloxy group" means an alkanoyloxy group having the above-mentioned C2-C7 alkanoyl group, and it includes, for example, an acetoxy group, an acetoxy group, a propionyloxy group, a butyryloxy group, an isoformyloxy group, a valeroyloxy group, an isovaleroyloxy group, and a pivaloyloxy group.

"C2-C7 alkanoyloxy-C1-C6 alkyl group" means the above-mentioned C1-C6 alkyl group substituted with one or two or more, preferably one above-mentioned C2-C7 alkanoyloxy group at any substitutable position thereof, and it includes, for example, an acetoxyethyl group, a propionyloxyethyl group, a butyroyloxyethyl group, an isoformyloxyethyl group, a valeroyloxyethyl group, an isovaleroyloxyethyl group, and a pivaloyloxyethyl group.

"Carbamoyl group optionally substituted with a C1-C6 alkyl group or a cyclo-C3-C6 alkyl group" means a carbamoyl group which may be substituted with the above-mentioned C1-C6 alkyl group and/or the above-mentioned cyclo-C3-C6 alkyl group, and it includes, for example, a carbamoyl group, a methylcarbamoyl group, a dimethylcarbamoyl group, a cyclopropylcarbamoyl group, and a cyclopropyl(methyl)carbamoyl group.

"A pharmaceutically acceptable salt" of the compound of formula (I) means pharmaceutically acceptable and common salts, including, for example, base addition salts of the compound having a carboxyl group, a hydroxyl group or an acidic heterocyclic group such as a tetrazolyl group, with a base added to the carboxyl group, the hydroxyl group or the acidic heterocyclic group of the compound; and acid addition salts of the compound having an amino group or a basic heterocyclic group, with an acid added to the amino group or the basic heterocyclic group of the compound.

The base addition salt include, for example, alkaline metal salts such as sodium salts, potassium salts; alkaline earth metal salts such as calcium salts, magnesium salts; ammonium salts; and organic amine salts such as trimethylamine salts, triethylamine salts, dicyclohexylamine salts, ethanolamine salts, diethanolamine salts, triethanolamine salts, procaine salts, N,N'-dibenzylethlenediamine salts.
The acid addition salt include, for example, inorganic acid salts such as hydrochlorides, sulfates, nitrates, phosphates, perchlorates; organic acid salts such as maleates, fumarates, tartrates, citrates, ascorbates, trifluoroacetates; and sulfonates such as methanesulfonates, isethionates, benzenesulfonates, p-toluenesulfonates.

"A pharmaceutically acceptable ester" of the compound of formula (I) mean those of the compound having a carboxyl group, which are esterified at the carboxyl group of the compound and which are pharmaceutically acceptable and common esters, including, for example, esters with a C1-C6 (cyclo)alkyl group such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a cyclopropyl group, a cyclobutyl group or cyclopentyl group; esters with an aralkyl group such as a benzyl group or a phenethyl group; esters with a C2-C6 alkenyl group such as an allyl group (2-propenyl group), or a 2-butenyl group; esters with a C1-C6 alkoxy-Cl-C6 alkyl group such as a methoxymethyl group, a 2-methoxyethyl group or a 2-ethoxyethyl group; esters with a C2-C7 alkanoyloxy-Cl-C6 alkyl group such as an acetoxyethyl group, a pivaloyloxyethyl group or a 1-pivaloyloxyethyl group; esters with a C2-C7 alkoxy(carbonyl)-Cl-C6 alkyl group such as a methoxycarbonylmethyl group or an isopropoxycarbonylmethyl group; esters with a carboxy-Cl-C6 alkyl group such as a carboxymethyl group; esters with a C2-C7 alkoxy(carbonyloxy)-Cl-C6 alkyl group such as a 1-(ethoxycarbonyloxy)ethyl group or a 1-(cyclohexyloxy)carbonyloxyethyl group; esters with a carbamoyloxy-Cl-C6 alkyl group such as a carbamoyloxymethyl group; esters with aphathalidyl group; and esters with a (5-substituted-2-oxo-1,3-dioxol-4-yl)methyl group such as a (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl group.

"Therapeutical agent" means a medicine used for the treatment and/or prevention of various disorders.

For more concrete disclosure of the compounds of formula (I) of the invention, the symbols used in formula (I) are described in detail hereinunder with reference to their preferred examples.

ArI represents a group formed from an aromatic ring selected from a group consisting of indole, benzimidazole and 1,2-benzisoxazole, having R.3 and R.4, and optionally having a substituent selected from a group consisting of a halogen atom, a hydroxyl group, a C1-C6 alkyl group, a halo-Cl-C6 alkyl group, a hydroxy-Cl-C6 alkyl group, a cyclo-C3-C6 alkyl group, a C1-C6 alkoxy group, a halo-Cl-C6 alkoxy group and carbamoyl group.

"Group formed from an aromatic ring selected from a group consisting of indole, benzimidazole and 1,2-benzisoxazole" means an atomic group formed by formally removing the hydrogen atom from the ring-constituting atoms of the aromatic ring. The group includes an at least tri-substituted group, necessarily bonding to the adjacent carbonyl group and to R.3 and R.4.
and as the case may be, it may have an additional substituent, and may include a 4-substituted or
5-substituted or more poly-substituted group, bonding to the substituent. Each independently, R₃
and R₄ may be a hydrogen atom, and therefore, the group includes a mono-substituted or di-
substituted group.

The substituent which the group may additionally have may be one or two or more,
preferably one selected from a group consisting of a halogen atom, a hydroxyl group, a C₁-C₆
alkyl group, a halo-Cl-C₆ alkyl group, a hydroxy-Cl-C₆ alkyl group, a cyclo-C₃-C₆ alkyl group,
a C₁-C₆ alkoxy group, a halo-Cl-C₆ alkoxy group and carbamoyl group.

ArI js especially preferably a 3-substituted or 4-substituted group, which is formed from
an aromatic ring such as indole, benzimidazole or 1,2-benzisoxazole, more preferably indole.

R₃ and R₄ may bond each independently to any bondable position on ArI.

The substituent selected from a group consisting of a halogen atom, a hydroxyl group, a
C₁-C₆ alkyl group, a halo-Cl-C₆ alkyl group, a hydroxy-Cl-C₆ alkyl group, a cyclo-C₃-C₆ alkyl
group, a C₁-C₆ alkoxy group, a halo-Cl-C₆ alkoxy group and carbamoyl group may be on any
desired and substitutable position of ArI except the position at which the above mentioned R₃
and R₄ bond.

The halogen atom for the substituent is, for example, preferably a fluorine atom, a
chlorine atom, a bromine atom.

The C₁-C₆ alkyl group for the substituent is, for example, preferably a methyl group, an
ethyl group.

The halo-Cl-C₆ alkyl group for the substituent is, for example, preferably a fluoromethyl
group, a difluoromethyl group, a trifluoromethyl group.

The hydroxyl group, a hydroxy-Cl-C₆ alkyl group for the substituent is, for example, preferably a
hydroxymethyl group, a 1-hydroxyethyl group, a 2-hydroxyethyl group.

The cyclo-C₃-C₆ alkyl group for the substituent is, for example, preferably a cyclopropyl
group.

The C₁-C₆ alkoxy group for the substituent is, for example, preferably a methoxy group, an
ethoxy group.

The halo-Cl-C₆ alkoxy group for the substituent is, for example, preferably a difluoromethoxy
group.

R₃ and R₄ each independently represent a hydrogen atom, a halogen atom, nitro group, a
cyclo-C₃-C₆ alkyl group, a carbamoyl group optionally substituted with a C₁-C₆ alkyl or cyclo-
C₃-C₆ alkyl group, a C₁-C₆ alkoxy group optionally substituted with a hydroxyl group, or a C₁-
C₆ alkyl group optionally substituted with a hydroxyl group.

The halogen atom for R₃ and R₄ is, for example, preferably a fluorine atom, a chlorine
atom.
The cyclo-C₃-C₆ alkyl group for R₃ and R₄ is, for example, preferably a cyclopropyl group.

The carbamoyl group optionally substituted with a C₁-C₆ alkyl group or a cyclo-C₃-C₆ alkyl group for R₃ and R₄ is, for example, preferably a carbamoyl group, a methylcarbamoyl group, a dimethylcarbamoyl group.

The C₁-C₆ alkoxy group optionally substituted with a hydroxyl group for R₃ and R₄ is, for example, preferably a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a 2-hydroxyethoxy group, more preferably a methoxy group, an ethoxy group.

The C₁-C₆ alkyl group optionally substituted with a hydroxyl group for R₃ and R₄ is, for example, preferably a methyl group, an ethyl group, an isopropyl group, a hydroxymethyl group, a 2-hydroxyethyl group.

R₃ and R₄ are, for example, preferably a nitro group, a cyclo-C₃-C₆ alkyl group, a carbamoyl group, a C₁-C₆ alkoxy group optionally substituted with a hydroxyl group, or a C₁-C₆ alkyl group optionally substituted with a hydroxyl group; more preferably, R₃ is a C₁-C₆ alkoxy group optionally substituted with a hydroxyl group, and R₄ is a cyclo-C₃-C₆ alkyl group, a C₁-C₆ alkoxy group or a C₁-C₆ alkyl group.

Accordingly, in the compounds of the invention, the group of the following formula:

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R³

Ar¹

R⁴
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is preferably formed through combination of the above-mentioned preferred groups; for example, it is preferably a 1-ethyl-4-(2-hydroxyethoxy)-6-indolyl group, a 1,4-dimethoxy-6-indolyl group, a 1,4-dienethoxy-6-indolyl group, a 1-cyclopropyl-4-methoxy-6-indolyl group, a 1-cyclopropyl-4-ethoxy-6-indolyl group, a 1-cyclopropyl-4-(2-hydroxyethoxy)-6-indolyl group, a 3-chloro-1-cyclopropyl-4-methoxy-6-indolyl group, a 3-chloro-1-cyclopropyl-4-ethoxy-6-indolyl group, a 1-cyclopropyl-3-methyl-4-methoxy-6-indolyl group, a 1-cyclopropyl-4-ethoxy-3-methyl-6-indolyl group, a 3-ethyl-7-methoxybenzimidazol-5-yl group, a 3-cyclopropyl-7-ethoxy-1,2-benzisoxazol-5-yl group; more preferably a 1-cyclopropyl-4-methoxy-6-indolyl group or a 1-cyclopropyl-3-methyl-4-methoxy-6-indolyl group.

R¹ represents a phenyl group optionally substituted with a carboxyl group, a tetrazolyl group optionally substituted with a C₂-C₇ alkanoyloxy-C₁-C₆ alkyl group, a pyridyl group optionally substituted with a C₁-C₆ alkyl group or a carboxyl group, a dihydro-1,2,4-triazolyl group optionally substituted with an oxo group, or a dihydro-1,2,4-oxadiazolyl group optionally substituted with an oxo group.

Examples of R¹ include, for example, a phenyl group, a 3-carboxyphenyl group, a 1-tetrazolyl group, a 5-tetrazolyl group, a 2-pivaloyloxyethyl-5-tetrazolyl group, a 2-pyridyl group.
group, a 4-carboxy-2-pyridyl group, a 5-carboxy-2-pyridyl group, a 3-pyridyl group, a 5-carboxy-3-pyridyl group, a 5-carboxy-6-methyl-3-pyridyl group, a 4-pyridyl group, a 2-carboxy-4-pyridyl group, a 5-oxo-4,5-dihydro-1,2,4-triazol-3-yl group, a 3-oxo-2,3-dihydro-1,2,4-triazol-4-yl group, a 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl group. Of those, preferred are a 3-carboxyphenyl group, a 5-tetrazolyl group, a 4-carboxy-2-pyridyl group, a 5-carboxy-3-pyridyl group, a 5-carboxy-6-methyl-3-pyridyl group, a 6-carboxy-3-pyridyl group, a 2-carboxy-4-pyridyl group, a 5-oxo-4,5-dihydro-1,2,4-triazol-3-yl group, a 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl group; more preferred are a 3-carboxyphenyl group, a 5-tetrazolyl group, a 4-carboxy-2-pyridyl group, a 5-carboxy-3-pyridyl group, a 6-carboxy-3-pyridyl group, a 2-carboxy-4-pyridyl group, a 5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl group; even more preferred are a 5-tetrazolyl group, a 5-carboxy-3-pyridyl group.

R2 represents a hydrogen atom, a halogen atom, a C1-C6 alkyl group, or a C1-C6 alkoxy group.

The halogen atom for R2 is, for example, preferably a chlorine atom, a bromine atom.

The C1-C6 alkyl group for R2 is, for example, preferably a methyl group, an ethyl group, a propyl group, an isopropyl group, a tert-butyl group.

The C1-C6 alkoxy group for R2 is, for example, preferably a methoxy group, an ethoxy group, a propoxy group.

R2 is preferably a hydrogen atom.

In the compounds of formula (I), R2 may be positioned at any substitutable position of the skeleton of the following formula:

![Chemical Structure Image]

"A substitutable position" and "a bondable position" mean a position of a group at which the group has a chemically-substitutable hydrogen atom on the carbon atom, the nitrogen atom, the oxygen atom and/or the sulfur atom thereof, and the substitution gives a chemically-stable compound; or mean that a chemical bond gives a chemically-stable compound not resulting from the substitution of the type.

Depending on the type of the substituents therein and on the form of their salts, the compounds of the invention include stereoisomers and tautomers such as optical isomers, diastereoisomers and geometrical isomers, and the compounds of the invention encompass all these stereoisomers and tautomers and their mixtures.

The invention encompasses various crystals, amorphous phases, salts, hydrates and solvates of the compounds of the invention.
Further, prodrugs of the compounds of the invention are also within the scope of the invention. In general, such prodrugs are functional derivatives of the compounds of the invention, and they can be readily converted into the compounds that are needed in bodies. Accordingly, the term "administer" as referred to herein for the method of treating various disorders includes not only the administration of a specific compound but also the administration of a compound which, after administered to patients, may be converted into the specific compound in bodies. General methods for selection and production of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985; Hydrolysis in Drug and Prodrug Metabolism, Chemistry, Biochemistry and Enzymology, B. Testa and J. M. Mayer, Wiley-VCH, 2003; and their entire descriptions are referred to and incorporated herein as a part of the specification of the present application. Metabolites of these compounds include active compounds that are produced by leaving the compounds of the invention in a biological environment, and they are within a scope of the invention. Specific examples of the compounds of formula (1), and their salts and esters are, for example, as follows:

(1) 1-[(1-Ethyl-4-methoxy-1H-benzimidazol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one,
(2) 1'-[(1-Cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidin]-4-one,
(3) Sodium 3-(r-[[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-y]benzoate,
(4) 5-[r-[(1-Cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl] nicotinic acid sodium salt,
(5) r-[H^ Dimethoxy-1H-indol- φ-yl]carbonyll- φ-ClH-tetrazol-S-y^spirochroman^ν-piperidin]-4-one,
(6) r-[(1-Cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one sodium salt,
(7) 1'-[(1-CyclopropyM-ethoxy-S-methyl 1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro [chroman-2,4'-piperidin]-4-one,
(8) 5- [1'-[(1-Cyclopropyl-4-ethoxy-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl] nicotinic acid sodium salt,
(9) 5- [1'-[(1-Cyclopropyl-4-methoxy-3-methyl-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl] nicotinic acid sodium salt,
(10) 5- [1'-[(3-Chloro-1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl] nicotinic acid sodium salt,
(11) 5- [1'-[(1-Cyclopropyl-4-methoxy-3-methyl-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl] nicotinic acid,
(12) r-[(3-cyclopropyl-7-ethoxy-l,2-benzisoxazol-5-yl)carbonyl]-6-(lH-tetrazol-5-
yl)spiro[chroman-2,4'-piperidin]-4-one,
(13) 1-cyclopropyl-M-ethoxy-6-[(4-oxo-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-1-
yl]carbonyl]-lH-indole-3-carboxamide,
(14) r-[(l-cyclopropyl-4-(2-hydroxyethoxy)-lH-indol-6-yl]carbonyl]-6-(1H-tetrazol-5-
yl)spiro[chroman-2,4'-piperidin]-4-one,
(15) 3-(r-[[3-carbamoyl-1-cyclopropyl-4-ethoxy-lH-indol-6-yl]carbonyl]-4-oxospiro[chroman-
2,4'-piperidin]-6-yl]benzoic acid,
(16) 4-{r-[(l-cyclopropyl-4-methoxy-3-methyl-lH-indol-6-yl)carbonyl]-4-oxospiro[chroman-
2,4'-piperidin]-6-yl]pyridine-2-carboxylic acid,
(17) 5-{r-[(l-cyclopropyl-4-methoxy-3-methyl-lH-indol-6-yl)carbonyl]-4-oxospiro[chroman-
2,4'-piperidin]-6-yl]-2-methylnicotinic acid,
(18) 5-{r-[(l-cyclopropyl-4-ethoxy-3-methyl-lH-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-
piperidin]-6-yl]nicotinic acid,
(19) 4-{'[(1-cyclopropyl-4-methoxy-S-methyl-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-
piperidin]-6-yl]pyridine-2-carboxylic acid,
(20) 5-{r-[(l,4-dimethoxy-3-methyl-lH-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-
piperidin]-6-yl]nicotinic acid,
(21) l'-[(l-cyclopropyl-4-methoxy-lH-indol-6-yl)carbonyl]-6-(5-oxo-4,5-dihydro-lH-1,2,4-
triazol-3-yl)spiro[chroman-2,4'-piperidin]-4-one, or
(22) r-[(l-cyclopropyl-4-methoxy-3-methyl-lH-indol-6-yl)carbonyl]-6-(lH-tetrazol-5-
yl)spiro[chroman-2,4'-piperidin]-4-one.

In one embodiment of the present invention, the compounds of formula I are
selected from:
3-{r-[(l-cyclopropyl-4-methoxy-lH-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-
piperidin]-6-yl]benzoic acid, or a pharmaceutically acceptable salt or ester thereof;
5-{'[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-
6-yl]nicotinic acid, or a pharmaceutically acceptable salt or ester thereof;
l'-[(1-cyclopropyl-4-methoxy-lH-indol-6-yl]carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'
piperidin]-4-one, or a pharmaceutically acceptable salt thereof;
l'-(1-cyclopropyl-4-ethoxy-3-methyl-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-
yl)spiro[chroman-2,4'-piperidin]-4-one, or a pharmaceutically acceptable salt thereof; or
5-{r-[(l-cyclopropyl-4-methoxy-3-methyl-lH-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'
piperidin]-6-yl]nicotinic acid, or a pharmaceutically acceptable salt or ester thereof.

Methods for producing the compounds of the invention are described below.
The compounds (I) of the invention may be produced according to the production method mentioned below, or according to the methods shown in Examples and Reference Examples given hereinunder. However, the production of the compounds (I) of the invention should not be restricted by these reaction examples.

Production Method

A compound protected with a suitable group (II in the following drawing) is deprotected, and then condensed with an aromatic carboxylic acid or its reactive derivative of a formula (III):

\[
\text{HO-}(\text{Ar}^1)_{R^3}-(\text{Ar}^4)_{R^4}
\]

wherein ArI, R3 and R4 have the same meanings as above, according to a chemical process well known in the field of organic chemistry.

wherein Ar represents a group of the following formula:

\[
\begin{align*}
\text{Ar}^1 & \text{ Ar}^4 \\
R^3 & \\
\end{align*}
\]
and ArI, R.3 and R.4 have the same meanings as above.

The protective group (PG) may be, for example, a tert-butoxycarbonyl, benzyloxy carbonyl or benzoyl group, and may also be any other known protective group. For selecting suitable protective groups and their deprotection, for example, referred to is Protective Groups in Organic Synthesis (Theodora W. Greene & Peter G. M. Wuts, John Woly & Sons, 1999).

In the above series of reaction, the functional groups such as hydroxyl group, amino group, imino group and carboxyl group which are not concerned with the reaction may be suitably protected, if desired, and they may be deprotected after the reaction.

Not specifically defined, "protective group for hydroxyl group" may be any one having its function and includes, for example, a C1-C6 alkyl group such as a methyl group, an ethyl group, a propyl group, an isopropyl group, a tert-butyl group; a C1-C6 alkysilyl group such as a trimethylsilyl group, a tert-butyldimethylsilyl group; a C1-C6 alkoxy methyl group such as a methoxymethyl group, a 2-methoxyethoxymethyl group; a tetrahydropyranyl group; a trimethylsilyl ethoxymethyl group, an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a 2,3-dimethoxybenzyl group, an o-nitrobenzyl group, a p-nitrobenzyl group, a trityl group; an acyl group such as a formyl group, an acetyl group. Especially preferred are a methyl group, a methoxymethyl group, a tetrahydropyranyl group, a trityl group, a trimethylsilyl ethoxymethyl group, a tert-butyldimethylsilyl group, an acetyl group.

Also not specifically defined, "protective group for amino group and imino group" may be any one having its function and includes, for example, an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a 3,4-dimethoxybenzyl group, an o-nitrobenzyl group, a p-nitrobenzyl group, a benzhydryl group, a trityl group; a C2-C7 alkanoyl group such as a formyl group, an acetyl group, a propionyl group, a butyryl group, a pivaloyl group; a benzoyl group; an arylalkanoyl group such as a phenylacetyl group, a phenoxyacetyl group; a C2-C7 alkoxy carbonyl group such as a methoxy carbonyl group, an ethoxycarbonyl group, a propoxy carbonyl group, a tert-butoxycarbonyl group; an aralkyloxycarbonyl group such as a benzyloxycarbonyl group, a p-nitrobenzyloxycarbonyl group, a phenethyloxycarbonyl group; a C1-C6 alkylsilyl group such as a trimethylsilyl group, a tert-butyldimethylsilyl group; a tetrahydropyranyl group; a trimethylsilyl ethoxymethyl group; a C1-C6 alkylsulfonyl group such as a methylsulfonyl group, an ethylsulfonyl group; an arylsulfonyl group such as a benzenesulfonyl group, a toluenesulfonyl group. Especially preferred are an acetyl group, a benzoyl group, a tert-butoxycarbonyl group, a benzyloxycarbonyl group, a trimethylsilyl ethoxymethyl group, a methylsulfonyl group.

Also not specifically defined, "protective group for carboxyl group" may be any one having its function and includes, for example, a C1-C6 alkyl group such as a methyl group, an
ethyl group, a propyl group, an isopropyl group, a tert-butyl group; a halo-Cl-C6 alkyl group such as a 2,2,2-trichloroethyl group; a C2-C6 alkenyl groups such as a 2-propenyl group; an aralkyl group such as a benzyl group, a p-methoxybenzyl group, a p-nitrobenzyl group, a benzhydryl group, a trityl group. Especially preferred are a methyl group, an ethyl group, a tert-butyl group, a 2-propenyl group, a benzyl group, a p-methoxybenzyl group, a benzhydryl group.

For the introduction and the removal of the protective groups, referred to are the above references.

The substituent R1 may be converted into a group of any other type (R'I, R"I) in any suitable stage according to a chemical process per-se well known in the field of organic chemistry.

For example, when R1 is a bromide group, then it may be converted into a cyano group and may be further into a tetrazolyl group. The conversion reaction may be attained according to a chemical process well known in the field of organic chemistry.

In the above drawing, the condensation of the amino compound derived from the compound of formula (IT), with an aromatic carboxylic acid may be attained in the same manner. In general, from 0.5 mol to an excessive molar amount, preferably from 1 mol to 1.5 mols of an aromatic carboxylic acid is used relative to one mol of the amino compound.

The reaction may be attained generally in an inert solvent. The inert solvent is preferably methylene chloride, chloroform, tetrahydrofuran, dimethylformamide, pyridine or their mixtures.

Preferably, the reaction is effected in the presence of a condensing agent. The condensing agent includes, for example, N,N'-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, benzotriazol-1-yloxy-tris-pyrrolidinophosphonium hexafluorophosphate, bromotris-(dimethylamino)phosphonium hexafluorophosphate, diphenylphosphoryl azide, 1,1'-carbonyldimidazole.

The condensing agent may be used in an amount of from 1 mol to an excessive molar amount, preferably from 1 mol to 1.5 mols relative to 1 mol of the aromatic carboxylic acid.

The reaction temperature may be generally from -50°C to 100°C, preferably from -20°C to 50°C.

The reaction time may be generally from 30 minutes to 7 days, preferably from 1 hour to 24 hours.

In place of the aromatic carboxylic acid, a reactive derivative of the carboxylic acid may be reacted with the amino compound to produce the intended product.
The reactive derivative of the aromatic carboxylic acid usable herein includes, for example, acid halides, mixed acid anhydrides, active esters, and active amides.

The acid halide may be prepared by reacting the aromatic carboxylic acid with a halogenating agent in an ordinary manner. The halogenating agent includes, for example, thionyl chloride, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, phosphorus trichloride, oxalyl chloride, phosgene.

The mixed acid anhydride may be prepared by reacting the aromatic carboxylic acid with an alkyl chlorocarbonate such as ethyl chlorocarbonate or with an aliphatic carboxylic acid chloride such as pivaloyl chloride, in an ordinary manner.

The active ester may be prepared by reacting the aromatic carboxylic acid with an N-hydroxy compound such as N-hydroxysuccinimide, N-hydroxyphthalimide, and 1-hydroxybenzotriazole, or with a phenol compound such as 4-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol, and pentachlorophenol, in the presence of a condensing agent such as N,N'-dicyclohexylcarbodiimide and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, in an ordinary manner.

The active amide may be prepared by reacting the aromatic carboxylic acid with, for example, 1,l'-carbonyldiimidazole or 1,r-carbonyl bis(2-methylimidazole) in an ordinary manner.

The reaction between the amino compound and the reactive derivative of the carboxylic acid may be attained, generally using from 0.5 mols to an excessive molar amount, preferably from 1 mol to 1.5 mols of the reactive derivative of the carboxylic acid, per 1 mol of the amino compound.

The reaction may be effected generally in an inert solvent. The inert solvent is, for example, preferably methylene chloride, chloroform, tetrahydrofuran, dimethylformamide, pyridine and their mixtures.

The reaction may go on in the absence of a base, but for more smoothly promoting it, the reaction is preferably effected in the presence of a base.

The base includes an organic base such as triethylamine, diisopropylethylamine, pyridine, and 4-dimethylaminopyridine; and inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and sodium hydrogencarbonate.

In general, the base is used preferably in an amount of from 1 mol to an excessive molar amount relative to 1 mol of the amino compound. When the base is liquid, then the base may serve also as a solvent.

The reaction temperature may be generally from -50°C to 130°C, preferably from -20°C to 100°C.
The reaction time may be generally from 5 minutes to 7 days, preferably from 30 minutes to 24 hours.

After the reaction, the system may be processed in an ordinary manner to give a crude product of the intended compound. The thus-obtained compound may be purified in an ordinary manner, or not purified, it may be subjected to the next reaction, if desired.

After the reaction, when the product has a protective group, then the protective group may be removed. When the product does not have a protective group, it may be processed in any ordinary manner, and the intended final product may be thus produced.

The compounds of formula (IT) and (JE) may be commercial products, or may be prepared according to a known method or according to a method similar to a known method, or with reference to the methods described in Examples and Reference Examples, suitably as combined, if desired.

The compounds of formula (I) may be administered orally or parenterally, and after formulation into preparations suitable for the intended administration route, they can be used as therapeutic agents, for example, for vascular diseases such as hypertension, cardiac angina, heart failure, cardiac infarction, stroke, claudication, diabetic nephropathy, diabetic retinopathy, eyesight failure, electrolyte abnormality and arteriosclerosis; nervous system diseases such as bulimia and diabetic neuropathy; metabolic diseases such as metabolic syndrome, obesity, diabetes, insulin resistance, hyperlipemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, non-alcoholic fatty liver disease, hormone secretion failure, gout and hepatic steatosis; genital diseases such as emmeniopathy, sexual dysfunction; digestive system diseases such as liver dysfunction, pancreatitis, cholecystitis and gastroesophageal reflux; respiratory diseases such as Pickwickian syndrome and sleep apnea syndrome; infectious diseases caused by bacteria, fungi or parasites; malignant neoplasm; and inflammatory diseases such as arthritis and skin ulcer.

The following "diabetes related disorders" are diseases, disorders and conditions that are related to Type 2 diabetes, and therefore may be treated, controlled or in some cases prevented, by treatment with the compounds of this invention: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component. In Syndrome X, also known as Metabolic Syndrome, obesity is thought to promote
insulin resistance, diabetes, dyslipidemia, hypertension, and increased cardiovascular risk. Therefore, ACC 1/2 inhibitors may also be useful to treat hypertension associated with this condition.

One aspect of the present invention provides a method for the treatment or prevention of disorders, diseases or conditions responsive to the modulation of ACC-I or ACC-2 in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

Another aspect of the present invention provides a method for the treatment or prevention of metabolic syndrome, fatty liver, hyperlipemia, dyslipidemia, non-alcoholic fatty liver disease, obesity, diabetes, bulimia, malignant neoplasm or an infectious disease in a subject in need thereof which comprises administering to said subject a therapeutically or prophylactically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

Another aspect of the present invention provides a method for the treatment of metabolic syndrome, fatty liver, hyperlipemia, obesity, diabetes, bulimia, malignant neoplasm or infectious diseases, which comprises administering to a subject in need thereof a therapeutically effective amount of the compound or its salt or ester of Claim 1.

Another aspect of the present invention provides a method for the treatment or prevention of diabetes in a subject in need thereof which comprises administering to said subject a therapeutically or prophylactically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

Another aspect of the present invention provides a method for the treatment or prevention of obesity in a subject in need thereof which comprises administering to said subject a therapeutically or prophylactically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

Another aspect of the present invention provides a method for the treatment or prevention of an obesity-related disorder selected from the group consisting of overeating, binge eating, hypertension, elevated plasma insulin concentrations, insulin resistance, hyperlipidemia, endometrial cancer, breast cancer, prostate cancer, colon cancer, kidney cancer, osteoarthritis, obstructive sleep apnea, heart disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, metabolic syndrome, insulin resistance syndrome, sexual and reproductive dysfunction, infertility, hypogonadism, hirsutism, obesity-related gastroesophageal reflux, Pickwickian syndrome, inflammation, systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease,
gout, constipation, irritable bowel syndrome, inflammatory bowel syndrome, cardiac hypertrophy, left ventricular hypertrophy, in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

Another aspect of the present invention provides a method for the treatment or prevention of hyperlipemia or dyslipidemia in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof.

Another aspect of the present invention provides a method for caloric intake in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof. Another aspect of the present invention provides a method for reducing food intake in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof. Another aspect of the present invention provides a method for increasing satiety in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof. Another aspect of the present invention provides a method for reducing appetite in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof.

The present invention also relates to methods for treating or preventing obesity by administering a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof, in combination with a therapeutically or prophylactically effective amount of another agent known to be useful to treat or prevent the condition.

The present invention also relates to methods for treating or preventing diabetes by administering a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof, in combination with a therapeutically or prophylactically effective amount of another agent known to be useful to treat or prevent the condition.

The present invention also relates to methods for treating or preventing fatty liver disease in a subject in need thereof which comprises administering to said subject a therapeutically or prophylactically effective amount of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof.

The present invention also relates to methods for treating or preventing hyperlipemia or dyslipidemia by administering a compound of formula (T), or a pharmaceutically acceptable salt
or ester thereof, in combination with a therapeutically or prophylactically effective amount of another agent known to be useful to treat or prevent the condition.

Another aspect of the present invention provides a pharmaceutical composition comprising a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable carrier.

Yet another aspect of the present invention relates to a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, for use in medicine.

Yet another aspect of the present invention relates to the use of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment or prevention, or suppression of a disease mediated by ACC-I or ACC-2 in a subject in need thereof.

Yet another aspect of the present invention relates to the use of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment or prevention of metabolic syndrome, hyperlipemia, dyslipidemia, non-alcoholic fatty liver disease, obesity, diabetes, bulimia, malignant neoplasm or an infectious disease in a subject in need thereof.

Yet another aspect of the present invention relates to the use of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment or prevention of obesity in a subject in need thereof.

Yet another aspect of the present invention relates to the use of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment or prevention of diabetes in a subject in need thereof.

Yet another aspect of the present invention relates to the use of a compound of formula (T), or a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament useful for the treatment or prevention of hyperlipemia or dyslipidemia in a subject in need thereof.

Yet another aspect of the present invention relates to the use of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, and a therapeutically effective amount of an agent selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4 or DP-IV) inhibitor, a glucagon-like peptide 1 (GLP-1) agonist, a HMG-CoA reductase inhibitor, a serotonergic agent, a β3-adrenoceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y2 agonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CB1 receptor antagonist or inverse agonist, a melanin-concentrating hormone receptor antagonist, a melanocortin 4 receptor agonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, PYY, PYY3-36, and a NK-I antagonist, or a pharmaceutically
acceptable salt thereof, for the manufacture of a medicament useful for the treatment, control, or prevention of obesity, diabetes, a diabetes related disorder, or an obesity-related disorder in a subject in need of such treatment.

Yet another aspect of the present invention relates to the use of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, and a therapeutically effective amount of an agent selected from the group consisting of an insulin sensitizier, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4 or DP-IV) inhibitor, a glucagon-like peptide 1 agonist, a HMG-CoA reductase inhibitor, a serotonergic agent, a 1/33-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y2 agonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CBi receptor antagonist or inverse agonist, a melanin-concentrating hormone receptor antagonist, a melanocortin 4 receptor agonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, PYY, PYY3-36, and a NK-I antagonist, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of obesity, diabetes, a diabetes related disorder, or an obesity-related disorder which comprises an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, and an effective amount of the agent, together or separately.

Yet another aspect of the present invention relates to a product containing a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof; and a therapeutically effective amount of an agent selected from the group consisting of an insulin sensitizier, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4 or DP-IV) inhibitor, a HMG-CoA reductase inhibitor, a serotonergic agent, a 1/33-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y2 agonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CBi receptor antagonist or inverse agonist, a melanocortin 4 receptor agonist, a melanin-concentrating hormone receptor antagonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, PYY, PYY3-36, and a NK-I antagonist, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use in obesity, diabetes, a diabetes related disorder, or an obesity-related disorder.

Yet another aspect of the present invention relates to the use of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or ester thereof, and a therapeutically effective amount of at least one agent selected from the group consisting of: simvastatin, mevastatin, ezetimibe, atorvastatin, sitagliptin, metformin, sibutramine, orlistat, Qnexa, topiramate, phentermine, losartan, losartan with hydrochlorothiazide, or a CB1 antagonist/inverse agonist selected from: rimonabant, N-[3-(4-chlorophenyl)-2(S)-phenyl-1(S)-methylpropyl]-2-(4-trifluoromethyl-2-pyrimidyloxy)-2-methylpropanamide, N-[1S,2S]-3-(4-
chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-\{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide, N\-[3-(4-chlorophenyl)-2-(5-chloro-3-pyridyl)-l-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide, 3-\{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene\} -3-(3,5-difluorophenyl)-2,2-dimethylpropanenitrile, 1-\{1-[1-(4-chlorophenyl)pentyl]-azetidin-3-yl\} -l-(3,5-difluoro phenyl)-2-methylpropan-2-ol, 3-((5)-(4-chlorophenyl){3-[(15)-1-(3,5-difluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}methyl)benzonitrile, 3-((5)-(4-chlorophenyl)\{3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl] azetidin-1-yl\}methyl)benzonitrile, 3-((4-chlorophenyl)\{3-1-(3,5-difluorophenyl)-2,2-dimethylpropyl\}azetidin-1-yl)methylbenzonitrile, 3-((15)-l-\{1-[5-(3-cyanophenyl)(4-cyanophenyl)methyl]azetidin-3-yl\} -2-fluoro-2-methylpropyl\}-5-fluorobenzonitrile, 3-((5)-(4-chlorophenyl)(3-\{(15\)-2-fluoro-1-[3-fluoro-5-(4H-1,2,4-triazol-4-yl)phenyl]-2-methylpropyl\}azetidin-1-yl)methyl)benzonitrile, and 5-\{(4-chlorophenyl)\{3-\{1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl\}azetidin-1-yl\}methyl\}thiophene-3-carbonitrile, or a pharmaceutically acceptable salt or ester or prodrug thereof, for the manufacture of a medicament useful for the treatment, control, or prevention of obesity, diabetes, a diabetes related disorder, or an obesity-related disorder in a subject in need of such treatment.

In clinical use of the compounds of the invention, pharmaceutically-acceptable additives may be added thereto to formulate various preparations in accordance with the intended administration route thereof, and the preparations may be administered. Various additives generally used in the field of pharmaceutical compositions may be used herein, including, for example, gelatin, lactose, sucrose, titanium oxide, starch, crystalline cellulose, methyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, corn starch, microcrystalline wax, white petrolatum, magnesium metasilicate aluminate, anhydrous calcium phosphate, citric acid, trisodium citrate, hydroxypropyl cellulose, sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxyethylene, hardened castor oil, polyvinylpyrrolidone, magnesium stearate, palmitoleic acid, light silicic acid anhydride, talc, vegetable oil, benzyl alcohol, gum arabic, propylene glycol, polyalkylene glycol, cyclodextrin, and hydroxypropylcyclodextrin.

Combined with such additives, the compound of the invention may be formulated into various forms of preparations, for example, solid preparations such as tablets, capsules, granules, powders and suppositories; and liquid preparations such as syrups, elixirs and injections. These preparations can be produced in any method known in the field of pharmaceutical compositions. The liquid preparations may be in such a form that is dissolved or suspended in water or in any other suitable medium before use. Especially for injections, the preparation may be dissolved or suspended, if desired, in a physiological saline or glucose solution, and a buffer and a preservative may be added thereto.
The compounds of the invention are effective for animals including humans and other mammals and plants that require the treatment with the compound. For the mammals, humans are preferred and they may be either men or women. The mammals except humans are, for example, companion animals such as dogs and cats. The compounds of the invention are effective also for obesity and obesity-related disorders of dogs and cats. Any ordinary physicians, veterinarians and clinicians may readily determine the necessity, if any, of the treatment with the compound of the invention.

When the compound of the invention is, for example, put into clinical use, then its dose and its administration frequency may vary depending on the sex, the age, the body weight and the condition of the patient and on the type and the range of the necessary treatment with the compound, hi oral administration, in general, the dose of the compound may be from 0.01 to 100 mg/kg of adult/day, preferably from 0.03 to 1 mg/kg of adult/day, and the administration frequency is preferably from one to a few times; and in parenteral administration, the dose may be from 0.001 to 10 mg/kg of adult/day, preferably from 0.001 to 0.1 mg/kg of adult/day, more preferably from 0.01 to 0.1 mg/kg of adult/day, and the administration frequency is preferably from one to a few times. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 mg of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

When treating or preventing obesity and/or diabetes mellitus and/or hyperlipemia and/or dyslipidemia and/or non-alcoholic fatty liver disease, or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 mg to about 100 mg per kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 mg to about 1000 mg, preferably from about 1 mg to about 50 mg. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 mg to about 350 mg. This dosage regimen may be adjusted to provide the optimal therapeutic response.

Ordinary physicians, veterinarians and clinicians may readily determine the effective dose of the pharmaceutical compound necessary to treat, prevent, inhibit, retard or stop the intended disease, and may readily treat the diseased patient with the compound.
The preparation may contain the compound of the invention in an amount of from 1.0 to 100 % by weight, preferably from 1.0 to 60 % by weight of the preparation. The preparation may contain any other therapeutically-effective compound.

In their use, the compounds of the invention may be combined with any other therapeutic agents that are useful for the treatment of disorders, for example, vascular diseases such as hypertension, cardiac angina, heart failure, cardiac infarction, stroke, claudication, diabetic nephropathy, diabetic retinopathy, eyesight failure, electrolyte abnormality and arteriosclerosis; nervous system diseases such as bulimia and diabetic neuropathy; metabolic diseases such as metabolic syndrome, obesity, diabetes, pre-diabetes, insulin resistance, hyperlipemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, non-alcoholic fatty liver disease, hormone secretion failure, gout and hepatic steatosis; genital diseases such as emmeniopathy and sexual dysfunction; digestive tract diseases such as liver dysfunction, pancreatitis, cholecystitis and gastroesophageal reflux; respiratory system diseases such as Pickwickian syndrome and sleep apnea syndrome; infectious diseases caused by bacteria, fungi or parasites; malignant neoplasm; and inflammatory diseases such as arthritis and skin ulcer. The individual ingredients to be combined may be administered at the same time or at different times during the treatment period, either as one preparation or as different preparations. Accordingly, the invention should be so interpreted that it encompasses any and every administration mode at the same time or at different times, and the administration in the invention should be interpreted so. The range of the combination of the compound of the invention and the other therapeutic agent useful for the above-mentioned disorders encompasses, in principle, all combinations of the compound of the invention and any and every pharmaceutical agent useful for the above-mentioned disorders.

The combination includes not only the composition of compounds of the invention and one other active substance but also the composition of compounds of the invention and two or more other active substances. There are a lot of examples of the combinations of a compound of the invention and one, two or more active substances selected from the therapeutic agents for the above-mentioned disorders. For example, for the treatment, management and prevention of metabolic syndrome, a combination of a compound of the invention and one, two or more active substances selected from hypolipidemic agents, lipid lowering agents, and anti-diabetic agents is useful. In particular, a composition that also contains an anti-obesity agent and an anti-hypertension agent, in addition to an anti-diabetic agent and/or a hypolipidemic agent or lipid lowering agent, may exhibit a synergistic effect for treatment, management and prevention of metabolic syndrome.

The pharmaceutical agents that maybe combined with the compound of the invention are, for example, ACAT inhibitor, α-blocker, aldose reductase inhibitor, α-amylase inhibitor, angiotensin-converting enzyme inhibitor, angiotensin receptor antagonist, anion exchange resin,
anorectic, antioxidant, antiplatelet, β-blocker, biguanide agent, calcium antagonist, CBl receptor inverse agonist/antagonist, CETP inhibitor, cholesterol absorption inhibitor, DGAT inhibitor, DP-IV inhibitor, diuretic, eicosapentaenoic acid, endothelin antagonist, FLAP inhibitor, FXR modulator, Ghrelin antagonist, GLP-I agonist, GLP-I secretagogue, glucagon antagonist, glucokinase activator, glucocorticoid receptor ligand, α-glucosidase inhibitor, GPAT inhibitor, histamine-H3 receptor ligand, HMG-CoA reductase inhibitor, HSD inhibitor, 11-beta HSD-I inhibitor, insulin and insulin mimetics, kinase inhibitors such as VEGF inhibitor and PDGF inhibitor, leptin, lipase inhibitor, 5-LO inhibitor, LXR ligand, melanocortin agonist, MCH antagonist, MTTP inhibitor, orexin antagonist, opioid antagonist, neuropeptide Y antagonist, nicotinic acid agonist, PPAR ligand, PTP-IB inhibitor, SCD-I inhibitor, serotonin transporter inhibitor, SGLT inhibitor, SUR ligand, thyroid hormone agonist, UCP activator, VPAC receptor agonist.

More concretely, examples of the other active ingredients that can be combined with a compound of the invention as different or the same pharmaceutical compositions are shown below, which, however, do not restrict the invention.

(a) Anti-diabetic medicines or agents, for example, (1) glitazones (e.g., ciglitazone, darglitazone, englitazone, isaglitazone (MCC-555), pioglitazone, rosiglitazone, troglitazone, tularik, BRL49653, CLX-0921, 5-BTZD), and PPAR-γ agonists such as GW-0207, LG-100641 and LY-300512; (2) biguanides such as buformin, metformin and phenformin; (3) protein tyrosine phosphatase-IB (PTP-IB) inhibitors; (4) sulfonlyureas such as acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, glipizide, glipizide, glitazone, tolazamide and tolvaptamid; (5) meglitinides such as repaglinide, nateglinide, and the like; (6) α-glucosidase inhibitors such as acarbose, adiposine, camiglibose, emilgitate, miglitol, voglibose, pradiminc-Q, salbostatin, CKD-71 I, MDL-25,637, MDL-73,945, and M0R14; (7) α-amylase inhibitors such as tendamistat, trestatin, and Al-3688; (8) insulin secretagogues such as linoglitiride, A-4166 and the like; (9) fatty acid oxidation inhibitors such as clomoxir, and etomoxir; (10) α-2 antagonists such as midaglizole, isaglidole, deriglidole, idazoxan, ecaroxan, and fluparoxan; (11) insulin and insulin mimetics such as biota, LP-100, novaparid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente), Lys-Pro insulin, GLP-I (73-7) (insulinintropin), and GLP-I (7-36)-NH2; (12) non-thiazolidinediones such as JT-501, farglitazar (GW-2570/GI-262579), and muraglitazar; PPAR α/δ agonists, such as muraflitazar, and the compounds disclosed in US 6,414,002; (13) PPAR-α/γ dual agonists such as MK-0767/KRP-297, CLX-0940, GW-1536, GW-1929, GW-2433, L-796449, LR-90, and SB2 19994; (14) other insulin sensitizers; (15) VPAC2 receptor agonists; (16) glucokinase activators; and (17) DPP-4 inhibitors, such as sitagliptin (JanuviaTM),
isooleucine thiazolidide (P32/98); NVP-DPP-728; vildagliptin (LAF 237); P93/01; denaglaptin 
(GSK 823093), SYR322, RO 0730699, TA-6666, and saxagliptin (BMS 4771 18).

(b) lipid lowering agents, for example, (1) bile acid sequestrants such as cholestyramine, 
colesevelam, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran, Colestid®, 
LoCholest®, and Questran®, and the like; (2) HMG-CoA reductase inhibitors such as 
atorvastatin, itavastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rivastatin, rosuvastatin, 
and simvastatin, ZD-4522, and the like; (3) HMG-CoA synthase inhibitors; (4) cholesterol 
absorption inhibitors such as stanol esters, β-sitosterol, sterol glycosides such as tiqueside, and 
azetidinones like ezetimibe; (5) acyl coenzyme A-cholesterol acyl-transferase (ACAT) inhibitors 
such as avasimibe, eficunime, KY505, and SMP797, and the like; (6) CETP inhibitors such as 
JTT705, torcetrapib, CP532632, BAY63-2149, SC591, and SC795, and the like; (7) squalene 
synthase inhibitors; (8) antioxidants such as probucol; (9) PPAR-α agonists such as beclofibrate, 
benzafibrate, ciprofibrate, clofibrate, efofibrate, fenofibrate, gemcabene, gemfibrozil, and other 
iblic acid derivatives, e.g., GW7647, BMI 70744, LYS18674, Atromid®, Lopid®, and Tricor®, 
and compounds described in WO 97/36579, and the like; (10) FXR receptor modulators such as 
GW4064, SR103912, and the like; (11) LXR receptor ligands such as GW3965, T9013137, and 
XTCO179628, and the like; (12) lipoprotein synthesis inhibitors such as niacin; (13) 
renin/angiotensin system inhibitors; (14) PPAR-δ partial agonists; (15) bile acid reabsorption 
inhibitors such as BARI1453, SC435, PHA384640, S8921, AZD7706, and the like; (16) PPAR-δ 
agonists such as GW501516, GW590735, and compounds described in WO97/28149, and the 
like; (17) triglyceride synthesis inhibitors, (18) microsomal triglyceride transport (MTTP) 
inhibitors such as inplitapide, LAB687, and CP346086; (19) transcription modulators, (20) 
squalene epoxidase inhibitors; (21) low-density lipoprotein (LDL) receptor inducers; (22) platelet 
aggregation inhibitors; (23) 5-LO or FLAP inhibitors; and (24) niacin receptor agonists; and 

(c) anti-hypertensive agents, for example, (1) diuretics such as thiazides including 
chlorthalaicone, chlorothiazide, dichlorphenamide, hydroflumethiazide, indapamide and 
hydrochlorothiazide; loop diuretics such as bumetanide, ethacrynic acid, furosemide, and 
torsemide; potassium sparing agents such as amiloride, triamterene; aldosterone antagonists such 
as spironolactone, and epirenone, and the like; (2) β-adrenergic blockers such as acebutolol, 
atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, 
idenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertilolol, 
tilisotol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, 
azelnidipine, barnidipine, benhidpine, bebrilid, cinaldipine, crvedipine, diltiazem, efonidipine, 
felodipine, gallopamil, isradipine, lacidipine, lemilidipine, lercanidipine, nicardipine, nifedipine, 
nivadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and 
the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril,
cilazapril, delapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, quinapril, quinaprilat, ramipril, perindopril, perindopril, quanipril, spirapril, tenocapril, trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril, ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as bosentan, tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol; (8) angiotensin II receptor antagonists such as candesartan, eprosartan, irbesartan, losartan, losartan and hydrochlorothiazide, pratosartan, tasosartan, valsartan, EXP-3137, Fl6828K, and RNH6270, and the like; (9) α/β-adrenergic blockers such as nipradilol, arotinolol, and amosulalol; (10) α1 blockers such as terazosin, urapidil, prazosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHIP 164, and XENO1O; (11) α2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine, and guanobenz; (12) aldosterone inhibitors; and

(d) anti-obesity agents, for example, (1) 5HT (serotonin) transporter inhibitors such as paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertraline, and imipramine; (2) NE (norepinephrine) transporter inhibitors such as GW320659, despiramine, talsupram, nomifensine, and the like; (3) CB-1 (cannabinoid-1 receptor) antagonists/inverse agonists such as rimonabant (Sanofi Synthelabo), SR-147778 (Sanofi Synthelabo), BAY65-2520 (Bayer), SLV319 (Solvey); and the compounds disclosed in USP 5,532,237, 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,624,941, 6,028,084, WO96/33159, WO98/33765, WO98/43636, WO98/43635, WO01/09120, WO01/96330, WO98/31227, WO98/41519, WO98/37061, WO00/10967, WO00/10968, WO97/29079, WO99/02499, WO01/58869, WO02/076949, WO01/64632, WO01/64633, WO01/64634, WO03/006007, WO03/007887, WO04/04317, WO05/00809, and EPO NO. EP-658546, EP656354, EP576357; (4) ghrelin antagonists such as those disclosed in WO01/87335, WO02/08250; (5) H3 (histamine H3) antagonists/inverse agonists such as thioperamide, 3-(3H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), A331440, and those disclosed in WO02/15905, O-[3-(3H-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-355 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-932 (2001)), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm. (Weinheim) 334:45-52 (2001)), substituted N-phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-86 (2000)), and proxixifan derivatives (Sasse, A. et al., J. Med. Chem., 43:3335-3343 (2000)); (6) melanin-concentrating hormone-1 receptor (MCHIR) antagonists such as T-226296 (Takeda), SNP-7941 (Synaptic), and those disclosed in WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, and Japanese Patent Application No. JP13226269, JP2004-139909; (7) MCH2R (melanin-
concentrating hormone 2R) agonists/antagonists; (8) NPY1 (neuropeptide Y Y1) antagonists such as BIBP3226, 2-[1-(5-chloro-3-isopropoxy carbonylaminophenyl)ethylamino]-6-[2-(5-ethyl-4-methyl-l,3-thiazol-2-yl)ethyl]-4-mo \phi holinopyridine, BIBO3304, LY-357897, CP-671906, GI-264879A, and those disclosed in USP 6,001,836, WO96/14307, WO01/23387, WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528; (9) NPY5 (neuropeptide Y Y5) antagonists such as L-152,804, GW-569180A, GW-594884A, GW-587081X, GW-5481 18X, FR235,208, FR-226928, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY366377, PD-160170, SR-120562A, SR-120819A, JCF-104, H409/22, and the compounds disclosed in USP 6,057,335, 6,043,246, 6,140,354, 6,166,038, 6,180,653, 6,191,160, 6,258,837, 6,313,298, 6,337,332, 6,329,395, 6,340,683, 6,326,375, 6,329,395, 6,337,332, 6,335,345, 6,388,077, 6,462,053, 6,649,624, 6,723,847, EPO EP-01010691, EP-01044970, PCT WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/23379, WO01/23388, WO01/23399, WO01/44201, WO01/62737, WO01/62738, WO01/09120, WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/094789, WO02/094825, WO03/014083, WO03/10191, WO03/092889, WO2004/002986, WO2004/031 175, and Norman et al., J. Med. Chem., 43:4288-4312 (2000); (10) leptins such as recombinant human leptin (PEG-OB, Hoffman La Roche), and recombinant methionyl human leptin (Amgen); (11) leptin derivatives such as those disclosed in UPS 5,552,524, 5,552,523, 5,552,522, 5,521,283, PCT WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520; (12) opioid antagonists such as nalmefene (Revex®), 3-methoxynaltrexone, naloxone, naltrexone, and the compounds disclosed in WOOO/21509; (13) orexin antagonists such as SB-334867-A, and the compounds disclosed in WO01/96302, WO01/68609, WO02/51232, WO02/51838, and WO03/023561; (14) BRS3 (bombesin receptor subtype 3) agonists such as [D-Phe6,beta-Alal 1,Phel3,Nlel4]Bn(6-14) and [D-Phe6,Phel3]Bn(6-13)propylamide, and those compounds disclosed in Pept. Sci. 2002 Aug; 8(8): 461-75; (15) CCK-A (cholecystokinin-A) agonists such as AR-R15849, GI181771, JMVM-180, A-71378, A-71623, SR146131, and the compounds disclosed in USP 5,739,106; (16) CNTF (ciliary neurotrophic factors) such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, and PD 170292 and PD 149164 (Pfizer); (17) CNTF derivatives such as axokine (Regeneron), and the compounds disclosed in WO94/09134, WO98/22128, and WO99/43813; (18) GHS (growth hormone secretagogue receptor) agonists such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429, L-163,255, and the compounds disclosed in USP 5,536,716, 6,358,951, USP Application Nos. 2002/049196, 2002/022637, WO01/56592, and WO02/32888; (19) 5HT2c (serotonin receptor 2c) agonists such as BVT933,
DPCA37215, IK264, PNU22394, WAY161503, R-1065, YM348, and the compounds disclosed in USP 3,914,250, WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457; (20) Mc3r (melanocortin-3 receptor) agonists; (21) Mc4r (melanocortin-4 receptor) agonists such as CHIR86036 (Chiron), ME-10142 and ME-10145 (Melacure), PT-141 and PT-14 (Palatin), and the compounds disclosed in USP No. 6,410,548, 6,294,534, 6,350,760, 6,458,790, 6,472,398, 6,376,509, and 6,818,658, USP Application No. US2002/0137664, US2003/0236262, US2004/009751, US2004/0092501, WO99/64002, WO00/74679, WO01/991752, WO01/74844, WO01/70708, WO01/70337, WO01/91752, WO02/059095, WO02/059107, WO02/059108, WO02/059117, WO02/12166, WO02/1175, WO02/12178, WO02/15909, WO02/068387, WO02/068388, WO02/067869, WO03/007949, WO03/007951, WO04/024720, WO04/078716, WO04/078717, WO04/087159, WO04/089307 and WO05/009950; (22) monoamine reuptake inhibitors such as sibutramine (Meridia®/Reductil®) and its salts, and the compounds disclosed in USP 4,746,680, 4,806,570, 5,436,272, USP Publication No. 2002/0006964, and WO01/27068, and WO01/62341; (23) serotonin reuptake inhibitors such as dexfenfluramine, fluoxetine, paroxetine, sertraline, and the compounds disclosed in USP 6,365,633, and WO01/27060, and WO01/62341; (24) GLP-I (glucagon-like peptide-1) agonists; (25) topiramate (Topimax®); (26) Phytopharm compound 57 (CP644,673); (27) ACC2 (acytetyl-CoA carboxylase-2) inhibitors; (28) β3 (β-adrenergic receptor-3) agonists such as AD9677/TAK677 (Dainippon/Takeda), CL-316, 243, SB418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW427353, trecadrine, Zeneca D71 14, SR591 19A, and the compounds disclosed in USP Application No. 5,705,515, USP 5,451,677, and WO94/18161, WO95/29159, WO97/46556, WO98/04526, WO98/32753, WO01/74782 and WO02/32897; (29) DGAT1 (diacylglycerol acyltransferase-1) inhibitors; (30) DGAT2 (diacylglycerol acyltransferase-2) inhibitors; (31) FAS (fatty acid synthase) inhibitors such as cerulenin, C75; (32) PDE (phosphodiesterase) inhibitors such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; (33) thyroid hormone-β agonists such as KB-2611 (KaroBioBMS), and the compounds disclosed in WO02/15845 and Japanese Patent Application No. JP2000256190; (34) UCP-I (uncoupling protein-1), 2 and 3 activators such as phytic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyllbenzoic acid (TTNPB), retinoic acid, and the compounds disclosed in WO99/00123; (35) acyl-estrogens such as oleoyl-estrones disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-209 (2001); (36) glucocorticoid antagonists; (37) 11βHSD-1 (11-β-hydroxysteroid dehydrogenase type 1) inhibitors such as BVT3498, BVT2733, and the compounds disclosed in WO01/90091, WO01/90090, and WO01/90092, and USP No. 6,730,690 and USP Application No. 2004/0133011; (38) SCD-I (stearoyl-CoA desaturase-1) inhibitors; (39) dipeptidyl peptidase IV (DP-IV) inhibitors such as isoleucine thiazolidide, valine
pyrrolidide, NVP-DPP728, LAFL237, P93/01, TSL225, TMC-2A/2B/2C, FE99901 i, P9310/K364, VIPO177, SDZ274-444, and the compounds disclosed in USP No. 6,699,871, WO03/004498, WO03/004496, EP1258476, WO02/083128, WO02/062764, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/000180, and WO03/000181; (40) lipase inhibitors such as tetrahydrodrolipstatin (orlistat/Xenical®), Triton WRI 339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebac lactone A, ebac lactone B, RHC80267, and the compounds disclosed in WO01/77094, USP 4,598,089, 4,452,813, 5,512,565, 5,391,571, 5,602,151, 4,405,644, 4,189,438, and 4,242,453; (41) fatty acid transporter inhibitors; (42) dicarboxylate transporter inhibitors; (43) glucose transporter inhibitors; (44) phosphate transporter inhibitors; (45) melanocortin agonists such as melanotan II and the compounds described in WO99/64002, and WO00/746799; (46) melanin condensing hormone antagonists such as the compounds disclosed in WO01/21577 and WO01/21 169; (47) galanin antagonists; (48) CCK agonists; (49) corticotropin-releasing hormone agonists; and (50) phosphodiesterase-3B (PDE3B) inhibitors; (51) 5HT-2 agonists; (52) histamine receptor-3 (H3) modulators; (53) β-hydroxy steroid dehydrogenase-1 inhibitors (β-HSD-1); (54) anti-obesity serotoninergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (55) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM-43073D, BIM-43004C (Olitvak, D.A. et al., Dig. Dis. Sci. 44(3):643-48 (1999)), and those disclosed in US 5,026,685, US 5,604,203, US 5,574,010, US 5,696,093, US 5,936,092, US 6,046,162, US 6,046,167, US, 6,093,692, US 6,225,445, U.S. 5,604,203, US 4,002,531, US 4, 179,337, US 5,122,614, US 5,349,052, US 5,552,520, US 6, 127,355, WO 95/06058, WO 98/32466, WO 03/026591, WO 03/057235, WO 03/027637, and WO 2004/066966, which are incorporated herein by reference; (56) Neuropeptide Y2 (NPY2) receptor agonists such NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (57) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP) as described in Batterham et al., J. Clin. Endocrinol. Metab. 88:3989-3992 (2003), and other Y4 agonists such as 1229U91; (58) cyclooxygenase-2 inhibitors such as etoricoxib, celecoxib, valdecoxib, parecoxib, lumiracoxib, BMS347070, tiracoxib or JTE522, ABT963, CS502 and GW406381, and pharmaceutically acceptable salts thereof; (59) aminorex; (60) amphechloral; (61) amphetamine; (62) benzphetamine; (63) chlorphentermine; (64) clonborex; (65) clof orex; (66) clominorex; (67) clortermine; (68) cyclexedrine; (69) dextroamphetamine; (70) diphemethoxidine, (71) N-ethylamphetamin e; (72) fenbutrazate; (73) fenisorex; (74) fenproporex; (75) fiudorex; (76) fluminorex; (77) furfurylethylamphetamine; (78) levamfetamine; (79) levophacetoperane; (80) mefenorex; (81) metamphetamine; (82) methamphetamine; (83) norpseudoephedrine; (84) pentorex; (85) phendimetramine; (86) phenmetrazine; (87) picilorex; (88) zonisamide, and (89)
Neurokinin-1 receptor antagonists (NK-I antagonists) such as the compounds disclosed in: U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, and 5,637,699; PCT International Patent Publication Nos. WO 90/05525, WO 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01 159, 93/01 165, 93/01 169, 93/01 170, 93/06099, 93/091 16, 93/10073, 93/14084, 93/141 13, 93/18023, 93/19064, 93/21 155, 93/21 181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/1531 1, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942, 97/21702, and 97/49710; (90) Qnexa; and (91) bupropion; and

(e) (1) Glucagon Receptor Agonists; (2) G Protein Receptor Agonist-40 (GPR-40) also called SNORF 55 such as BG 700, and those disclosed in WO 04/041266, 04/022551, 03/099793; (3) G Protein Receptor Agonist-119 (GPR1 19, also called RUP3; SNORF 25) - such as RUP3, HGPRBMY26, PFI 007, SNORF 25; (4) G protein coupled receptor 131; (5) Selective Peroxisome Proliferator Activator Receptor Modulator (SPPARMS, also known as selective PPAR gamma modulators) - such as T131 (Amgen), FK614 (Fujisawa), netoglitazone, and metaglidase; (6) oxyntomodulin; (7) SGLT inhibitors (sodium dependent glucose transporter inhibitors) - such as AVE 2268, KGT 1251, T1095/RWJ 394718.

The present agent may be combined with non-drug therapy such as kinesitherapy, dietetic treatment, and radiation therapy.

The compound and the combined compositions of the invention are effective for treating and preventing diabetes. The term "diabetes" as used herein includes both insulin-dependent diabetes (that is, also known as IDDM, type-1 diabetes), and insulin-independent diabetes (that is, also known as NIDDM, type-2 diabetes).

Diabetes is characterized by a fasting plasma glucose level of greater than or equal to 126 mg/dl. A diabetic subject has a fasting plasma glucose level of greater than or equal to 126 mg/dl. Prediabetes is characterized by an impaired fasting plasma glucose (FPG) level of greater than or equal to 110 mg/dl and less than 126 mg/dl; or impaired glucose tolerance; or insulin resistance. A prediabetic subject is a subject with impaired fasting glucose (a fasting plasma glucose (FPG) level of greater than or equal to 110 mg/dl and less than 126 mg/dl); or impaired
glucose tolerance (a 2 hour plasma glucose level of $\geq 140$ mg/dl and $<200$ mg/dl); or insulin resistance, resulting in an increased risk of developing diabetes.

The compounds and compositions of the invention are useful for treatment of both type-1 diabetes and type-2 diabetes. The compounds and compositions are especially useful for treatment of type-2 diabetes. The compounds and compositions of the invention are especially useful for treatment and/or prevention of pre-diabetes. Also, the compounds and compositions of the invention are especially useful for treatment and/or prevention of gestational diabetes mellitus.

Treatment of diabetes mellitus refers to the administration of a compound or combination of the present invention to treat a diabetic subject. One outcome of the treatment of diabetes is to reduce an increased plasma glucose concentration. Another outcome of the treatment of diabetes is to reduce an increased insulin concentration. Still another outcome of the treatment of diabetes is to reduce an increased blood triglyceride concentration. Still another outcome of the treatment of diabetes is to increase insulin sensitivity. Still another outcome of the treatment of diabetes may be enhancing glucose tolerance in a subject with glucose intolerance. Still another outcome of the treatment of diabetes is to reduce insulin resistance. Another outcome of the treatment of diabetes is to lower plasma insulin levels. Still another outcome of treatment of diabetes is an improvement in glycemic control, particularly in type 2 diabetes. Yet another outcome of treatment is to increase hepatic insulin sensitivity.

Prevention of diabetes mellitus, in particular diabetes associated with obesity, refers to the administration of a compound or combination of the present invention to prevent or treat the onset of diabetes in a subject in need thereof. A subject in need of preventing diabetes in a prediabetic subject.

The term "hypertension" as used herein includes essential, or primary, hypertension wherein the cause is not known or where hypertension is due to greater than one cause, such as changes in both the heart and blood vessels; and secondary hypertension wherein the cause is known. Causes of secondary hypertension include, but are not limited to obesity; kidney disease; hormonal disorders; use of certain drugs, such as oral contraceptives, corticosteroids, cyclosporin, and the like. The term "hypertension" encompasses high blood pressure, in which both the systolic and diastolic pressure levels are elevated, and isolated systolic hypertension, in which only the systolic pressure is elevated to greater than or equal to 140 mm Hg, while the diastolic pressure is less than 90 mm Hg. One outcome of treatment is decreasing blood pressure in a subject with high blood pressure.

Dyslipidemias or disorders of lipid metabolism, include various conditions characterized by abnormal concentrations of one or more lipids (i.e., cholesterol and triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B, C and E), and/or lipoproteins (i.e., the
macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as LDL, VLDL and IDL). Dyslipidemia includes atherogenic dyslipidemia. Hyperlipidemia is associated with abnormally high levels of lipids, LDL and VLDL cholesterol, and/or triglycerides. An outcome of the treatment of dyslipidemia, including hyperlipemia, is to reduce an increased LDL cholesterol concentration. Another outcome of the treatment is to increase a low-concentration of HDL cholesterol. Another outcome of treatment is to decrease very low density lipoproteins (VLDL) and/or small density LDL.

The term "metabolic syndrome", also known as syndrome X, is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP-IU). E.S. Ford et al., JAMA, vol. 287 (3), Jan. 16, 2002, pp 356-359. Briefly, a person is defined as having metabolic syndrome if the person has three or more of the following symptoms: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose. The criteria for these are defined in ATP-UJ.

The term "obesity" as used herein is a condition in which there is an excess of body fat, and includes visceral obesity. The operational definition of obesity is based on the Body Mass Index (BMI), which is calculated as body weight per height in meters squared (kg/m2). "Obesity" refers to a condition whereby an otherwise healthy subject has a Body Mass Index (BMI) greater than or equal to 30 kg/m2, or a condition whereby a subject with at least one co-morbidity has a BMI greater than or equal to 27 kg/m2. An "obese subject" is an otherwise healthy subject with a Body Mass Index (BMI) greater than or equal to 30 kg/m2 or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m2. A "subject at risk of obesity" is an otherwise healthy subject with a BMI of 25 kg/m2 to less than 30 kg/m2 or a subject with at least one co-morbidity with a BMI of 25 kg/m2 to less than 27 kg/m2.

The increased risks associated with obesity occur at a lower Body Mass Index (BMI) in Asians than that in Europeans and Americans. In Asian countries, including Japan, "obesity" refers to a condition whereby a subject with at least one obesity-induced or obesity-related co-morbidity, that requires weight reduction or that would be improved by weight reduction, has a BMI greater than or equal to 25 kg/m2. In Asia-Pacific, a "subject at risk of obesity" is a subject with a BMI of greater than 23 kg/m2 to less than 25 kg/m2.

As used herein, the term "obesity" is meant to encompass all of the above definitions of obesity.

Obesity-induced or obesity-related co-morbidities include, but are not limited to, diabetes, impaired glucose tolerance, insulin resistance syndrome, dyslipidemia, hypertension, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, fatty liver; cerebral infarction, cerebral thrombosis,
transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, and infertility. In particular, co-morbidities include: hypertension, hyperlipidemia, dyslipidemia, glucose intolerance, cardiovascular disease, sleep apnea, diabetes mellitus, and other obesity-related conditions.

Treatment of obesity and obesity-related disorders refers to the administration of the compounds or combinations of the present invention to reduce or maintain the body weight of an obese subject. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject's body weight immediately before the administration of the compounds or combinations of the present invention. Another outcome of treatment may be decreasing body fat, including visceral body fat. Another outcome of treatment may be preventing body weight gain. Another outcome of treatment may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from weight loss.

Prevention of obesity and obesity-related disorders refers to the administration of the compounds or combinations of the present invention to reduce or maintain the body weight of a subject at risk of obesity. One outcome of prevention may be reducing the body weight of a subject at risk of obesity relative to that subject's body weight immediately before the administration of the compounds or combinations of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, Type 2 diabetes, polycystic ovary disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.
The invention is described more concretely with reference to Examples and Reference Examples mentioned below, which, however, do not restrict the invention.

In thin-layer chromatography in Examples, Silica gel6(F254 (Merck)) was used as the plate; and a UV detector was used for detection. In column silica gel, used was WakogelTM C-300 or C-200 (Wako Jun-yaku), FLASH+ cartridge (Biotage) or Chromatorex (FUJI SILYSLA CHEMICAL). In high-performance partitioning liquid chromatography, used was ODS (C18) filler. The MS spectrum was determined through electrospray ionization (ESI), using Micromass ZQ2000 (Waters). In NMR spectrometry, used was dimethyl sulfoxide as the internal standard in a deuterated dimethyl sulfoxide solution, or used was tetramethylsilane as the internal standard in a deuterated chloroform solution. For it, used was a spectrophotometer of JNM-AL400 (JEOL), Mercury400 (400MHz; Varian) or Inova400 (400MHz; Varian), and the total δ value was shown as ppm.

Abbreviations in NMR have the following meanings: s: singlet; d: doublet; dd: double doublet; t: triplet; dt: double triplet ; q: quartet; m: multiplet; br: broad; br m: broad multiplet; J: coupling constant; Hz: hertz; DMSO-d6: deuterated dimethyl sulfoxide; and CDCl3: deuterated chloroform.

Abbreviations in Examples have the following meanings: aq: aqueous; HOBT: 1-hydroxybenzotriazole hydrate; NMP: N-methylpyrrolidone; WSC: l-(3-dimethylaminopropyl)-3-ethylcarbodiimide; DMF: dimethylformamide; Et: ethyl; Et2O: diethyl ether; Et3N: triethylamine; EtOAc: ethyl acetate; EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; TEA: triethylamine; g: gram; HCl: hydrochloric acid; Hex: hexane; kg: kilogram; l or L: liter; mL or mL: milliliter; mg: milligram; MeOH: methanol; N: normal; NMO: N-methylmorpholine N-oxide; TPAP: tetrapropylammonium perruthenate; THF: tetrahydrofuran; TFA: trifluoroacetic acid; TrFO2: trifluoromethanesulfonic anhydride; CHCl3: chloroform; µL: microliter; r.t.: room temperature; sat: saturated; Me: methyl; EtOH: ethanol; BuOH: butanol; EtI: ethyl iodide; MeI: methyl iodide; Ts: tosylate; AcOK: potassium acetate; AcOEt: ethyl acetate; h: hour; min: minute(s); dil: dilute; DMAP: 4-dimethyaminopyridine; Boc: tert-butoxy; TBSCI: tert-butyl(dimethyl)silyl chloride; ODS: Octadecysilica; mol: mole; and DPPF or dpff: 1,1'-bis(diphenyl-phosphino)ferrocene.

Example 1

\[
\text{1-(1-Ethyl-4-methoxy-1H-benzimidazol-6-yl)carbonyl-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-} \
piperidinel-4-one
\]

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A TFA salt of S-ethyl-T-methoxy-SH-benzimidazole-S-carboxylic acid methyl ester (182 mg, 0.523 mmol) was dissolved in THF (3 mL) and MeOH (3 mL), aqueous 5 N sodium hydroxide solution (0.52 mL, 2.62 mmol) was added thereto and stirred at room temperature for 2 hours and at 60°C for 1 hour. This was cooled to room temperature, then 5 N hydrochloric acid (0.55 mL, 2.75 mL) was added thereto, the solvent was evaporated under reduced pressure, and this was azeotroped twice with methanol and once with toluene to obtain a white solid. This material was dissolved in DMF (4 mL) and water (1 mL), and 6-(1H-tetrazol-5-yl)spiro-chroman-2,4'-piperidin-1-4-one hydrochloride (202 mg, 0.628 mmol), triethylamine (0.21 mL, 1.57 mmol), HOBT (106 mg, 0.785 mmol) and EDCI HCl (151 mg, 0.785 mmol) were added thereto. The reaction mixture was stirred at 90°C for 2 hours, then cooled to room temperature, and water was added thereto. The precipitated solid was collected by filtration, and dried under reduced pressure to obtain the intended compound as a white solid. 1H-NMR (400 MHz, DMSO-d6) δ: 8.42 (IH, d, J = 2.2 Hz), 8.24 (IH, dd, J = 8.8, 2.2 Hz), 8.21 (IH, s), 7.33 (IH, d, J = 8.8 Hz), 7.26 (IH, s), 6.73 (IH, s), 4.50-3.25 (4H, m), 4.26 (2H, q, J = 7.2 Hz), 3.95 (3H, s), 2.98 (2H, s), 2.15-1.75 (4H, m), 1.38 (3H, t, J = 7.2 Hz); MS [M+H]+ = 488.

Example 2

\[
\text{\textregistered}([!-\text{Cyclopropyl-4-methoxy-1H-indol-6-yl}]-\text{carbonyll-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl})\text{spiro[chroman-2,4'-piperidin1-4-one}}
\]

Et3N (58 µL), HOBT (32 mg) and WSC (40 mg) were added to a solution of 1-cyclopropyl-4-methoxy-1H-indol-6-carboxylic acid (40 mg) and 6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidin]-4-one hydrochloride (70 mg) in DMF (4 mL), and stirred overnight at room temperature. Water was added to the reaction mixture, and the formed solid was collected by filtration. The solid was washed thoroughly with water and ether. This was dried under reduced pressure to obtain the title compound. 1H-NMR (400 MHz, DMSO-d6) δ: 12.91(1H, brs), 8.20(1H, d, J=4.0 Hz), 8.00(1H, dd, J=8.0, 4.0 Hz), 7.36-7.26(2H, m), 7.22(1H, s), 6.57(1H, s), 6.39 (IH, d, J=4.0 Hz), 4.20-4.00(1H, m), 3.87(3H, s), 3.46-3.40(1H, m), 3.40-3.20(3H, m), 2.89(2H, s), 2.06-1.77(4H, m), 1.07-1.03(2H, m), 0.94-0.90(2H, m); MS [M+H]+ = 515.

Example 3

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Sodium 3-(r-[(l-cyclopropyl-4-methoxy-lH-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl)benzoate

N,N'-carbonyldiimidazole (130 mg) and triethylamine (0.446 ml) were added to a solution of l-cyclopropyl-4-methoxy-lH-indole-6-carboxylic acid (185 mg) in DMF (4 ml), and stirred at 70°C for 7 hours. To the reaction mixture was added 3-(4-oxo-spiro[chroman-2,4'-piperidin]-6-yl)benzoic acid hydrochloride (374 mg), which was further stirred at that temperature for 16 hours. 1 N hydrochloric acid and water were added to the reaction mixture, and the formed solid was collected by filtration. The resulting solid was recrystallized from methanol, and purified through silica gel column chromatography (chloroform/methanol) to obtain 3-{r-[l-cyclopropyl-4-methoxy-lH-indol-6-yl]carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl]benzoic acid (420 mg). This was suspended in water (5 ml), and aqueous 1 N sodium hydroxide solution (0.762 ml) was added thereto and stirred at room temperature for 30 minutes. The solution was purified through ODS reversed-phase column chromatography (water/methanol) to obtain the intended compound.

Example 4

5-{r-}[l-Cyclopropyl-4-methoxy-lH-indol-6-v]carbonyn-4-oxosporirhoman-2,4'-piperidinl-6-vUnicotinic acid sodium salt

\[\text{Na}^+\]

\(\delta\): 8.11-8.09 (IH, m), 7.96-7.93 (IH, m), 7.90 (IH, dd, J = 8.5, 2.4 Hz), 7.83-7.79 (IH, m), 7.56-7.50 (IH, m), 7.32 (IH, dd, J = 7.6, 7.6 Hz), 7.29 (IH, d, J = 3.2 Hz), 7.23 (IH, s), 7.20 (IH, d, J = 8.5 Hz), 6.59 (IH, s), 6.41-6.39 (IH, m), 4.45-4.11 (IH, br m), 3.86 (3H, s), 3.86-3.55 (IH, br m), 3.52-3.22 (3H, m), 2.93 (2H, s), 2.17-1.64 (4H, br m), 1.11-1.00 (2H, m), 0.96-0.88 (2H, m); MS [M+Na]+ = 573.
5-[(1-Cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl]nicotinic acid (434 mg) was suspended in water (5 ml), and aqueous 1 N sodium hydroxide solution (0.865 ml) was added thereto and stirred at room temperature for 1 hour. The solution was purified by ODS reversed-phase column chromatography (water/methanol, gradient) to obtain the intended compound. \textit{iH}-NMR (400 MHz, DMSO-d$_6$) $\delta$: 8.90 (IH, d, $J = 1.7$ Hz), 8.74 (IH, d, $J = 2.4$ Hz), 8.29-8.27 (IH, m), 7.99-7.94 (2H, m), 7.29 (IH, d, $J = 3.2$ Hz), 7.25-7.22 (2H, m), 6.59 (IH, s), 6.40 (IH, d, $J = 3.2$ Hz), 4.49-4.04 (IH, br m), 3.87 (3H, s), 3.82-3.58 (IH, br m), 3.51-3.28 (3H, m), 2.95 (2H, s), 2.13-1.90 (2H, br m), 1.88-1.75 (2H, br m), 1.09-1.02 (2H, m), 0.95-0.90 (2H, m); MS [M+Na$^+$] = 574.

Example 5

1'-{1,4-Dimethoxy-1H-indol-6-yl}carbonyl-6-(1H-tetrazol-5-yl)spirochroman-2,4'-piperidin]-4-one

Triethylamine (310 µl) and water (1.5 ml) were added to a solution of 1,4-dimethoxy-1H-indole-6-carboxylic acid (300 mg), 6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one hydrochloride (478 mg), WSC (311 mg) and HOBT (249 mg) in DMF (6 ml), and stirred at 90°C for 30 minutes. Water was added thereto at room temperature, and a white precipitate was thus obtained. This was dried under reduced pressure, washed with a mixed solvent of methanol and diethyl ether, and dried again under reduced pressure to obtain the above-described compound as a colorless solid. \textit{iH}-NMR (400 MHz, DMSO-d$_6$) $\delta$: 8.41 (IH, d, $J = 2.2$ Hz), 8.23 (IH, dd, $J = 8.5, 2.2$ Hz), 7.63 (IH, d, $J = 3.4$ Hz), 7.33 (IH, d, $J = 8.5$ Hz), 7.11 (IH, s), 6.58 (IH, s), 6.37 (IH, d, $J = 3.4$ Hz), 4.34-4.18 (IH, br m), 4.05 (3H, s), 3.89 (3H, s), 3.73-3.14 (3H, br m), 2.98 (2H, s), 2.15-1.76 (4H, br m); MS [M+H$^+$] = 489.
Example 6
1'-{F1,4-Dimethoxy-1H-indol-6-yl}carbonyl-6-(1H-tetrazol-5-yl)spirochroman-2,4'-piperidin-1-4-one sodium salt

Aqueous 1 N sodium hydroxide solution (495 µl) was added to a solution in water (8 ml) of the free compound (220 mg) obtained in Example 5, and stirred at room temperature for 30 minutes. Next, using Sep-Pak® cartridge (Waters), this was purified to obtain the title compound sodium salt as a colorless amorphous substance. 1H-NMR (400 MHz, DMSO-d6) δ:
8.30 (1H, d, J = 2.2 Hz), 8.15 (1H, dd, J = 8.7, 2.1 Hz), 7.62 (1H, d, J = 3.4 Hz), 7.12-7.08 (2H, m), 6.58 (1H, s), 6.37 (1H, dd, J = 3.4, 0.7 Hz), 4.30-4.18 (1H, br m), 4.05 (3H, s), 3.89 (3H, s), 3.69-3.25 (3H, br m), 2.90 (2H, s), 2.10-1.71 (4H, br m); MS [M+H]+ = 489.

Example 7
r-r-[1-Cyclopropyl-4-methoxy-1H-indol-6-yl]carbonyl-6-(1H-tetrazol-5-yl)spirochroman-2,4'-piperidin-4-one

The title compound was obtained as a colorless solid in the same manner as in Example 5 but using 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylic acid in place of 1,4-dimethoxy-1H-indole-6-carboxylic acid. 1H-NMR (400 MHz, DMSO-d6) δ: 8.42 (1H, d, J = 2.2 Hz), 8.24 (1H, dd, J = 8.8, 2.2 Hz), 7.34 (1H, d, J = 8.8 Hz), 7.29 (1H, d, J = 3.2 Hz), 7.23 (1H, s), 6.58 (1H, s), 6.40 (1H, d, J = 3.2 Hz), 4.47-4.10 (1H, br m), 3.87 (3H, s), 3.79-3.21 (4H, br m), 2.99 (2H, s), 2.14-1.73 (4H, br m), 1.08-0.90 (4H, br m); MS [M+H]+ = 499.

Example 8
r-r-[1-Cyclopropyl-4-methoxy-1H-indol-6-yl]carbonyl-6-(1H-tetrazol-5-yl)spirochroman-2,4'-piperidin-4-one sodium salt
In the same manner as in Example 6, the intended compound was obtained as a colorless amorphous substance from the compound (330 mg) of Example 7. 1H-NMR (400 MHz, DMSO-d6) δ: 8.30 (IH, d, J = 2.0 Hz), 8.15 (IH, dd, J = 8.5, 2.2 Hz), 7.28 (IH, d, J = 3.2 Hz), 7.24-7.21 (IH, br m), 7.10 (IH, d, J = 8.5 Hz), 6.59 (IH, s), 6.39 (IH, d, J = 3.2 Hz), 4.37-4.19 (IH, br m), 3.87 (3H, s), 3.75-3.25 (4H, br m), 2.90 (2H, s), 2.10-1.74 (4H, br m), 1.08-0.90 (4H, br m); MS [M+H]+ = 499.

Example 9

r-fd-Cyclopropyl^-ethoxy-S-methyl-lH-indol-6-carbonyll-dH-tetrazol-S-yl)spiro[chroman-2,4'-piperidin-4-one

The intended compound was obtained as a colorless solid in the same manner as in Example 5 but using 1-cyclopropyl-4-ethoxy-3-methyl-IH-indole-6-carboxylic acid in place of 1,4-dimethoxy-IH-indole-6-carboxylic acid. 1H-NMR (400 MHz, DMSO-d6) δ: 8.41 (IH, d, J = 2.4 Hz), 8.23 (IH, dd, J = 8.8, 2.4 Hz), 7.32 (IH, d, J = 8.8 Hz), 7.12 (IH, d, J = 1.0 Hz), 6.99 (IH, d, J = 1.0 Hz), 6.48 (IH, s), 4.30-4.14 (IH, br m), 4.08 (2H, q, J = 6.9 Hz), 3.79-3.13 (4H, br m), 2.98 (2H, s), 2.33 (3H, d, J = 1.0 Hz), 2.08-1.74 (4H, br m), 1.37 (3H, t, J = 6.8 Hz), 1.03-0.98 (2H, m), 0.89-0.84 (2H, m); MS [M+H]+ = 527.

Example 10

3-(r-[[l-Cyclopropyl-4-(2-hydroxyethoxy)-lH-indol-6-yl]carbonyU-4-oxo-spiro[chroman-2,4'- piperidin1-6-yl]benzoic acid
Triethylamine (164 µl) was added to a solution of 1-cyclopropyl-4-(2-hydroxyethoxy)-1H-indole-6-carboxylic acid (166 mg), 3-(4-oxo-spiro[chroman-2,4'-piperidin]-6-yl)benzoic acid methyl ester hydrochloride (124 mg), EDCI-HCl (124 mg) and HOBT (99 mg) in DMF (4 ml), and stirred at 60°C for 1 hour. Next, this mixture was diluted with ethyl acetate at room temperature, washed with aqueous 1 N hydrochloric acid solution, saturated sodium bicarbonate water, water and saturated saline water in that order, and dried over sodium sulfate. After filtered and concentrated, the mixture was purified through a silica gel column (Biotage) to obtain the ester of the intended compound. Aqueous 5 N sodium hydroxide solution (240 µl) was added to a methanol solution (10 ml) of the ester derivative (380 mg), and stirred at 60°C for 4 hours. Next, aqueous 5N hydrochloric acid solution (250 µl) was added thereto at room temperature, extracted with a mixed solvent of chloroform and methanol, and dried over sodium sulfate. After filtered and concentrated, the residue was crystallized using a mixed solvent of ethyl acetate and hexane, the above compound was obtained as a colorless crystal. 1H-NMR (400 MHz, DMSO-d6) δ: 8.13 (IH, s), 7.98-7.95 (2H, m), 7.93-7.87 (2H, br m), 7.57 (IH, dd, J = 8.2, 8.2 Hz), 7.29 (IH, d, J = 3.2 Hz), 7.25-7.21 (2H, m), 6.58 (IH, s), 6.42 (IH, d, J = 3.2 Hz), 4.90-4.82 (IH, br m), 4.33-4.17 (IH, br m), 4.11 (2H, t, J = 5.1 Hz), 3.79-3.74 (2H, br m), 3.51-3.24 (4H, br m), 2.95 (2H, s), 2.10-1.74 (4H, br m), 1.08-1.02 (2H, m), 0.95-0.90 (2H, m); MS [M+H]+ = 581.

Example 11

5-[(1'-[1-Cyclopropyl-4-ethoxy-1H-indol-6-yl]carbonyll-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl]nicotinic acid sodium salt

The intended compound was obtained as a colorless amorphous substance according to the methods of Examples 10 and 6, but using 1-cyclopropyl-4-ethoxy-1H-indole-6-carboxylic acid in place of 1-cyclopropyl-4-(2-hydroxyethoxy)-1H-indole-6-carboxylic acid, and using 5-(4-oxo-spiro[chroman-2,4'-piperidin]-6-yl)nicotinic acid methyl ester hydrochloride in place of 3-(4-oxo-spiro[chroman-2,4'-piperidin]-6-yl)benzoic acid methyl ester hydrochloride. 1H-NMR (400 MHz, DMSO-d6) δ: 8.90 (IH, d, J = 1.7 Hz), 8.74 (IH, d, J = 2.4 Hz), 8.28 (IH, dd, J = 2.4, 1.7 Hz), 7.99-7.95 (2H, m), 7.28 (IH, d, J = 3.2 Hz), 7.25-7.20 (2H, m), 6.57 (IH, s), 6.39 (IH, d, J = 3.2 Hz), 4.35-4.20 (IH, br m), 4.15 (2H, q, J = 7.0 Hz), 3.75-3.26 (4H, br m), 2.95 (2H, s),
2.1 1.74 (4H, br m), 1.38 (3H, t, J 7.0 Hz), 1.08-1.02 (2H, m), 0.95-0.89 (2H, m); MS [M+H]+ = 566.

**Example 12**

5-{r-r(l-Cyclopropyl-4-methoxy-3-methyl-IH-indol-6-yl)carbonyll-4-oxo-spirochroman-2,4'-piperidin]-6-yl) nicotinic acid sodium salt

![Chemical Structure](image)

To a mixture of 5-(4-oxo-spiro[chroman-2,4'-piperidin]-6-yl)nicotinic acid methyl ester di-hydrochloride (2.98g), l-cyclopropyl-4-methoxy-3-methyl-IH-indole-6-carboxylic acid (1.717 g), EDCI (1.61 g), HOBT (1.286 g) and DMF (40 mL) was added TEA(2.83 g) and the mixture was stirred overnight. The mixture was diluted with EtOAc and H2O, and partitioned. The organic layer was washed with H2O, saturated NaHC03 aqueous, and brine, dried over Na2SO4, and concentrated. The residue was purified by Si02 column chromatography (Hexane-EtOAc gradient), crystallized from EtOAc/n-hexane and dried in vacuo to give the methyl ester of the title compound as a colorless solid. 3.0 g of the ester was suspended in 30 mL of THF and 30 mL of MeOH, then 1.5 mL of 5N NaOH aqueous was added thereo. The mixture was stirred overnight and then concentrated. The residue was diluted with 30 mL of MeOH and 22 mL of H2O, and 7.76 mL of IN HCl aqueous was added thereo. The precipitate was collected by filtration, washed with H2O, and dried in vacuo. The resulting solid was washed with EtOAc-nHexane and dried in vacuo. The material was suspended in water and then 7.76 mL of IN NaOH aqueous was added thereto. The mixture was purified by ODS column chromatography (MeOH-H2O gradient) to give the title compound as a colorless amorphous substance. 1H-NMR (400 MHz, DMSO-d6) δ: 8.91 (IH, d, J = 2.0 Hz), 8.75 (IH, d, J = 2.4 Hz), 8.29 (IH, dd, J = 2.4, 2.0 Hz), 7.99-7.96 (2H, m), 7.23 (IH, d, J = 8.8 Hz), 7.14 (IH, d, J = 1.0 Hz), 7.00 (IH, d, J = 1.0 Hz), 6.51 (IH, s), 4.38-4.17 (IH, br m), 3.84 (3H, s), 3.77-3.62 (IH, br m), 3.45-3.29 (3H, br m), 2.95 (2H, s), 2.32 (3H, s), 2.11-1.72 (4H, br m), 1.03-0.98 (2H, m), 0.89-0.85 (2H, m); MS [M+Na]+ = 588.

**Example 13**

5-π '-r(3-Chloro-l-cyclopropyl-4-methoxy-lH-indol-6-yl)carbonyll-4-oxo-spiro[chroman-2,4'-piperidinl-6-yl] nicotinic acid sodium salt
According to the methods of Example 10 and Example 6, the intended compound was obtained as a colorless amorphous substance, but using S-chloro-l-cyclopropyl-methoxy-1H-indole-6-carboxylic acid in place of l-cyclopropyl-4-(2-hydroxyethoxy)-1H-indole-6-carboxylic acid, and using 5-(4-oxo-spiro[chroman-2,4'-piperidin]-6-yl)nicotinic acid methyl ester hydrochloride in place of 3-(4-oxo-spiro[chroman-2,4'-piperidin]-6-yl)benzoic acid methyl ester hydrochloride. 

\[
\text{\textit{H-NMR (400 MHz, DMSO-d6) } \delta: 8.90 (1H, d, J = 2.0 Hz), 8.74 (1H, d, J = 2.4 Hz), 8.28 (1H, dd, J = 2.4, 2.0 Hz), 7.99-7.96 (2H, m), 7.44 (1H, s), 7.25-7.22 (2H, m), 6.62 (1H, s), 4.36-4.16 (1H, br m), 3.71-3.54 (1H, br m), 3.52-3.29 (3H, br m), 3.86 (3H, s), 2.95 (2H, s), 2.15-1.74 (4H, br m), 1.07-0.92 (4H, br m); MS [M+Na]+ = 608.}
\]

Example 14
5-{r-[(l-Cyclopropyl-4-methoxy-3-methyl-1H-indol-6-yl)carbonvn-4-oxo-spirochroman-2,4'-piperidinl-6-yl]nicotinic acid

To a stirred solution of the compound of Example 12 in MeOH (25 mL) and H2O (25 mL) was added 4 mL of IN HCl aqueous at 0 °C. 60 mL of MeOH was added thereto and the mixture was stirred at r.t. for 3 hours. The precipitate was filtered and dried at 60 °C in vacuo to give the title compound as a colorless solid. 

\[
\text{\textit{H-NMR (400MHz, DMSO-d6) } \delta: 13.56 (1H, s), 9.09 (1H, d, J = 2.2 Hz), 9.03 (1H, d, J = 2.2 Hz), 8.41 (1H, dd, J = 2.2, 2.2 Hz), 8.07-8.03 (2H, m), 7.29-7.25 (1H, m), 7.14 (1H, d, J = 1.0 Hz), 7.00 (1H, d, J = 1.0 Hz), 6.51 (1H, d, J = 1.0 Hz), 4.41-4.10 (1H, br m), 3.83 (3H, s), 3.51-3.41 (1H, br m), 3.51-3.26 (3H, br m), 2.96 (2H, s), 2.31 (3H, s), 2.13-1.74 (4H, br m), 1.06-0.85 (4H, m); MS [M+H]+ = 566.}
\]

Example 15
Ethyl 4-methoxy-l-methyl-lH-pyrazolo[3,4-b]pyridine-6-carboxylate (140 mg) was dissolved in THF (2.0 mL) and MeOH (2.0 mL), and aqueous 5 N sodium hydroxide solution (0.2 mL) was added to the solution, which was stirred at r.t. over night. The reaction mixture was added by 5 N hydrochloric acid (0.2 mL) and concentrated under reduced pressure. The residue was dissolved in DMF (3 mL) and water (1 mL), and 6-(lH-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one hydrochloride (212 mg), triethylamine (0.334 mL), HOBT (110 mg) and EDCI HCl (138 mg) were added thereto. The reaction mixture was stirred at 90°C for 3 hours, then cooled to room temperature, and water was added thereto and a colorless precipitate was then formed. The material was collected and dried under reduced pressure, washed with a mixed solvent of methanol and diethyl ether, and dried under reduced pressure to obtain the above-described compound as a colorless solid.  

**Example 16**

r-[(3-cyclopropyl-7-ethoxy-l,2-benzisoxazol-5-yl)carbonyll-6-(lH-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one

The intended compound was obtained as a colorless solid according to the method described in Example 15, but using methyl 3-cyclopropyl-7-ethoxy-l,2-benzisoxazole-5-carboxylate in place of ethyl 4-methoxy-l-methyl-lH-pyrazolo[3,4-b]pyridine-6-carboxylate.  

**IH-NMR (400MHz, DMSO-d6)** δ: 8.42 (IH, d, J = 2.4 Hz), 8.24 (IH, dd, J = 8.7, 2.3 Hz), 7.45 (IH, d, J = 1.0 Hz), 7.33 (IH, d, J = 8.8 Hz), 7.18 (IH, d, J = 1.0 Hz), 4.28-4.26 (IH, br m), 4.27
(2H, q, J = 7.0 Hz), 3.62-3.17 (3H, br m), 2.98 (2H, s), 2.41-2.33 (IH, m), 2.15-1.74 (4H, br m), 1.40 (3H, t, J = 7.0 Hz), 1.18-1.06 (4H, m); MS [M+H]+ = 515.

Example 17

l-cyclopropyl-4-ethoxy-6-(r4-oxo-6-(lH-tetrazol-5-yl)spiro[chroman-2,4'-piperidin-1-carbonyl]-l/-indole-3-carboxamide

The intended compound was obtained as a colorless solid according to the methods described in Example 5, but using 3-(carbamoyl)-l-cyclopropyl-4-ethoxy-lH-indole-6-carboxylic acid in place of 1,4-dimethoxy-lH-indole-6-carboxylic acid. 1H-NMR (400MHz, DMSO-d6) δ: 8.41 (IH, d, J = 2.4 Hz), 8.23 (2H, dd, J = 8.8, 2.4 Hz), 7.86 (IH, s), 7.34-7.28 (2H, m), 7.18 (IH, s), 6.78 (IH, s), 4.31-4.23 (IH, br m), 4.26 (2H, q, J = 7.0 Hz), 3.80-3.14 (4H, m), 2.98 (2H, s), 2.18-1.74 (4H, br m), 1.41 (3H, t, J = 7.0 Hz), 1.09-0.98 (4H, m); MS [M+H]+ = 556.

Example 18

r-(l-cyclopropyl-4-(2-hydroxyethoxy)-l H-indol-6-ylcarbonyl)-6-(l H-tetrazol-5-yl)spirochroman-2,4'-piperidin-1-4-one

According to the methods of Example 5, the intended compound was obtained as a colorless solid, but using l-cyclopropyl-4-(2-hydroxyethoxy)-l H-indole-6-carboxylic acid in place of M-dimethoxy-l H-indole-6-carboxylic acid. 1H-NMR (400MHz, DMSO-d6) δ: 8.42 (IH, d, J = 2.4 Hz), 8.23 (IH, dd, J = 8.7, 2.4 Hz), 7.33 (IH, d, J = 8.7 Hz), 7.29 (IH, d, J = 3.2 Hz), 7.21 (IH, s), 6.58 (IH, s), 6.42 (IH, d, J = 3.2 Hz), 4.90-4.82 (IH, br m), 4.30-4.20 (IH, br m), 4.10 (2H, t, J = 5.0 Hz), 3.79-3.74 (2H, br m), 3.48-3.26 (4H, br m), 2.99 (2H, s), 2.07-1.76 (4H, br m), 1.07-0.88 (4H, m); MS [M+H]+ = 529.

Example 19
3-(r-[[3-carbamoyl-1-cyclopropyl-4-ethoxy-1H-indol-6-yl]carbonyl]-4-oxospirochroman-2,4'-piperidin-6-yl)benzoic acid

Aqueous 5 N sodium hydroxide solution (0.32 mL) was added to a methanolic (10 mL) solution of the ester compound (523 mg), and the mixture was stirred at 60°C for 4 hours. The organic solvent was evaporated, and the residue was diluted with water. Aqueous 5 N hydrochloric acid solution (330 µl) was added thereto at room temperature, and the mixture was extracted with a mixed solvent of chloroform and methanol, and dried over sodium sulfate. The organic layer was filtered and concentrated to afford the title compound as a colorless solid. 

\[
\delta: 8.22 (IH, s), 8.15-8.12 (IH, br m), 7.99-7.85 (5H, m), 7.58 (IH, dd, J = 7.7, 7.7 Hz), 7.34 (IH, s), 7.24-7.16 (2H, m), 6.79 (IH, s), 4.32-4.24 (2H, br m), 4.27 (IH, q, J = 6.8 Hz), 3.72-3.19 (4H, br m), 2.95 (2H, s), 2.01-1.77 (4H, br m), 1.41 (3H, t, J = 6.8 Hz), 1.1 1-0.94 (4H, m); MS [M+H]+ = 608.
\]

Example 20

4-[[1'-IYl-cyclopropyl-methoxy-S-methyl-1H-indol-6-yl]carbonyl]-4-oxospirochroman-2,4'-piperidin-6-vUpyridine-2-carboxylic acid

Triethylamine (0.22 mL) was added to a solution of 1-cyclopropyl-4-methoxy-3-methyl-1H-indole-6-carboxylic acid (98 mg), methyl 4-(4-oxospiro[chroman-2,4'-piperidin]-6-yl)pyridine-2-carboxylate dihydrochloride (170 mg), WSC hydrochloride (109mg) and HOBT (74 mg) in DMF (3 mL) and the mixture was stirred at room temperature over night. The organic solvent was evaporated and the residue was purified through a silica gel column to obtain methyl ester of the intended compound as a colorless amorphous substance. Aqueous 1 N sodium hydroxide solution (1 mL) was added to a solution of the ester in methanol (3 ml) and THF (3 ml) and the mixture was stirred at room temperature for 4 hours. The mixture was concentrated, diluted with water, added by aqueous 1N hydrochloric acid solution (1 ml) at room temperature, and extracted with a mixed solvent of chloroform and methanol. The organic layer was dried
over sodium sulfate, filtered, and concentrated. The residue was crystallized from a mixed
solvent of hexane and ethyl acetate to afford the intended compound as a colorless solid. ¹H-
NMR (400MHz, DMSO-d₆) δ: 13.27 (IH, br s), 8.72 (IH, d, J = 4.9 Hz), 8.25 (IH, d, J = 1.0 Hz), 8.15-8.11 (2H, m), 7.95 (IH, dd, J = 4.9, 2.0 Hz), 7.29 (IH, dd, J = 6.3, 2.9 Hz), 7.14 (IH, d, J = 1.0 Hz), 7.00 (IH, d, J = 1.0 Hz), 6.50 (IH, d, J = 1.0 Hz), 4.42-4.14 (IH, br m), 3.84-3.58 (IH, br m), 3.83 (3H, s), 3.56-3.15 (3H, br m), 2.97 (2H, s), 2.31 (3H, d, J = 1.0 Hz), 2.08-1.76 (4H, br m), 1.03-0.98 (2H, m), 0.90-0.84 (2H, m); MS [M+H]+ = 566.

Example 21

5-[(r-r)(1-cyclopropyl-4-methoxy-3-methyl-lH-indol-6-yl)carbonyl]4-oxospirochroman-2,4'-
piperidinl-6-yl]2-methylnicotinic acid

The title compound was obtained as a colorless amorphous substance in the same manner
as described in Example 20, but using methyl 2-methyl-5-(4-oxospiro[chroman-2,4'-piperidin]-6-
yl)nicotinate dihydrochloride instead of methyl 4-(4-oxospiro[chroman-2,4'-piperidin]-6-
yl)pyridine-2-carboxylate dihydrochloride. ¹H-NMR (400MHz, DMSO-d₆) δ: 13.38 (0.8H, s),
8.89 (1.0H, d, J = 2.0 Hz), 8.33 (1.0H, d, J = 2.0 Hz), 8.02-7.99 (1.9H, m), 7.25 (1.0H, dd, J =
6.6, 2.0 Hz), 7.14 (1.0H, d, J = 1.0 Hz), 7.00 (0.9H, d, J = 1.0 Hz), 6.50 (0.9H, d, J = 1.0 Hz),
4.37-4.06 (1.0H, br m), 3.83 (2.8H, s), 3.83-3.59 (1.0H, br m), 3.36-3.26 (3.0H, m), 2.95 (1.8H, s),
2.73 (2.9H, s), 2.31 (3.1H, d, J = 1.0 Hz), 2.12-1.76 (3.6H, m), 1.03-0.98 (1.8H, m), 0.89-0.83
(2.0H, m); MS [M+H]+ = 580.

Example 22

5-[(r-r)(1-cyclopropyl-4-ethoxy-3-methyl-lH-indol-6-yl)carbonyl]4-oxospirochroman-2,4'-
piperidinl-6-yl]nicotinic acid

TEA (162mg) was added to a mixture of EDCI (92mg), HOBT (73.5mg), 1-cyclopropyl-
4-ethoxy-3-methyl-lH-indole-6-carboxylic acid (104mg), and methyl 5-(4-oxospiro[chroman-
2,4'-piperidin]-6-yl)nicotinate dihydrochloride (170mg) and DMF (3 ml), and the mixture was
stirred at r.t. for 5 hours. The mixture was evaporated and purified through SiO2 column chromatography (eluted with Hex-EtOAc, then MeOH-CHCl3) to give methyl ester of the title compound as a pale yellow solid. 1mL of IN NaOHaq was added to its solution in 3ml of MeOH and 3ml of THF, and the mixture was stirred at r.t. for 4h. Then the mixture was neutralized with IN HClaq and diluted with CHCl3-MeOH. The mixture was dried over Na2SO4, filtered, and concentrated. The residue was crystallized from EtOAc-n-hexane to give the title compound as a slightly yellowish powder.

1H-NMR (400MHz, DMSO-d6) δ: 13.57 (IH, s), 9.08 (IH, d, J = 2.0 Hz), 9.03 (IH, d, J = 2.0 Hz), 8.41 (IH, dd, J = 2.0, 2.0 Hz), 8.08-8.02 (2H, m), 7.26 (IH, dd, J = 7.8, 1.0 Hz), 7.12 (IH, d, J = 1.0 Hz), 7.00 (IH, d, J = 1.0 Hz), 6.48 (IH, s), 4.36-4.14 (IH, br m), 4.08 (2H, q, J = 7.0 Hz), 3.78-3.20 (4H, br m), 2.96 (2H, s), 2.33 (3H, d, J = 1.0 Hz), 2.09-1.73 (4H, m), 1.37 (3H, t, J = 7.0 Hz), 1.03-0.98 (2H, m), 0.89-0.85 (2H, m); MS [M+H]+ = 580.

Example 23

4-[(1'-[(1-cyclopropyl-4-ethoxy-3-methyl-lH-indol-6-yl)carbonyl]-4-oxospirochroman-2,4'-piperidin1-6-yl)pyridine-2-carboxylic acid

In the same manner as described in Example 20 except using 1-cyclopropyl-4-ethoxy-3-methyl-lH-indole-6-carboxylic acid and methyl 4-(4-oxospirochroman-2,4'-piperidin-6-yl)pyridine-2-carboxylate dihydrochloride, the title compound was obtained as a colorless amorphous substance. 1H-NMR (400MHz, DMSO-d6) δ: 8.72 (IH, d, J = 4.9 Hz), 8.25 (IH, d, J = 1.5 Hz), 8.15-8.11 (2H, m), 7.94 (IH, dd, J = 6.0, 2.0 Hz), 7.28 (IH, dd, J = 6.0, 2.9 Hz), 7.12 (IH, d, J = 1.0 Hz), 6.99 (IH, d, J = 1.0 Hz), 6.48 (IH, s), 4.45-4.10 (IH, br m), 4.08 (2H, q, J = 6.8 Hz), 3.67-3.19 (4H, m), 2.97 (2H, s), 2.32 (3H, s), 2.12-1.74 (4H, br m), 1.37 (3H, t, J = 6.8 Hz), 1.03-0.98 (2H, m), 0.88-0.85 (2H, m); MS [M+H]+ = 580.

Example 24

5-[(r-[(1,4-dimethoxy-3-methyl-lH-indol-6-yl)carbonyl]-4-oxospirochroman-2,4'-piperidinl-6-yl)unicotinic acid
The title compound was obtained as a colorless amorphous substance in the same manner as described in Example 20 but using 1,4-dimethoxy-3-methyl-1H-indole-6-carboxylic acid and methyl 5-(4-oxospiro[chroman-2,4'-piperidin]-6-yl)pyridine-3-carboxylate dihydrochloride. ¹H-NMR (400MHz, DMSO-d6) δ: 9.04 (IH, d, J = 2.2 Hz), 8.99 (IH, d, J = 2.2 Hz), 8.38 (IH, dd, J = 2.2, 2.2 Hz), 8.04-8.00 (2H, m), 7.32-7.30 (IH, br m), 7.25-7.22 (IH, m), 6.99 (IH, d, J = 1.0 Hz), 6.48 (IH, d, J = 1.0 Hz), 4.37-4.10 (IH, br m), 3.96 (3H, s), 3.83 (3H, s), 3.73-3.09 (3H, br m), 2.93 (2H, s), 2.30 (3H, d, J = 1.0 Hz), 2.10-1.72 (4H, br m); MS [M+H]+ = 556.

Example 25

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!'-[(! -cyclopropyl^-methoxy-S-methyl-lH-indol- -vDcarbonylj- -dH-tetrazol-S-
yl)spirofchroman-2,4'-piperidinl-4-one
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Et3N (209uL), HOBT (91.2mg) and WSC (115mg) were added to a suspension of 1-cyclopropyl-4-(methyloxy)-1H-indole-6-carboxylic acid (116mg) and 6-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)spiro[chroman-2,4'-piperidin]-4-one hydrochloride (202mg) in DMF (3ml), and the mixture was stirred overnight at 50°C. Water was added to the reaction mixture, and the formed solid was collected by filtration. The solid was purified by silicagel column chromatography (CHC13/MeOH) to obtain the intended compound as colorless foam. ¹H-NMR (400 MHz, DMSO-d6) δ: 8.06 (IH, d, J = 2.3 Hz), 8.00 (IH, dd, J = 8.7, 2.3 Hz), 7.29 (IH, d, J = 3.2 Hz), 7.26 (IH, d, J = 8.7 Hz), 7.24-7.21 (3H, m), 6.58 (IH, d, J = 1.0 Hz), 6.40 (IH, dd, J = 3.2, 1.0 Hz), 4.44-4.08 (IH, br m), 3.87 (3H, s), 3.80-3.25 (4H, m), 2.97 (2H, s), 2.10-1.70 (4H, m), 1.09-1.01 (2H, m), 0.96-0.89 (2H, m); MS [M+H]+ = 514.

Example 26

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!'-[(! -cyclopropyl^a-methoxy-S-methyl-lH-indol-6-vDcarbonylj-6-dH-tetrazol-S-
yl)spirofchroman-2,4'-piperidinl-4-one
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The intended compound was obtained as a slightly yellowish substance, according to the method of Example 5 but using 1-cyclopropyl-S-methylmethoxy-lH-indole-6-carboxylic acid in place of 1,4-dimethoxy-lH-indole-6-carboxylic acid. IH-NMR (400MHz, DMSO-d$_6$) δ: 8.42 (IH, d, J = 2.0 Hz), 8.24 (IH, dd, J = 8.8, 2.0 Hz), 7.35 (IH, d, J = 8.8 Hz), 7.14 (IH, d, J = 1.0 Hz), 7.01-7.00 (IH, br m), 6.50 (IH, d, J = 1.0 Hz), 4.58-3.98 (IH, br m), 3.83 (3H, s), 3.74-3.29 (4H, br m), 2.99 (2H, s), 2.31 (3H, d, J = 1.1 Hz), 2.08-1.77 (4H, m), 1.03-0.98 (2H, m), 0.89-0.85 (2H, m); MS [M+H]$^+$ = 513.

Reference Example 1

1-Cyclopropyl-1H-pyrrole-2-carbaldehyde 44.46ml of POCl$_3$ was added to a stirred solution of 1-cyclopropyl-1H-pyrrole (46.46g) in 37ml of DMF with cooling with ice, then the mixture was stirred at room temperature overnight. The mixture was poured into 336ml of 5N NaOHaq with cooling with ice, and the mixture was made basic with an additional 5N NaOHaq. The mixture was extracted with CH2C12 and the organic extract was dried over Na2SO4, concentrated, and the residue was purified on SiO2 column chromatography (n-hexane-EtOAc system) to give 38.91g of 1-cyclopropyl-1H-pyrrole-2-carbaldehyde as a colorless oil.

Reference Example 2

Ethyl 4-acetoxy-1-cyclopropyl-1H-indole-6-carboxylate 14.57g of Na was added portionwise to 400ml of EtOH. To the mixture was added a solution of 38.91g of 1-cyclopropyl-1H-pyrrole-2-carbaldehyde and 48.23ml of diethyl succinate in 100ml of EtOH at 50 °C, then the mixture was refluxed overnight. 140ml of 5N HCl was added to the mixture at 0 °C and EtOH was evaporated. The concentrate was extracted with CHCl3 and the extract was dried over Na2SO4 and concentrated to give red oil. The material was dissolved in 400ml of acetic anhydride and 47.40g of AcOK was added thereto. The mixture was refluxed for 30min and allowed to cool to room temperature. The mixture was filtrated and the filtrate was concentrated. The residue was purified on SiO2 column chromatography (n-hexane-EtOAc system) to give 72.3g of ethyl 4-acetoxy-1-cyclopropyl-1H-indole-6-carboxylate as red oil.

Reference Example 3

Ethyl 1-cyclopropyl-4-hydroxy-1H-indole-6-carboxylate To a solution of 72.33g of ethyl 4-acetoxy-1-cyclopropyl-1H-indole-6-carboxylate in 360ml of EtOH placed in a 2L flask was added 69.58g of K2CO3 and the mixture was stirred at room temperature for 4 hrs. EtOH was evaporated and the concentrate was diluted with EtOAc. The mixture was washed with water and saturated brine, dried over Na2SO4, and concentrated. The residue was triturated with toluene and n-hexane to give 49.78g of ethyl 1-cyclopropyl-4-hydroxy-1H-indole-6-carboxylate as a pale tan solid.

Reference Example 4
Ethyl 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylate  To a stirred suspension of 14.56g of ethyl 1-cyclopropyl-4-hydroxy-1H-indole-6-carboxylate and 16.2g of K2CO3 and 220ml of DMF was added 7.48ml of MeI and the mixture was stirred at 60 °C for 3 hrs. The mixture was allowed to cool, diluted with EtOAc, washed with water and saturated brine successively, dried over Na2SO4, then concentrated. The residue was purified on SiO2 column chromatography (n-hexane-EtOAc) to afford 15.15g of ethyl 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylate as a pale yellow oil.

Reference Example 5

Ethyl 1-cyclopropyl-4-ethoxy-1H-indole-6-carboxylate  The compound was prepared according to the procedure for ethyl 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylate but using EtI in place of MeI.

Reference Example 6

1-Cyclopropyl-4-ethoxy-1H-indole-6-carboxylic acid  The compound was prepared according to the procedure for 1-Cyclopropyl-4-methoxy-1H-indole-6-carboxylic acid but using ethyl 1-cyclopropyl-4-ethoxy-1H-indole-6-carboxylate in place of ethyl 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylate.

Reference Example 7

1-Cyclopropyl-4-methoxy-1H-indole-6-carboxylic acid  35ml of 5N NaOHaq was added to a solution of 15.15g of ethyl 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylate in MeOH and the mixture was stirred at 60 °C for 8 hrs. The mixture was cooled to 0 °C and 35ml of 5N HCl was added thereto. The precipitate was filtered and dried in vacuo to give 13.8g of 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylic acid as a colorless solid.

Reference Example 8

Ethyl 1-cyclopropyl-3-formyl-4-methoxy-1H-indole-6-carboxylate  1.28ml of POCl3 was added dropwise to a solution of 3.24g of ethyl 1-cyclopropyl-4-methoxy-1H-indole-6-carboxylate in 30ml of DMF and the mixture was stirred at 0 °C for 2 hrs. The mixture was diluted with EtOAc and 25ml of IN NaOH was added. Then the mixture was made basic using saturated NaHCO3aq. The mixture was extracted with EtOAc and the extract was washed with water and saturated brine, dried over Na2SO4, then concentrated. The residue was purified on SiO2 column chromatography (EtOAc-n-Hexane system) to give 2.4 g of ethyl 1-cyclopropyl-3-formyl-4-methoxy-1H-indole-6-carboxylate.

Reference Example 9

Ethyl 1-cyclopropyl-S-methyl-4-methoxy-1H-indole-6-carboxylate  To a stirred solution of 3.30g of ethyl 1-cyclopropyl-3-formyl-4-methoxy-1H-indole-6-carboxylate in 33ml of EtOH was added 2.57g of TsNHNH2 and the mixture was refluxed for 30min. After evaporation of EtOH, the mixture was diluted with 28ml of DMF and 28ml of sulfolane, then 2.89g of NaBH3CN and
0.57g of TsOH H2O was added thereto successively. The mixture was refluxed for 30min and cooled to room temperature. After diluted with Et2O, the mixture was washed successively with water, saturated NaHCClaq, and saturated brine, dried over Na2SO4, concentrated. The residue was purified on SiO2 column chromatography (EtOAc/ n-hexane system) to give 2.78g of Ethyl 1-cyclopropyl-3-methyl-4-methoxy-1H-indole-6-carboxylate as a colorless powder.

Reference Example 10  
Ethyl 3-chloro-4-methoxy-1H-indole-6-carboxylate  To a stirred solution of 1.29g of ethyl 1-cyclopropylM-methoxy-1H-indole-6-carboxylate in 13ml of THF was added 801mg of N-chlorosuccinimide and the mixture was stirred at 60 °C for 2 hrs. After diluted with EtOAc, the mixture was washed successively with water and saturated brine, dried over Na2SO4, and concentrated. The residue was purified on SiO2 column chromatography to afford 1.03g of ethyl 3-chloro-1-cyclopropyl-4-(methoxy)-1H-indole-6-carboxylate as a colorless solid.

Reference Example 11  
3-chloro-1-cyclopropyl-4-methoxy-1H-midole-6-carboxylic acid  To a stirred solution of 1.03g of ethyl 3-chloro-1-cyclopropyl-4-(methyloxy)-1H-indole-6-carboxylate in 15ml of MeOH and 10ml of THF was added 2ml of 5N NaOHaq and the mixture was stirred at 60 °C for 9 hrs. After evaporation of MeOH and THF, the mixture was diluted with water and 2ml of 5N HClaq was added thereto. The precipitate was collected by filtration and dried in vacuo to give 798mg of 3-chloro-1-cyclopropyl-4-(methoxy)-1H-indole-6-carboxylic acid as a colorless solid.

Reference Example 12  
1-Cyclopropyl-3-methyl-4-methoxy-1H-indole-6-carboxylic acid  4.66 mL of 5N NaOH aqueous was added to a solution of 3.19 g of ethyl 1-cyclopropyl-S-methyM-methoxy-1H-indole-6-carboxylate in 32 mL of MeOH and the mixture was stirred at 60 °C overnight. The mixture was cooled and 46.6 mL of 1 N HCl was added thereto. The precipitate was filtered, collected and dried in vacuo to afford 2.70 g of 1-Cyclopropyl-S-methylM-methoxy-1H-indole-6-carboxylic acid as a colorless solid.

Reference Example 13  
6-bromo-r-(tert-butoxycarbonyl)spirochroman-2,4'-piperidin1-4-one.  60 mL of MeOH, 7.97 g of N-Boc-piperidin-4-one, and 3.34 mL of pyrrolidine were added to 8.60 g of 5-bromo-2-hydroxyacetophenone put in a 200- mL flask equipped with a condenser, and the mixture was overnight heated under reflux. The reaction mixture was cooled to room temperature, and concentrated. The residue was purified through silica gel column chromatography (eluted with n-hexane/EtOAc=6/1) to obtain the intended compound as a pale yellow solid.

Reference Example 14  
6-bromospiro[chroman-2,4'-piperidin1-4-one hydrochloride.  A mixture of 25.0 g of 5-bromo-2-hydroxyacetophenone, 25.0 g of N-Boc-piperidin-4-one, 9.68 mL of pyrrolidine and 250 mL of
MeOH was heated under reflux overnight. The reaction mixture was cooled to room temperature and concentrated. The residue was put into 300 mL of 1,4-dioxane, and 100 mL of concentrated hydrochloric acid was added thereto and stirred at room temperature for 4 hour. The reaction solution was poured into water, and stirred overnight. The resulting precipitate was taken out through filtration, washed with water and n-hexane, and dried under reduced pressure to obtain the intended compound as an yellow solid.

Reference Example 15
tert-butyl 6-cyano-4-oxospirochroman-2,4'-piperidine-r-carboxylate. A mixture of tert-butyl 6-bromo-4-oxospiro[chroman-2,4'-piperidine]-r-carboxylate (143 g, 0.36 mol), Zn(CN)2 (84.7 g, 0.72 mol), Pd(PPh3)4 (20 g, 17 mmol) and dry DMF (1 liter) was stirred under an argon atmosphere at 90°C for 6 hours. The resulting mixture was, after cooled, diluted with ethyl acetate (1 liter), and washed with aqueous 12% ammonia, water, and saturated brine in order. The organic layer was dried over sodium sulfate, and concentrated, and the residue was treated with methanol, and the resulting insoluble solid was washed and filtered, and dried under a reduced pressure to obtain tert-butyl 6-cyano-4-oxospiro[chroman-2,4'-piperidine]-r-carboxylate as a colorless solid.

Reference Example 16
tert-butyl 4-oxo-6-(1 H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-1'-carboxylate. 67.5 g of sodium azide, 143 g of triethylamine hydrochloride, and 1.2 liters of dry DMF were added to the cyano compound (119 g) produced in Reference Example 15, and the mixture was stirred under a nitrogen atmosphere at 100°C for 12 hours. After cooled, the reaction mixture was partitioned between 1 N hydrochloric acid (200 mL), water and ethyl acetate. The aqueous layer was further extracted three times with ethyl acetate, and the combined organic layers were washed with water and brine, dried over sodium sulfate and concentrated. The residue was triturated with methanol, and the insoluble solid was collected through filtration and dried under reduced pressure to obtain tert-butyl 4-oxo-6-(1 H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-r-carboxylate as a colorless solid.

Reference Example 17
6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one. 4 N HCl-1,4-dioxane (200 mL) was added to 40.6 g tert-butyl 4-oxo-6-(1 H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-r-carboxylate produced in Reference Example 16, and stirred at room temperature for 5 hours. The reaction mixture was concentrated, and the residue was triturated with methanol. The insoluble solid was collected through filtration, and dried under reduced pressure to obtain 6-(1 H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one as a colorless solid.

Reference Example 18
5-Bromo-nicotinic acid tert-butyl ester. 5-Bromo-nicotinic acid (20.2 g, 100 mmol) was dissolved in CHCl₃ (200 mL) and tert-ButOH (40 mL); and WSC (21.1 g, 110 mmol) and DMAP (21.1 g, 110 mmol) was added thereto in order, and stirred at room temperature over night. The reaction mixture was diluted with chloroform, washed with 0.5N HCl aq. (220 mL), 0.5N NaOH aq. (100 mL), brine and dried over MgSO₄ and silica gel. After filtration, the solvents were removed in vacuo to afford 5-Bromo-nicotinic acid tert-butyl ester as a colorless solid. This solid was used for the next step without further purification.

Reference Example 19

5-(r- tert-butoxycarbonyl)-4-oxospirochroman-2,4'-piperidin-6-yl|nicotinic acid tert-butyl ester. tert-butyl-6-bromo-4-oxospiro[chroman-2,4'-piperidine]-r-carboxylate (19.8 g, 50.0 mmol), bis(pinacolato)diboran (14.0 g, 55.0 mmol), Pd(OAc)₂ (560 mg, 2.50 mmol), DPPF (2.77 g, 5.00 mmol), and AcOK (5.82 g, 60.0 mmol) were suspended in dioxane (250 mL) and heated at 100°C for 10 hours. After cooling down to room temperature, 5-bromo-nicotinic acid tert-butyl ester (14.2 g, 55.0 mmol), Pd(PPh₃)₃ (5.78 g, 5.00 mmol) and 2M Na₂CO₃ aq. (125 mL, 250 mmol) were added to the reaction mixture; and then heated at 100°C for 15 hours. The reaction mixture was diluted with EtOAc and H₂O, organic layer was washed with brine and dried over MgSO₄. After filtration, the solvents were removed in vacuo and the residue was purified by silica gel column chromatography (hexane/EtOAc = 10/0 to 6/4) and the obtained brown solid was crystallized from EtOAc/hexane (1/1) to afford 5-[{r-tert r-butoxycarbonyl]-4-oxospiro[chroman-2,4'-piperidine]-6-yl|nicotinic acid tert-butyl ester as a pale yellow solid.

Reference Example 20

5-[4-oxospirochroman-2,4'-piperidin-6-yl|nicotinic acid di-hydrochloride. 5-[1'-tert-butoxycarbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl|nicotinic acid tert-butyl ester (14.0 g, 28.3 mmol) was dissolved in CHCl₃ (70 mL) and 4N HCl in dioxane (210 mL) was added thereto, and stirred at room temperature for 20h. The resulted precipitate was filtered and washed with CHCl₃ and Et₂O to afford 5-[4-oxospiro[chroman-2,4'-piperidine]-6-yl|nicotinic acid di-hydrochloride as a colorless solid.

Reference Example 21
tert-butyl 6-cyano-4-hydroxy-rh-spiro]-chroman-2,4'-piperidine1-r-carboxylate. To a solution of 15 g of tert-butyl 6-cyano-4-oxospiro[chroman-2,4'-piperidin]-r-carboxylate in 250 mL of EtOH-THF(1 : 4) at 0°C was added NaBH₄ portionwise, and the reaction mixture was allowed to warm up to r.t. After stirring for Ih, NFLClaq was added to the reaction mixture and the aqueous mixture was extracted with AcOEt twice. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in reduced pressure to give the intended compound as a pale yellow solid.

Reference Example 22
**Example 23**

To a solution of 18.2 g of tert-butyl 4-[[tert-butyl(dimethyl)silyl]oxy]-6-cyanospiro[chroman-2,4'-piperidine]-l'-carboxylate in EtOH was added 16.3 mL of Et3N and 8.12 g of hydroxyamine hydrochloride at rt, and the reaction mixture was stirred at 85 °C for Id. The resultant solution was cooled to r.t., and concentrated in reduced pressure. The residue was added H2O, the resultant white solid was filtered, washed with H2O, and dried in vacuo to give a crude product, which was used in the next step without further purification.

**Reference Example 24**

To a solution of tert-butyl 6-[amino(hydroxyimino)methyl]-4-[[tert-butyl(dimethyl)silyl]oxy]spiro[chroman-2,4'-piperidine]-l'-carboxylate in 80 mL of DMF were added 3.78 mL of pyridine and 8.4 mL of 2-Ethylhexyl chloroformate at 0 °C, and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was poured into ice-cold brine, and extracted with AcOEt twice. The combined organic layers were washed with H2O and brine, dried over Na2SO4, filtered, and concentrated in reduced pressure to give a crude product, which was used in the next step without further purification.

**Reference Example 25**

A solution of tert-butyl 6-[amino(2-ethylhexyl)oxy|carbonyl|_oxy)imino|methyl]-4-[[tert-butyl(dimethyl)silyl]oxy]spiro[chroman-2,4'-piperidine]-l'-carboxylate in 100 mL of xylene was stirred at 145 °C for 14 h. The reaction mixture was cooled to r.t., and concentrated in reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexane-AcOEt (100/0 - 80/20) as eluent to give the intended compound.
eluent to give the product as an off-white solid.

Reference Example 26
tert-butyl 4-hydroxy-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spirochroman-2,4'-piperidine-1'-carboxylate. To a solution of 13.4 g of tert-butyl 4-{{[tет-butyl(dimethyl)silyl]oxy}-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidine]-r-carboxylate in 200 mL of EtOH-THF (5.5 : 1) at 0 °C was added 67 mL of 1 M HClaq dropwise, and the reaction mixture was stirred at r.t. for 18 h. The reaction mixture was cooled to 0 °C, and the mixture was basified with NaHCO₃. The mixture was concentrated in reduced pressure, and the residue was acidified with 1 M HClaq. The aqueous mixture was extracted with a mixture of CHCl₃-MeOH (9:1) three times, and the combined organic layers was washed with brine, dried over Na₂SO₄, and concentrated in reduces pressure to give the product as a pale brown solid.

Reference Example 27
tert-butyl 4-oxo-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidin-1-r-carboxylate. To a solution of 1.0 g of tert-butyl 4-hydroxy-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidine]-r-carboxylate in 40 mL of THF-CH₃CN (1:1) at r.t. were added 2.0 g of MS 4A, 435 mg of NMO, and 88 mg of TPAP, and the reaction mixture was stirred at r.t. overnight. The mixture was filtered through a Celite pad, washed with CHCl₃ and CHCl₃-MeOH (9:1), and the filtrate was concentrated in reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexane- AcOEt (100/0-0/100) as eluent to give the intended compound as a colorless solid.

Reference Example 28
6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidin-1-4-one hydrochloride. A suspension of 437 mg of tert-butyl 4-oxo-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidine]-r-carboxylate in 10 mL of 4N HCl in dioxane was stirred at r.t for 1h, the resultant white solid was filtered, and washed with ether. The collected white solid was dried in vacuo at 50 °C to give the intended compound as a colorless solid.

Reference Example 29
l-tert-butoxycarbonyl-6-(4",4",5",5"-tetramethyl-1".3".2"-dioxaborolan-2"-yl) spirochroman-2,4'-piperidin-4-one, tert-Butyl 6-bromo-4-oxospiro[chroman-2,4'-piperidine]-r-carboxylate (99.0 g, 250 mmol), bis(pinacolato)diboran (70.2 g, 275 mmol), Pd(OAc)₂ (2.80 g, 12.5 mmol), DPPF (13.9 g, 25.0 mmol), and AcOK (29.1 g, 300 mmol) were suspended in dioxane (500 ml) and heated at 100°C for 20 h. After cooling down to room temperature, MeOH (500 ml) was added and further stirred for 1h. The resulted precipitate was filtered and the cake was washed with MeOH to obtain the intended compound as a pale brown solid.

Reference Example 30
5-(r-tert-butoxycarbonyl-4-oxospirorchroman-2,4'-piperidinl-6-v nicotinic acid methyl ester. l'-tert-butoxycarbonyl-6-(4",4",5",5"-tetramethyl-l",3",2"-dioxaborolan-2"-yl)spiro[chroman-2,4'-piperidin]-4-one (2.00 g, 4.51 mmol), 5-bromonicotinic acid methyl ester (1.17 g, 5.42 mmol), Pd(0Ac)2 (50.6 mg, 0.226 mmol), DPPF (250 g, 0.451 mmol), and K3PO4 (1.91 g, 9.02 mmol) were suspended in DME (500 mL) and heated at 100°C for 18 hours. The reaction mixture was filtered through Celite, the residue on the Celite was washed with chloroform, and the filtrate and the washing were combined and concentrated under a reduced pressure. The resulting residue was purified through silica gel column chromatography (hexane / EtOAc = 10 / 0 to 2 / 8) to obtain the intended compound as a pale yellow solid.

Reference Example 31

5-(4-oxospiro[chroman-2,4'-piperidin]-6-yl)nicotinic acid methyl ester di-hydrochloride. 5-(l'-tert-butoxycarbonyl-4-oxospiro[chroman-2,4'-piperidin]-6-yl)nicotinic acid methyl ester (22.0 g, 48.6 mmol) was suspended in MeOH (110 mL) and 4 N HCl in dioxane (220 mL) was added thereto, and stirred at room temperature for 14 hours. The solvents were removed in vacuo and the resulting solid was washed with MeOH / Et2O (50 mL / 200 mL) to obtain the intended compound as a colorless solid.

Reference Example 32

3"-{1'-tert-butoxycarbonyl]-4-oxospiro[chroman-2,4'-piperidinl-6-yl] benzoic acid. tert-buty16-bromo-4-oxospiro[chroman-2,4'-piperidine]-r-carboxylate (39.6 g, 100 mmol), 3-carboxyphenylboronicacid (16.6 g, 100 mmol), Pd(PPh3)4 (5.78 g, 5.00 mmol), and 2M Na2CO3 aq. (250 mL, 500 mmol) were suspended in 1,4-dioxane (400 mL) and heated at 100°C for 18 h. The reaction mixture was diluted with CHCl3 and dil HCl aq. (1.1 mol), the aqueous layer was extracted with CHCl3. The combined organic layer was washed with H2O and brine, dried over MgSO4. The desiccant was removed through filtration and the filtrate was concentrated under reduced pressure. The residue was triturated with EtOAc and the insoluble solid was collected through filtration to obtain the intended compound as a colorless solid.

Reference Example 33

Methyl 3"-{1'-grr-butoxycarbonyll-4-oxospir|chroman-2,4'-piperidinl-6-vU benzoate. 3"-{l'-tert-butoxycarbonyl-4-oxospiro[chroman-2,4'-piperidin]-6-yl] benzoic acid (24.0 g, 54.9 mmol) was dissolved in CHCl3 (120 ml), and MeOH (24 ml), WSC (15.8 g, 82.4 mmol) and DMAP (10.0 g, 82.4 mmol) was added thereto in this order, and the mixture was stirred at room temperature over night. The reaction mixture was diluted with CHCl3 and diluted HCl aq. (220 mmol). The organic layer was washed with 0.5N NaOH aq., brine and dried over MgSO4 and silica gel. The desiccant was removed through filtration and the filtrate was concentrated under reduced pressure. The residue was triturated with MeOH and the insoluble solid was collected through filtration to obtain the intended compound as a pale yellow solid.

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Reference Example 34

Methyl 5-(4-oxospiro[chroman-2,4'-piperidin-1'-6-yl]benzoate. The intended compound was produced according to the synthetic procedure for 5''-(4-oxospiro[chroman-2,4'-piperidin]-6-yl)nicotinic acid methyl ester di-hydrochloride but using methyl 3''-[r- tert-butoxycarbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl]benzoate in place of 5''-[r- tert-butoxycarbonyl]-4-oxospirofchroman-1''-piperidin-6-yl]nicotinic acid methyl ester.

Reference Example 35

6-(1H-tetrazol-5-yl)spirochroman-2,4'-piperidine-1'-4'-one hydrochloride salt. A mixture of 5-bromo-2-hydroxyacetophenone (104.35 g, 485.26 mmol), N-Boc-piperidin-4-one (98.62 g, 494.96 mmol), 20 mL of pyrrolidine (17.26 g, 242.63 mmol) and 261 mL of MeOH was heated under reflux until the reaction was complete. The mixture was cooled, then 87 mL of H2O were added, and the mixture was filtered and dried to give tert-butyl 6-bromo-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate. Alternatively, 10 mL of pyrrolidine (121.31 mmol) may be used in this procedure. To a solution of tert-butyl 6-bromo-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (6593 g, 16.6 mol) and DMF (33 L) was added Zn(CN)2 (1947 g, 16.6 mol) and Pd(PPh3)4 (192 g, 17 mol). The slurry was heated to 90°C for 3 hours, then cooled to room temperature and filtered. Water (16 L) was added to the filtrate. The resulting slurry was cooled to 5°C, stirred for 1 hour and filtered. The solid was washed with DMF/water (2:1) and dried under vacuum to give tert-butyl 6-cyano-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate. A solution of 23 g of tert-butyl 6-cyano-4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate (67.17 mmol), 13.10 g sodium azide (201.52 mmol), 27.74 g of triethylamine hydrochloride (201.52 mmol), and 460 mL of dry DMF was stirred under a nitrogen atmosphere at 100°C for 12 hours. After cooling to room temperature, 506 mL of EtOAc were added, followed by 322 mL of IM HCl (322 mmol). Alternatively, 0.5M HCl may be added until pH = 3. The resulting layers were separated, the organic layer was washed with water/methanol (115 mL/46 mL), and then concentrated to give tert-butyl 4-oxo-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-1'-carboxylate. A solution of 5.08 g of tert-butyl 4-oxo-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-1'-carboxylate (13.18 mmol), 8.8 mL of 12 M HCl (105.44 mmol) and 8 mL of methanol was heated to 50°C until the reaction was complete. The resulting slurry was filtered, washed with 25 mL of methanol at room temperature, and dried to give 6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one hydrochloride salt.

Reference Example 36

Ethyl 3-methoxy-5-nitro-4-[(Ytrifluoromethyl)sulfonyl]oxy)benzoate. 17.7ml of Tf2O was added to a solution of 16.8g of ethyl 4-hydroxy-3-(methylxy)-5-nitrobenzoate and 11.3ml of pyridine in 500ml of CHC13 at 0°C. The mixture was stirred for 30 min, then washed successively with water, HClaq, and saturated NaHCO3aq, dried over Na2SO4,
concentrated. The residual solid was washed with a mixed solvent of CHCl3 and n-hexane to
give a 22.0g of the intended compound as a pale orange solid.

Reference Example 37
Ethyl 4-methyl-3-(methoxyV5-nitrobenzoate  To a stirred solution of 4.92g of MeB(OH)2,
33.9g of K2CO3, 25.6g of ethyl 3-methoxy-5-nitro-4-{{[(trifluoromethyl)sulfonyl]oxy}benzoate
in 500ml of THF and 50ml of water was added 5.03g of PdC12 dppf and the mixture was stirred
under argon atmosphere at 80 °C overnight. The mixture was diluted with AcOEt and water,
filtered through Celite and the filtrate was extracted with AcOEt. The extract was washed
successively with saturated NaCO3aq and saturated brine, dried over Na2SO4, and concentrated.
The residue was purified on SiO2 column chromatography and the fractions containing the
intended compound were concentrated. The resulting solid was washed with n-hexane and dried
to give 12.9g of the intended compound as a yellow solid.

Reference Example 38
Ethyl 3-(methoxyV5-nitro-4-(2-oxoethyl )benzoate  13.3 ml of Me2NCH(OMe)2 was added to a
solution of 4.78g of ethyl 4-methyl-3-(methoxy)-5-nitrobenzoate in 10ml of dimethylacetamide
and the mixture was heated at 80 °C in a sealed tube for 40 minutes. The mixture was diluted
with CHC13, washed with water, dried over Na2SO4, and concentrated. The residue was purified
on SiO2 column chromatography to give 4.02g of the intended compound as a pale tan solid.

Reference Example 39
Ethyl 1,4-dimethoxy-1H-indole-6-carboxylate  250mg of ethyl 3-(methoxy)-5-nitro-4-(2-
oxoethyl)benzoate was dissolved in 5ml of DMF and the solution was stirred over 50mg of 10%
Pd/C (50% wet) under hydrogen atmosphere for 6 hrs. Then the mixture was purged with N2 and
126 uL of MeI and 276mg of K2CO3 was added thereto. After stirred for 2 hrs, the mixture was
diluted with Et20, filtered through Celite. The filtrate was concentrated and purified on SiO2
column chromatography to give 184mg of the intended compound as colorless oil.

Reference Example 40
Ethyl 1,4-dimethoxy-1H-indole-6-carboxylic acid  513mg of ethyl 1,4-dimethoxy-1H-indole-6-
carboxylate was dissolved in 10ml of MeOH and 1ml of 5N NaOHaq was added thereto. The
mixture was heated at 80 °C with stirring overnight. After cooled to 0 °C, the mixture was
neutralized by 1ml of 5N HClaq and extracted with CHC13 and MeOH. The extract was dried
over Na2SO4, concentrated. The resulting solid was washed with a mixed solvent of n-hexane,
diethyl ether and MeOH to afford 352mg of the intended compound as a pale purple solid.

Reference Example 41
Ethyl 3-O-tert-butyl 6-O-ethyl l-cyclopropyl-4-ethoxy-lH-indole-3,6-dicarboxylate  (COC1)2
(713 ul) was added to the solution of ethyl l-cyclopropylM-ethoxy-lH-indole-6-carboxylate
(1.36 g) in Et20 20 ml at r.t. and stirred for over night. The solvent was evaporated away and the
residue was dissolved in toluene 20 ml. The reaction mixture was stirred at reflux for 1 h and cooled to room temperature. Pyridine (810 ul) and tert-butanol (3 ml) were added to the mixture, stirred for 1 h at r.t.. The reaction mixture was quenched with saturated aqueous sodium bicarbonate, then washed with water, and saturated saline water in that order, and dried with sodium sulfate. This was filtered, concentrated, and purified through silica gel column chromatography (hexane/ethyl acetate) to obtain the title compound (1.71 g) as a colorless solid.

Reference Example 42
Ethyl 3-carbamoyl-1-cyclopropyl-4-ethoxy- lH-indole-6-carboxylate (COC1)2 (713 ul) was added to the solution of ethyl 1-cyclopropyl-4-ethoxy- lH-indole-6-carboxylate (5.46 g) in Et20 70 ml at r.t. and stirred for over night. The solvent was evaporated away and the residue was dissolved in toluene 70 ml. The reaction mixture was stirred at reflux for 1 h and cooled to room temperature and 0.5 N solution of NH3 in dioxane (100 ml) was added dropwise and stirred for 2 h at r.t.. The reaction mixture was diluted with ethyl acetate and water, washed with water and saturated saline water in that order, and dried with sodium sulfate. This was filtered, concentrated, and crystallized from mixed solvent of hexane and ethyl acetate to give the title compound (5.06 g) as a colorless solid.

Reference Example 43
Ethyl 1-cyclopropyl-4-ethoxy-3-methylcarbamoyl-lH-indole-6-carboxylate  3-O-tert-Butyl 6-O-ethyl 1-cyclopropyl-4-ethoxy- lH-indole-3,6-dicarboxylate (1.23 g) was added to 4N solution of hydrochloric acid in dioxane (5 ml) at r.t. and the mixture was stirred for 1 h, evaporated and crystallized from hexane to give carboxylic acid of intended compound (996 mg ) as a colorless solid. (COC1)2 (117 ul) to the solution of this carboxylic acid (217 mg) in chloroform (5 ml) and then one portion of DMF was added at 0 °C. The reaction mixture was stirred for 2 h at r.t., evaporated, and dissolved in THF (5 ml). 2M solution of methylamine in THF (3 ml) was added to the reaction mixture, stirred for 30 min at r.t., diluted with ethyl acetate and water, washed with water and saturated saline water in that order, and dried with sodium sulfate. This was filtered, concentrated to give title compound (216 mg).

Reference Example 44
Ethyl 1-cyclopropyl-4-(2-hydroxyethoxy)- lH-indole-6-carboxylate The compound was prepared according to the procedure for ethyl 1-cyclopropyl-4-methoxy-l H-indole-6-carboxylate but using bromoethyl acetate in place of MeI.

Reference Example 45
Ethyl 4-((1-methyl-2-oxoethyl)-3-nitrobenzoate Sodium bicarbonate (318 mg) was added to the mixture of ethyl 3-nitro-4-(2-oxoethyl)benzoate (401 mg) and MeI (426 mg) in DMF (5 ml), stirred for over night at r.t., diluted with ethyl acetate, washed with water and saturated saline water in that order, and dried with sodium sulfate. This was filtered, concentrated, and purified
through silica gel column (hexane/ethyl acetate) to give title compound (227 mg) as a colorless oil.

Reference Example 46
Ethyl 1,4-dimethoxy-3-methyl-1H-indole-6-carboxylate According to the methods of Reference Example 39, the intended compound was obtained as a colorless oil, but using ethyl 5-methoxy-4-(2-methyl-2-oxoethyl)-3-nitrobenzoate in place of ethyl 3-methoxy-5-nitro-4-(2-oxoethyl)benzoate.

Reference Example 47
tert-Butyl 6-f(l-methyl-lH-pyrazol-5-yl)amino-1-4-oxo-spiro[chroman-2,4'-piperidinel-6-carboxylate tert-Butyl 6-bromo-4-oxo-spiro[chroman-2,4'-piperidine]-r-carboxylate (16.3g), 5-amino-1-methyl-lH-pyrazole (4.00g), palladium acetate (922mg), 2-(di-t-butylphosphino)-biphenyl (1.23g) and cesium carbonate (16.1g) were suspended in 1,4-dioxane (20 mL), and heated under reflux at 110°C for 5 hours. The reaction liquid was filtered through Celite, the residue on the Celite was washed with chloroform, and the filtrate was concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (hexane/EtOAc) to obtain the intended compound as a yellow amorphous substance.

Reference Example 48
4-Oxospiro[chroman-2,4'-piperidine]-6-carboxylic acid carboxamoylmethyl amide hydrochloride
The intended compound was produced according to the Reference Example 17 but using 1'-tert-butoxycarbonyl-[4-oxospiro[chroman-2,4'-piperidine]-6-yl]-carboxylic acid N-carbamoyl-methylamide in place of tert-butyl 4-oxo-6-(lH-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-l'-carboxylate.

The usefulness of the compounds of the invention as medicines is demonstrated, for example, by the following pharmacological test example.

**BIOLOGICAL ASSAYS**

A. Pharmacological Test Example (acetyl CoA carboxylase (ACO activity inhibition test)

A test compound is dissolved in dimethyl sulfoxide (DMSO) to a concentration of 10 mM and then diluted with DMSO to give a 100-fold concentrated solution of the compound compared with target assay concentration. The ACC enzyme activity inhibition test is carried out according to a modification of Thampy & Wakil's method (*J. Biol. Chem.*, Vol. 260, pp. 6318-6323 (1985)). Concretely, 0.8μl of the diluted test compound is added to each well of 96-well assay plate (Perkin Elmer Opti Plate), then 40 μl of a substrate solution (50 mM Hepes sodium (pH 7.5), 2 mM DTT, 10 mM ATP, 500 μM acetyl CoA, 0.17 mM NaH[14C]0 3 (58 mCi/mmole,
by Amersham), 8 mM NaHCO3) is added to each well, and 40 µL of an enzyme solution (1 to 2 nM human ACC1 or human ACC2, 50 mM Hepes sodium (pH 7.5), 2 mM DTT, 40 mM MgCl2, 40 mM tripotassium citrate 1 mg/ml fetal bovine serum albumin) is added thereto. Then, the upper side of the plate is sealed up, and the plate is incubated with gently stirring at 37°C for 40 minutes. Next, 20 µl of 1 N HCl is added to each well to stop the enzyme reaction, and the assay plate is stirred overnight to remove the unreacted NaH[14C]O3. Next, 100 µl of a scintillator (Perkin Elmer's Microscinti 40) is added to each well and the plate is stirred, then the radioactivity of the fixed [14C] is counted using a microplate scintillation counter (Perkin Elmer's Topcount), the radioactivity of which represents the enzyme activity in each well. The human ACC1 and human ACC2 enzyme-inhibition activities of the test compounds are calculated, based on the radioactivity of the well added by DMSO without test compound as a control.

The compounds of the invention were tested according to this method and the compounds tested all inhibited both ACC1 and ACC2. The results are shown in the following Table. Inhibition (%) by 1 μmol/liter Chemical

<table>
<thead>
<tr>
<th>Compound</th>
<th>human ACC1</th>
<th>human ACC2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>91 %</td>
<td>89 %</td>
</tr>
<tr>
<td>Example 2</td>
<td>100 %</td>
<td>97 %</td>
</tr>
<tr>
<td>Example 3</td>
<td>99%</td>
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<tr>
<td>Example 4</td>
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<td>99%</td>
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<tr>
<td>Example 5</td>
<td>99 %</td>
<td>99%</td>
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<tr>
<td>Example 7</td>
<td>99 %</td>
<td>98%</td>
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<tr>
<td>Example 9</td>
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<td>99%</td>
</tr>
<tr>
<td>Example 12</td>
<td>99%</td>
<td>98%</td>
</tr>
<tr>
<td>Example 13</td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td>Example 16</td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td>Example 18</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Example 22</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Representative compounds of the present invention, including the compounds of Example 1-26, were tested in the above assay and found to have a percent inhibition of greater than or equal to 50% for ACC-1 and a percent inhibition of greater than or equal to 50% for ACC-2 in the acetyl CoA carboxylase (ACC) activity inhibition test.

B. Effect of ACC1/2 inhibitor on in vivo body weight, fat mass, fatty liver and plasma glucose levels
Effect of ACC 1/2 inhibitor on body weight, fat mass, fatty liver and plasma glucose level can be determined in either high fat diet induced obese or KKcy diabetic mice.

Male C57black/6J mice at approximately 6 weeks old are individually housed and maintained on chow diet for 2 weeks prior to the study. Then the mice are fed with a 60% fat diet for 5 weeks before dosing. The mice (n = 8) on the high fat diet are orally dosed with either vehicle control (0.5% methylcellulose solution) or an ACC 1/2 inhibitor (various doses) for 6 weeks. Body weight is determined on a daily basis and fat mass is measured by NMR every other week. Hepatic triglyceride content is determined at week 6. Effective ACC 1/2 inhibitors result reduced body weight gain, reduced fat mass gain, and reduced hepatic triglyceride content in ACC1/2 inhibitor treated male C57black/6J mice in contrast to the vehicle control group.

Male KKcy mice at approximately 8 weeks old are individually housed and maintained on for 2 weeks prior to the study. The mice (n = 10) are orally dosed with either vehicle control (0.5% methylcellulose solution) or an ACC 1/2 inhibitor (various doses) for 2 weeks. At week 2, blood is collected at 23 hours post dose and plasma glucose concentration is determined. Effective ACC 1/2 inhibitors result in reduced plasma glucose levels in ACC1/2 inhibitor treated KKcy mice in contrast to the vehicle control group.

C. Human study for effect on food intake and glucose/insulin levels

800 people with a BMI >30 who have impaired fasting plasma glucose levels, impaired glucose tolerance, or elevated serum insulin, indicative of a prediabetic insulin resistant state, and who may have elevated serum glucose levels, indicative of type II diabetes, are advised to diet and increase their physical activity. After a two-week placebo run-in period, which includes a standardized program of diet, physical activity, and lifestyle changes, the patients are randomized into 2 treatment groups: placebo; and an effective dose of a compound of formula (I). The compound of formula (I) is given once or more per day, as previously determined to be effective. Patients are treated for 6 months, body weights are measured biweekly, and appetite, hunger, satiety are measured weekly using standard questionnaires. Serum glucose, insulin levels and body weight are determined at day 0, monthly, and after the final dose.

Effective compounds result in body weight loss or an improvement in serum insulin levels, indicative of improved insulin sensitivity or lower fasting blood glucose levels.

Formulation Preparation Example 1:

20.0 g of the compound of Example 1, 1,417 g of lactose, 80 g of crystalline cellulose and 80 g of partially-alphatized starch are mixed in a V-shape mixer, and 3.0 g of magnesium stearate is added to it and mixed. The mixture powder is tableted according to an ordinary method to obtain 3000 tablets each having a diameter of 7.0 mm and a weight of 150 mg.
Ingredients of Tablet (150 mg)

<table>
<thead>
<tr>
<th>Compound of Example 1</th>
<th>5.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>104.25 mg</td>
</tr>
<tr>
<td>Crystalline cellulose</td>
<td>20.0 mg</td>
</tr>
<tr>
<td>Partially-alphatized starch</td>
<td>20.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.75 mg</td>
</tr>
</tbody>
</table>

Formulation Preparation Example 2:

10.8 g of hydroxypropyl cellulose 2910 and 2.1 g of polyethylene glycol 6000 are dissolved in 172.5 g of pure water, and 2.1 g of titanium oxide is dispersed therein to prepare a coating liquid. Using a high-coater-mini, 2500 tablets of Preparation Example 1 that is prepared separately is sprayed with the coating liquid to obtain film-coated tables each having a weight of 155 mg.

Ingredients of Tablet (155 mg)

<table>
<thead>
<tr>
<th>Tablet of Preparation Example 1</th>
<th>150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropyl cellulose 2910</td>
<td>3.6 mg</td>
</tr>
<tr>
<td>Polyethylene glycol 6000</td>
<td>0.7 mg</td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>0.7 mg</td>
</tr>
</tbody>
</table>

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the subject or mammal being treated obesity, diabetes, obesity-related disorders, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and embodiments of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.
WHAT IS CLAIMED IS:

1. A compound of a general formula (I):

   \[
   \text{(I)}
   \]

   wherein ArI represents a group formed from an aromatic ring selected from a group consisting of indole, benzimidazole and 1,2-benzisoxazole, having R3 and R4, and optionally having a substituent selected from a group consisting of a halogen atom, a hydroxyl group, a C1-C6 alkyl group, a halo-C1-C6 alkyl group, a hydroxy-C1-C6 alkyl group, a C1-C6 alkoxy group, a halo-C1-C6 alkoxy group and carbamoyl group; R1 represents a phenyl group optionally substituted with a carboxyl group, a tetrazolyl group optionally substituted with a carboxyl group or a pyridyl group optionally substituted with a C1-C6 alkoxy group; and R2 represents a hydrogen atom, a halogen atom, a C1-C6 alkyl group, or a C1-C6 alkoxy group; and R3 and R4 each independently represent a hydrogen atom, a halogen atom, nitro group, a cyclo-C3-C6 alkyl group, a carbamoyl group optionally substituted with a C1-C6 alkyl or cyclo-C3-C6 alkyl group, a C1-C6 alkoxy group optionally substituted with a hydroxyl group, or a pharmaceutically acceptable salt or ester thereof.

2. The compound as claimed in claim 1, or a pharmaceutically acceptable salt or ester thereof, wherein ArI represents a group formed from indole.

3. The compound as claimed in claim 1, or a pharmaceutically acceptable salt or ester thereof, wherein R1 is a phenyl group substituted with a carboxyl group; a tetrazolyl group; or a pyridyl group substituted with a carboxyl group.

4. The compound as claimed in claim 1, or a pharmaceutically acceptable salt or ester thereof, wherein R1 is a pyridyl group substituted with a carboxyl group.
5. The compound as claimed in claim 1, or a pharmaceutically acceptable salt or ester thereof, wherein R3 is a C1-C6 alkoxy group optionally substituted with a hydroxyl group; and R4 is a cyclo-C3-C6 alkyl group, a C1-C6 alkoxy group or a C1-C6 alkyl group.

6. The compound as claimed in claim 1, or a pharmaceutically acceptable salt or ester thereof, which is selected from the following:

(1) 1'-(1-Ethyl-4-methoxy-1H-benzimidazol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one,
(2) 1'-(1-Cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)spiro[chroman-2,4'-piperidine]-4-one,
(3) Sodium 3-[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidine]-6-yl benzoate,
(4) 5-(r-[1-Cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidine]-6-yl] nicotinic acid sodium salt,
(5) 1'-[(1,4-Dimethoxy-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one,
(6) 1'-(1-Cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one sodium salt,
(7) 1'-[(1-Cyclopropyl-4-ethoxy-3-methyl-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one,
(8) 5-[r-[1-Cyclopropyl-4-ethoxy-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidine]-6-yl] nicotinic acid sodium salt,
(9) 5-1'-[1-Cyclopropyl-4-methoxy-3-methyl-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidine]-6-yl] nicotinic acid sodium salt,
(10) 5-1'-[3-Chloro-1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidine]-6-yl] nicotinic acid sodium salt,
(11) 5-1'-[1-Cyclopropyl-4-methoxy-3-methyl-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidine]-6-yl] nicotinic acid,
(12) r-[3-cyclopropyl-7-ethoxy-1,2-benzisoxazol-5-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one,
(13) 1-cyclopropyl-4-ethoxy-6-[[4-oxo-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidm]r-yl]carbonyl]-1H-indole-3-carboxamide,
(14) 1'-[1-cyclopropyl-4-(2-hydroxyethoxy)-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidine]-4-one,
(15) 3-(1'-[3-carbamoyl-1-cyclopropyl-4-ethoxy-1H-indol-6-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidine]-6-yl] benzoic acid,
7. A compound which is 3-{1'-[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl}benzoic acid, or a pharmaceutically acceptable salt or ester thereof.

8. A compound which is 5-{1'-[(1-cyclopropyl-M-methoxy-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl}nicotinic acid, or a pharmaceutically acceptable salt or ester thereof.

9. A compound which is 1'-[(1-cyclopropyl-4-methoxy-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one, or a pharmaceutically acceptable salt thereof.

10. A compound which is 1'-[(1-cyclopropyl-4-ethoxy-3-methyl-1H-indol-6-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one, or a pharmaceutically acceptable salt thereof.

11. A compound which is 5-{1'-[(1-cyclopropyl-4-methoxy-3-methyl-1H-indol-6-yl)carbonyl]-4-oxo-spiro[chroman-2,4'-piperidin]-6-yl} nicotinic acid, or a pharmaceutically acceptable salt or ester thereof.
12. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable additive.

13. A therapeutical agent for the treatment of metabolic syndrome, fatty liver, hyperlipemia, obesity, diabetes, bulimia, malignant neoplasm or infectious diseases, which comprises the pharmaceutical composition of claim 12.

14. Use of the compound of claim 1 or a pharmaceutically acceptable salt or ester thereof for manufacturing a medicament for the treatment of metabolic syndrome, fatty liver, hyperlipemia, obesity, diabetes, bulimia, malignant neoplasm or infectious diseases.
# INTERNATIONAL SEARCH REPORT

**PCT/US2008/000223**

## A. CLASSIFICATION OF SUBJECT MATTER

| INV. | C07D491/10 | A61K31/438 | A61P3/00 |

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

- C07D
- A61K
- A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

- EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.  
[X] See patent family annex.

Special categories of cited documents:

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
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Date of the actual completion of the international search: 23 April 2008  
Date of mailing of the international search report: 13/05/2008

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. 31651 epo nl,  
Fax. (+31-70) 340-3016

Marzi, Elena
**INTERNATIONAL SEARCH REPORT**

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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