Diarylcycloalkyl derivatives, method for their production and their use as medicaments

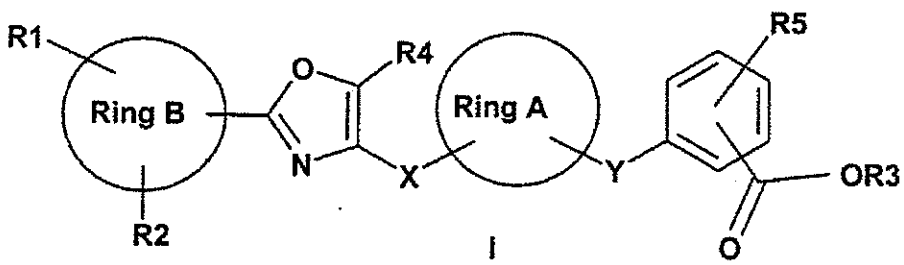
The invention relates to diarylcycloalkyl derivatives and to their physiologically acceptable salts and physiologically functional derivatives.

Compounds of a similar structure have already been described in the prior art for the treatment of hyperlipidemia and diabetes (WO 2000/64876 and WO 03/020269).

It was an object of the invention to provide compounds which allow a therapeutically exploitable modulation of lipid and/or carbohydrate metabolism, and are thus suitable for the prevention and/or treatment of diseases such as type 2 diabetes and atherosclerosis and their various sequelae.

Surprisingly, a series of compounds which modulate the activity of PPAR receptors has been found. In particular, the compounds are suitable for the activation of PPARalpha and PPARgamma, and the extent of the relative activation can be different depending on the compounds.

Accordingly, the invention relates to compounds of the formula I



I

in which

Ring A is $(C_3$-$C_8)$-cycloalkanediyl or $(C_3$-$C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl; or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3$-$C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

c) in the case ring B = a) and R4 = phenyl:
$(C_1$-$C_6)$-alkyl or O-$(C_1$-$C_6)$-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

c) in the case ring B = a) and R1 = a):
$(C_1$-$C_6)$-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is $(C_1\text{-}C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

Y is $(C_1\text{-}C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

and their physiologically acceptable salts.

Preference is given to compounds of the formula I in which

Ring A is $(C_3\text{-}C_8)$-cycloalkanediyl or $(C_3\text{-}C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3\text{-}C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, $OCF_2\text{-}CHF_2$, O-phenyl, O-$(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_3)$-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $OCF_2\text{-}CF_3$, SCF_3, $OCF_2\text{-}CHF_2$, O-phenyl, $(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_3)$-alkyl;

c) in the case ring B = a) and R4 = phenyl:
$(C_1\text{-}C_6)$-alkyl or O-$(C_1\text{-}C_6)$-alkyl;

R is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

c) in the case ring B = a) and R1 = a):
$(C_1$-$C_6)$-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is CH_2-O;

Y is $(C_1$-$C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms.

Preference is furthermore given to compounds of the formula I in which

Ring A is $(C_3$-$C_8)$-cycloalkanediyl in which one carbon atom may be replaced by an oxygen atom;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3$-$C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

b) in the case ring B = b):

H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1 = a):
(C_1-C_6)-alkyl;

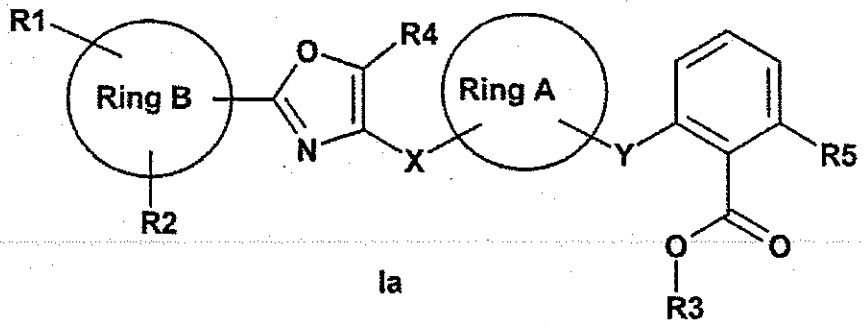
R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

R3 is H or (C_1-C_6)-alkyl;

X is CH_2-O;

Y is CH_2-O.

Particular preference is given to compounds of the formula Ia



Ia

in which ring A, ring B, R1, R2, R3, R4, R5, X and Y are as defined above.

Particular preference is furthermore given to compounds of the formula Ia in which

R3 is H and

R5 is methyl

or

to compounds of the formula Ia in which

Ring A is (C_5-C_7)-cycloalkanediyl;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or (C_3-C_8)-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2,

O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1/R2 = a):
(C_1-C_6)-alkyl;

R5 is methyl;

R3 is H;

X is CH_2-O;

Y is CH_2-O.

Very particular preference is given to compounds of the formulae I and Ia

in which the central cycloalkanediyl ring is attached 1,3-cis.

The present invention also encompasses all combinations of the "preferred embodiments" of the invention described herein.

The alkyl radicals in the substituents R1, R2, R3, R4 and R5 can be straight-chain

or branched.

Aryl is to be understood as meaning an aromatic, carbocyclic, mono- or bicyclic ring system which contains from 6 to 10 atoms in the ring or in the rings.

Heteroaryl is a mono- or bicyclic, aromatic ring system having from 4 to 11 ring members, in which at least one atom in the ring system is a heteroatom from the group of N, O and S.

The compounds of the formula I contain at least two centers of asymmetry and may contain more. The compounds of the formula I may therefore be present in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and diastereomer mixtures. The present invention encompasses all of these isomeric forms of the compounds of the formula I. These isomeric forms may, even when some of them are not described expressis verbis, be obtained by known methods.

Pharmaceutically acceptable salts are particularly suitable for medical applications because of their greater solubility in water compared with the starting or base compounds. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acids. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts) and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the scope of the invention as useful

intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula I of the invention, for example an ester which is able, on administration to a mammal such as, for example, to a human, to form (directly or indirectly) a compound of the formula I or an active metabolite thereof.

Physiologically functional derivatives also include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves have activity or not.

The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the scope of the invention and are a further aspect of the invention.

All references hereinafter to "compound(s) of formula I" refer to compound(s) of the formula I as described above, and to the salts, solvates and physiologically functional derivatives thereof as described herein.

Use

This invention relates further to the use of compounds of the formula I and their pharmaceutical compositions as PPAR receptor ligands. The PPAR receptor ligands of the invention are suitable as modulators of the activity of the PPAR receptors.

Peroxisome proliferator-activated receptors (PPAR) are transcription factors which can be activated by ligands and belong to the class of nuclear hormone receptors. There are three PPAR isoforms, PPARalpha, PPARgamma and PPARdelta, which are encoded by different genes (Peroxisome proliferator-activated receptor

(PPAR): structure, mechanisms of activation and diverse functions: Motojima K, Cell Struct Funct., 1993 Oct, 18(5), 267-77).

There exist two variants of PPARgamma, PPARgamma$_1$ and -gamma$_2$, which are the result of alternative use of promoters and differential mRNA splicing (Vidal-Puig et al., J. Clin. Invest., 97:2553-2561, 1996). The various PPAR receptors have a different tissue distribution and modulate different physiological functions. The PPAR receptors play a key role in different aspects of the regulation of a multitude of genes, whose gene products are crucially involved directly or indirectly in lipid and carbohydrate metabolism. Thus, for example, PPARalpha receptors play an important role in the regulation of fatty acid catabolism or lipoprotein metabolism in the liver, while PPARgamma is crucially involved, for example, in the regulation of adipose cell differentiation.

In addition, PPAR receptors are also involved in the regulation of many further physiological processes, including those which are not directly connected with carbohydrate or lipid metabolism. The activity of the different PPAR receptors can be modulated to varying extents by various fatty acids, fatty acid derivatives and synthetic compounds. For relevant reviews concerning functions, physiological effect and pathophysiology, see: Joel Berger et al., Annu. Rev. Med., 2002, 53, 409 – 435; Timothy Wilson et al., J. Med. Chem., 2000, Vol. 43, No. 4, 527-550; Steven Kliewer et al., Recent Prog Horm Res., 2001, 56, 239-63.

The present invention relates to compounds of the formula I which are suitable for modulating the activity of PPAR receptors, especially the activity of PPARalpha and PPARgamma. Depending on the profile of the modulation, the compounds of the formula I are suitable for the treatment, control and prophylaxis of the indications described hereinafter, and for a series of other, connected pharmaceutical applications (see, for example, Joel Berger et al., Annu. Rev. Med., 2002, 53, 409 – 435; Timothy Wilson et al., J. Med. Chem., 2000, 43(4), 527-550; Steven Kliewer et al., Recent Prog Horm Res., 2001, 56, 239-63; Jean-Charles Fruchart, Bart Staels and Patrick Duriez: PPARS, Metabolic Disease and Arteriosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52, 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease, NATURE, VOL. 405, 25 MAY 2000, 421-424; Ines Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome

proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12:2001, 245-254).

Compounds of this type are particularly suitable for the treatment and/or prevention of

1. - disorders of fatty acid metabolism and glucose utilization disorders
   - disorders in which insulin resistance plays a role

2. Diabetes mellitus, in particular type 2 diabetes, including the prevention of the associated sequelae.
   Particular aspects in this connection are
   - hyperglycemia,
   - improvement in insulin resistance,
   - improvement in glucose tolerance,
   - protection of the β-cells of the pancreas
   - prevention of macro- and microvascular disorders

3. Dyslipidemias and their sequelae, such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders, etc, especially those (but not restricted to those) which are characterized by one or more of the following factors:
   - high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations,
   - low HDL cholesterol concentration
   - low ApoA lipoprotein concentrations
   - high LDL cholesterol concentrations
   - small dense LDL cholesterol particles
   - high ApoB lipoprotein concentrations

4. Various other conditions which may be associated with metabolic syndrome are such as:
   - obesity (excess weight), including central obesity
   - thromboses, stages of hypercoagulability and prothrombosis (arterial and

venous)
- high blood pressure
- heart failure, such as, for example, (but not restricted to that) in the state after myocardial infarction, hypertensive heart disease or cardiomyopathy

5. Further disorders or conditions in which, for example, inflammatory processes or cell differentiation play a role:
   - Atherosclerosis, such as, for example, (but not restricted to) coronary sclerosis including angina pectoris or myocardial infarction, stroke
   - vascular restenosis or reocclusion
   - chronic inflammatory bowel diseases, such as, for example, Crohn's disease and ulcerative colitis
   - pancreatitis
   - other inflammatory states
   - retinopathy
   - adipose cell tumors
   - lipomatous carcinomas such as, for example, liposarcomas
   - solid tumors and neoplasms, such as, for example, (but not restricted to) carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumors, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas, etc.
   - acute and chronic myeloproliferative disorders and lymphomas
   - angiogenesis
   - neurodegenerative diseases
   - Alzheimer's disease
   - multiple sclerosis
   - Parkinson's disease
   - erythemato-squamous dermatoses such as, for example, psoriasis
   - acne vulgaris
   - other skin disorders and dermatological conditions which are modulated by PPAR
   - eczemas and neurodermatitis
   - dermatitis, such as, for example, seborrheic dermatitis or photodermatitis

- keratitis and keratoses, such as, for example, seborrheic keratoses, senile keratoses, actinic keratosis, photo-induced keratoses or keratosis follicularis
- keloids and keloid prophylaxis
- warts, including condylomata or condylomata acuminata
- human papilloma virus (HPV) infections, such as, for example, venereal papillomata, viral warts, such as, for example, molluscum contagiosum, leukoplakia
- papular dermatoses, such as, for example, lichen planus
- skin cancer, such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas
- localized benign epidermal tumors, such as, for example, keratoderma, epidermal naevi
- chilblains
- high blood pressure
- syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic disorders, such as, for example, rheumatoid arthritis
- vasculitis
- wasting (cachexia)
- gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS) ("shock lung")

Formulation

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of body weight,

for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active compound. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active compound. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical preparations for oral administration may be in the form of separate units such as, for example, capsules, wafers, suckable tablets or tablets, each of which contain a defined amount of the compound of formula I; as powders or granules, as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active compound and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one or more surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound which is in powder form and is moistened with an inert liquid diluent in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the

invention generally contain from 0.1 to 5% by weight of the active compound.

Pharmaceutical compositions suitable for rectal administration are preferably in the form of single-dose suppositories. These can be produced by mixing a compound of the formula I with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, crème, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active compound is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active compound in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active compound concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active compound to be released by electrotransport or iontophoresis as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The compounds of the formula I act favorably on metabolic disorders. They have a positive effect on lipid and sugar metabolism and, in particular, reduce the concentration of triglycerides, and they are suitable for preventing and treating type II diabetes and arteriosclerosis and their various sequelae.

Combinations with other medicaments

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances which have, for example,

favorable effects on metabolic disorders or diseases frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active compounds
6. active compounds for the treatment of malignant tumors
7. antithrombotic active compounds
8. active compounds for the treatment of high blood pressure
9. active compounds for the treatment of heart failure and
10. active compounds for the treatment and/or prevention of complications caused by diabetes or associated with diabetes.

They may be combined with the compounds of the formula I according to the invention in particular for synergistic improvement of the effect. Administration of the active compound combination may take place either by separate administration of the active compounds to the patients or in the form of combination products in which a plurality of active compounds are present in one pharmaceutical preparation.

Examples which may be mentioned are:

Antidiabetics

Suitable antidiabetics are disclosed, for example, in the Rote Liste 2001, chapter 12 or in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2003. Antidiabetics include all insulins and insulin derivatives, such as, for example, Lantus® (see www.lantus.com) or Apidra®, and other fast-acting insulins (see US 6,221,633), GLP-1 receptor modulators as described in WO 01/04146 or else, for example, those disclosed in WO 98/08871 of Novo Nordisk A/S.

The orally active hypoglycemic active compounds include, preferably,

sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, oral GLP-1 agonists, DPP-IV inhibitors, potassium channel openers such as, for example, those disclosed in WO 97/26265 and WO 99/03861, insulin sensitizers, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which alter lipid metabolism and lead to a change in the lipid composition of the blood, compounds which reduce food intake or food absorption, PPAR and PXR modulators and active compounds which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compounds of the formula I are administered in combination with insulin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with substances which influence the hepatic glucose production, such as, for example glycogen phosphorylase inhibitors (c.f.: WO 01/94300, WO 02/096864, WO 03/084923, WO 03/084922, WO 03/104188).

In one embodiment, the compounds of the formula I are administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

In another embodiment, the compounds of the formula I are administered in combination with a meglitinide, such as, for example, repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione, such as, for example, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 of Dr. Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment, the compounds of the formula I in combination with a DPPIV inhibitor, as described, for example, in WO98/19998, WO99/61431, WO99/67278, WO99/67279, WO01/72290, WO 02/38541, WO03/040174, in particular P 93/01 (1-cyclopentyl-3-methyl-1-oxo-2-pentanammonium chloride), P-31/98, LAF237 (1-[2-[3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2-(S)-carbonitrile), TS021 ((2S, 4S)-4-fluoro-1-[[(2-hydroxy-1,1-dimethylethyl)amino]acetyl]pyrrolidine-2-carbonitrile monobenzenesulfonate).

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist such as, for example, rosiglitazone, pioglitazone.

In one embodiment, the compounds of the formula I are administered in combination with compounds with an inhibitory effect on SGLT-1 and/or 2, as disclosed directly or indirectly, for example, in PCT/EP03/06841, PCT/EP03/13454 and PCT/EP03/13455.

In one embodiment, the compounds of the formula I are administered in combination with an α-glucosidase inhibitor such as, for example, miglitol or acarbose.

In one embodiment, the compounds of the formula I are administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Lipid modulators

In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA reductase inhibitor such as lovastatin, fluvastatin, pravastatin, simvastatin, ivastatin, itavastatin, atorvastatin, rosuvastatin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid absorption inhibitor (see, for example, US 6,245,744, US 6,221,897, US 6,277,831, EP 0683 773, EP 0683 774).

In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorber, such as, for example, cholestyramine, colesevelam.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor as described for example in WO 0250027, or ezetimibe, tiqueside, pamaqueside.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer (see, for example, US 6,342,512).

In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main)). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products, such as, for example, in bakery products or muesli bars.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPARalpha agonist.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, such as, for example, AZ 242 (Tesaglitazar, (S)-3-(4-[2-(4-methanesulfonyloxyphenyl)-ethoxy]phenyl)-2-ethoxypropionic acid), BMS 298585 (N-[(4-methoxyphenoxy)-carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine) or as described in WO 99/62872, WO 99/62871, WO 01/40171, WO 01/40169, WO96/38428, WO 01/81327, WO 01/21602, WO 03/020269, WO 00/64888 or WO 00/64876.

In one embodiment of the invention, the compounds of the formula I are

administered in combination with a fibrate such as, for example, fenofibrate, gemfibrozil, clofibrate, bezafibrate.

In one embodiment of the invention, the compounds of the formula I are administered in combination with nicotinic acid or niacin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, for example CP-529, 414 (torcetrapib).

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor, such as, for example, implitapide.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP citrate lyase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist.

Antiobesity agents

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor such as, for example, orlistat.

In one embodiment, the further active compound is fenfluramine or dexfenfluramine. In another embodiment, the further active ingredient is sibutramine.

In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.:Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists (for example N-{4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}-naphthalene-1-sulfonamide hydrochloride (CGP 71683A)), MC4 agonists (for example N-[2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-tetra-hydronaphthalene-2-carboxamide (WO 01/91752)), orexin antagonists (for example 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A)), H3 agonists (for example 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (for example [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (for example urocortin), urocortin agonists, β3 agonists (for example 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-di-methyl-1H-indol-6-yloxy)ethylamino]ethanol hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (for example {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)); serotonin reuptake inhibitors (for example dexfenfluramine), mixed serotoninergic and noradrenergic compounds (for example WO 00/71549), 5HT agonists (for example 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111)), bombesin agonists, galanin antagonists, growth hormone (for example human growth hormone), growth-hormone-releasing compounds (tert-butyl 6-benzyloxy-

1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), decoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881), DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors (for example WO 00/40569), PPAR modulators (for example WO 00/78312), RXR modulators or TR β agonists.

In one embodiment of the invention, the other active compound is leptin.

In one embodiment, the other active compound is dexamphetamine, amphetamine, mazindole or phentermine.

In one embodiment, the compounds of the formula I are administered in combination with medicaments having effects on the coronary circulation and the vascular system, such as, for example, ACE inhibitors (e.g. ramipril), medicaments which act on the angiotensin-renin system, calcium antagonists, beta blockers etc.

In one embodiment, the compounds of the formula I are administered in combination with medicaments having an antiinflammatory effect.

In one embodiment, the compounds of the formula I are administered in combination with medicaments which are employed for cancer therapy and cancer prevention.

It will be appreciated that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more further pharmacologically active substances is regarded as falling within the protection conferred by the present invention.

The activity of the compounds was tested as follows:

Determination of EC50 values of PPAR agonists in the cellular PPARalpha test

Principle

The potency of substances which bind to human PPARalpha and activate it in an agonistic manner is analyzed using a stably transfected HEK cell line (HEK = human embryo kidney) which is referred to here as PPARalpha reporter cell line. It contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) which mediates expression of the luciferase reporter element depending on a PPARalpha ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARalpha-LBD binds in the cell nucleus of the PPARalpha reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is integrated in the genome of the cell line. There is only little expression of the luciferase reporter gene without addition of a PPARalpha ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the test. PPARalpha ligands bind and activate the PPARalpha fusion protein and thereby bring about expression of the luciferase reporter gene. The luciferase which is formed can be detected by means of chemiluminescence via an appropriate substrate.

Construction of the cell line

The PPARalpha reporter cell line was prepared in two steps. Firstly, the luciferase reporter element was constructed and stably transfected into HEK cells. For this purpose, five binding sites of the yeast transcription factor GAL4 (in each case 5'-(GGAGTACTGTCCTCCGAG-3') were cloned in 5'-upstream of a 68 bp-long minimal MMTV promoter (Accession # V01175). The minimal MMTV promoter section contains a CCAAT box and a TATA element in order to enable efficient transcription by RNA polymerase II. The cloning and sequencing of the GAL4-MMTV construct took place in analogy to the description of Sambrook J. et. al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Then the

complete Photinus pyralis luciferase gene (Accession # M15077) was cloned in 3'-downstream of the GAL4-MMTV element. After sequencing, the luciferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene was recloned into a plasmid which confers zeozin resistance in order to obtain the plasmid pdeltaM-GAL4-Luc-Zeo. This vector was transfected into HEK cells in accordance with the statements in Ausubel, F.M. et al. (Current protocols in molecular biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Then zeozin-containing medium (0.5 mg/ml) was used to select a suitable stable cell clone which showed very low basal expression of the luciferase gene.

In a second step, the PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) was introduced into the stable cell clone described. For this purpose, initially the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Accession # P04386). The cDNA of the ligand-binding domain of the human PPARalpha receptor (amino acids S167-Y468; Accession # S74349) was cloned in at the 3' end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-human-PPARalpha-LBD) was recloned into the plasmid pcDNA3 (from Invitrogen) in order to enable constitutive expression therein by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase reporter element. The finished PPARalpha reporter cell line which contains a luciferase reporter element and constitutively expresses the PPARalpha fusion protein (GR-GAL4-human PPARalpha-LBD) was isolated by selection with zeozin (0.5 mg/ml) and G418 (0.5 mg/ml).

Test procedure

The activity of PPARalpha agonists is determined in a three-day test, described below:

Day 1

The PPARalpha reporter cell line is cultivated up to 80% confluence in DMEM

medium (# 41965-039, Invitrogen) with the following additives: 10% cs-FCS (fetal calf serum, #SH-30068.03, Hyclone), 0.5 mg/ml of zeozin (#R250-01, Invitrogen), 0.5 mg/ml of G418 (#10131-027, Invitrogen), 1% penicillin streptomycin solution (#15140-122, Invitrogen) and 2 mM of L-glutamine (#25030-024, Invitrogen). Cultivation is carried out in standard cell culture bottles (# 353112, Becton Dickinson) in a cell culture incubator at 37°C in the presence of 5% CO_2. The 80% confluent cells are washed once with 15 ml of PBS (#14190-094, Invitrogen), treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min, taken up in 5 ml of the DMEM medium described and counted in a cell counter. After dilution to 500 000 cells/ml, in each case 35 000 cells are sown into each well of a 96-well microtiter plate having a clear plastic bottom (#3610, Corning Costar). The plates are incubated in a cell incubator at 37°C and 5% CO_2 for 24 h.

Day 2

The PPARalpha agonists to be tested are dissolved in DMSO at a concentration of 10 mM. This stock solution is diluted in DMEM medium (#41965-039, Invitrogen) to which 5% of cs-FCS (#SH-30068.03, Hyclone), 2 mM of L-glutamine (#25030-024, Invitrogen) and the antibiotics already described (zeozin, G418, penicillin and streptomycin) had been added.

Test substances are tested at 11 different concentrations in the region of 10 µM to 100 pM. More potent compounds are tested in concentration ranges of from 1 µM to 10 pM or between 100 nM and 1 pM.

The medium of the PPARalpha reporter cell line sown on day 1 is completely removed by aspiration, and immediately, the test substances diluted in medium are added to the cells. Dilution and addition of the substances are carried out using a robot (Beckman FX). The end volume of the test substances diluted in medium is 100 µl per well of a 96-well microtiter plate. The DMSO concentration in the test is below 0.1% v/v to prevent cytotoxic effects of the solvent.

To demonstrate that the test is working in each individual plate, a standard PPARalpha agonist, which is also diluted to 11 different concentrations, is added to each plate. The test plates are incubated in an incubator at 37°C and 5% CO_2 for 24 h.

Day 3

The PPARalpha reporter cells treated with the test substances are removed from the incubator and the medium is aspirated off. The cells are lyzed by pipetting 50 µl of Bright Glo reagent (from Promega) into each well of a 96 well microtiter plate. After incubation at room temperature in the dark for 10 minutes, the microtiter plates are measured in the luminometer (Trilux from Wallac). The measuring time for each well of a microtiter plate is 1 sec.

Evaluation

The crude data of the apparatus for measuring luminescence are exported into a Microsoft Excel file. Dose-activity curves and EC50 values of PPAR agonists are calculated using the program XL.Fit according to the instructions of the manufacturer (IDBS).

The PPARalpha EC50 values for the compounds of examples 1 to 13 in this assay are in the range of from 0.05 nM to > 10 µM.

The results for the activity of some compounds of the formula I according to the invention are listed in table I below:

Table I

Example No.	**EC50 PPARalpha [nM]**
I	0.2
III	0.2
IV	0.6
X	0.3
XI	34
XII	26
XIII	0.06

It is evident from table I that the compounds of the formula I according to the invention activate the PPARalpha receptor, thus effecting, for example, analogously to clinically used fibrates, a lowering of the triglyceride concentration in the organism (see, for example, J.-Ch. Fruchard et al.: PPARS, Metabolic Disease and Atherosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52, 2001; S. Kersten et al.: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000, 421-4; I. Pineda et al.: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

Determination of EC50 values of PPAR agonists in the cellular PPARgamma test

Principle

A transient transfection system is employed to determine the cellular PPARgamma activity of PPAR agonists. It is based on the use of a luciferase reporter plasmid (pGL3basic-5xGAL4-TK) and of a PPARgamma expression plasmid (pcDNA3-GAL4-humanPPARgammaLBD). Both plasmids are transiently transfected into human embryonic kidney cells (HEK cells). There is then expression in these cells of the fusion protein GAL4-humanPPARgammaLBD which binds to the GAL4 binding sites of the reporter plasmid. In the presence of a PPARgamma-active ligand, the activated fusion protein GAL4-humanPPARgammaLBD induces expression of the luciferase reporter gene, which can be detected in the form of a chemiluminescence signal after addition of a luciferase substrate. As a difference from the stably transfected PPARalpha reporter cell line, in the cellular PPARgamma test the two components (luciferase reporter plasmid and PPARgamma expression plasmid) are transiently transfected into HEK cells because stable and permanent expression of the PPARgamma fusion protein is cytotoxic.

Construction of the plasmids

The luciferase reporter plasmid pGL3basic-5xGAL4-TK is based on the vector pGL3basic from Promega. The reporter plasmid is prepared by cloning five binding sites of the yeast transcription factor GAL4 (each binding site with the sequence 5´-CTCGGAGGACAGTACTCCG-3´), together with a 160 bp-long thymidine kinase promoter section (Genbank Accession # AF027128) 5'-upstream into pGL3basic. 3'-downstream of the thymidine kinase promoter is the complete luciferase gene from Photinus pyralis (Genbank Accession # M15077) which is already a constituent of the plasmid pGL3basic used. The cloning and sequencing of the reporter plasmid pGL3basic-5xGAL4-TK took place in analogy to the description in Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989).

The PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD was prepared by first cloning the cDNA coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386) into the plasmid pcDNA3 (from Invitrogen) 3´-downstream of the cytomegalovirus promoter. Subsequently, the cDNA of the ligand-binding domain (LBD) of the human PPARgamma receptor (amino acids I152-Y475; Accession # g1480099) was cloned 3'-downstream of the GAL4 DNA binding domain. Cloning and sequencing of the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD again took place in analogy to the description in Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Besides the luciferase reporter plasmid pGL3basic-5xGAL4-TK and the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD, also used for the cellular PPARgamma test are the reference plasmid pRL-CMV (from Promega) and the plasmid pBluescript SK(+) from Stratagene. All four plasmids were prepared using a plasmid preparation kit from Qiagen, which ensured a plasmid quality with a minimal endotoxin content, before transfection into HEK cells.

Test procedure

The activity of PPARgamma agonists is determined in a 4-day test which is described below. Before the transfection, HEK cells are cultivated in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% FCS

(#16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen).

Day 1

Firstly, solution A, a transfection mixture which contains all four plasmids previously described in addition to DMEM, is prepared. The following amounts are used to make up 3 ml of solution A for each 96 well microtiter plate for one test: 2622 µl of antibiotic- and serum-free DMEM (# 41965-039, Invitrogen), 100 µl of reference plasmid pRL-CMV (1 ng/µl), 100 µl of luciferase reporter plasmid pGL3basic-5xGAL4-TK (10 ng/µl), 100 µl of PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD (100 ng/µl) and 78 µl of plasmid pBluescript SK(+) (500 ng/µl). Then 2 ml of solution B are prepared by mixing 1.9 ml of DMEM (# 41965-039, Invitrogen) with 100 µl of PolyFect transfection reagent (from Qiagen) for each 96 well microtiter plate. Subsequently, 3 ml of solution A are mixed with 2 ml of solution B to give 5 ml of solution C, which is thoroughly mixed by multiple pipetting and incubated at room temperature for 10 min.
80%-confluent HEK cells from a cell culture bottle with a capacity of 175 cm^2 are washed once with 15 ml of PBS (#14190-094, Invitrogen) and treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min. The cells are then taken up in 15 ml of DMEM (# 41965-039, Invitrogen) which is mixed with 10% FCS (# 16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). After the cell suspension has been counted in a cell counter, the suspension is diluted to 250,000 cells/ml. 15 ml of this cell suspension are mixed with 5 ml of solution C for one microtiter plate. 200 µl of the suspension are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in a cell culture incubator at 37°C and 5% CO_2 for 24 h.

Day 2

PPAR agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (# 41965-039, Invitrogen) which is mixed with 2% Ultroser (#12039-012, Biosepra), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). Test

substances are tested in a total of 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM.

The medium of the HEK cells transfected and seeded on day 1 is completely removed by aspiration, and the test substances diluted in medium are immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 µl per well of a 96 well microtiter plate. Each plate is charged with a standard PPARgamma agonist, which is likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the test in each individual plate. The test plates are incubated in an incubator at 37°C and 5% CO_2 for 48h.

Day 4

After removal of the medium by aspiration, 50 µl of Dual-Glo™ reagent (Dual-Glo™ Luciferase Assay System; Promega) are added to each well in accordance with the manufacturer's instructions in order to lyze the cells and provide the substrate for the firefly luciferase (Photinus pyralis) formed in the cells. After incubation at room temperature in the dark for 10 minutes, the firefly luciferase-mediated chemiluminescence is measured in a measuring instrument (measuring time/well 1 sec; Trilux from Wallac). Then 50 µl of the Dual-Glo™ Stop & Glo reagent (Dual-Glo™ Luciferase Assay System; Promega) is added to each well in order to stop the activity of the firefly luciferase and provide the substrate for the Renilla luciferase expressed by the reference plasmid pRL-CMV. After incubation at room temperature in the dark for a further 10 minutes, a chemiluminescence mediated by the Renilla luciferase is again measured for 1 sec/well in the measuring instrument.

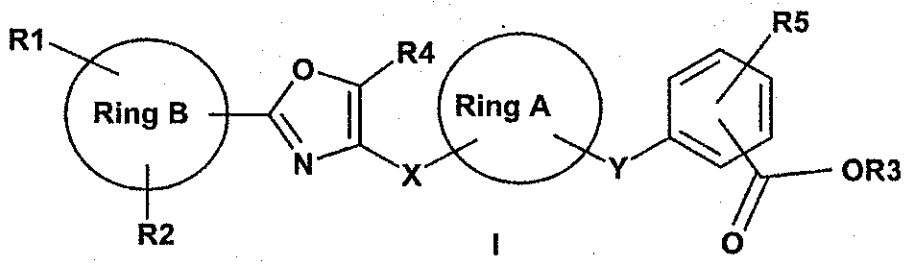
Evaluation

The crude data from the luminometer are transferred into a Microsoft Excel file. The firefly/Renilla luciferase activity ratio is determined for each measurement derived from one well of the microtiter plate. The dose-effect plots and EC50 values of PPAR agonists are calculated from the ratios by the XL.Fit program as

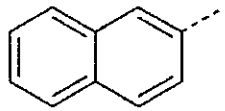
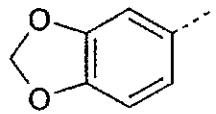
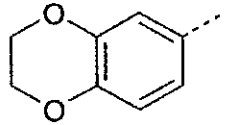
specified by the manufacturer (IDBS).

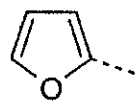
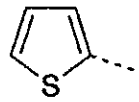
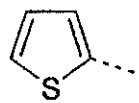
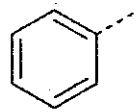
PPARgamma EC50 values in the range from 0.5 nM to >10 µM were measured for the PPAR agonists described in this application.

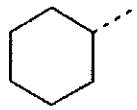
The examples given below serve to illustrate the invention, but without limiting it.



I

	R1	R2	Ring B	R4	X	Ring A	Y	R3	R5
I	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
II	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
III	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me

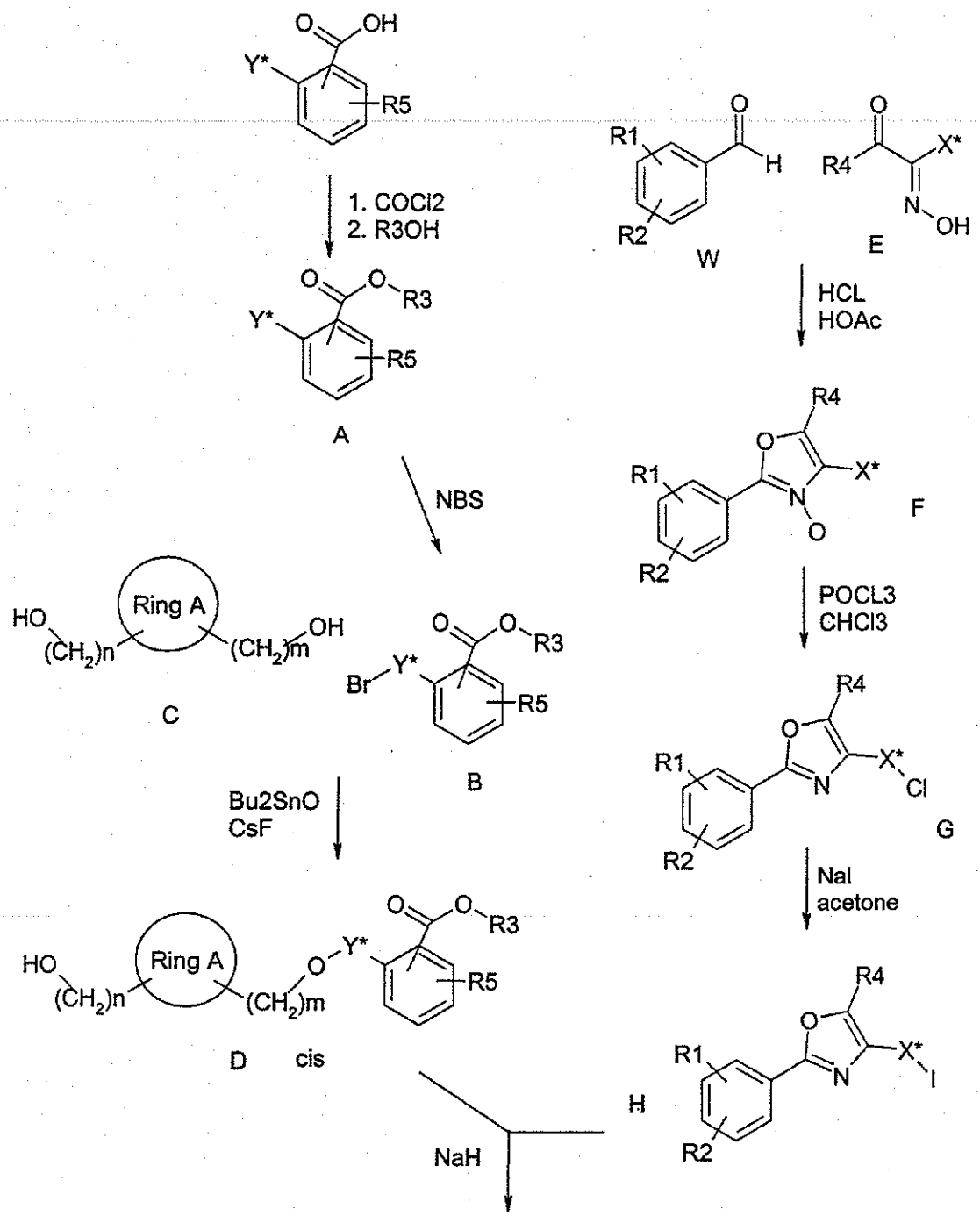
	R1	R2	Ring B	R4	X	Ring A	Y	R3	R5
IV	5-Me	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
V	5-Me	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
VI	4-SCF3	H	Ph	Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
VII	3-OCF2-CF2H	H	Ph	Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
VIII	4-OPh	H	Ph	Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
IX	H	H		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me
X	3-O-C2H4-O-Me	5-CF3		Me	CH2O	cis 1,3 Cy	CH2O	H	6-Me

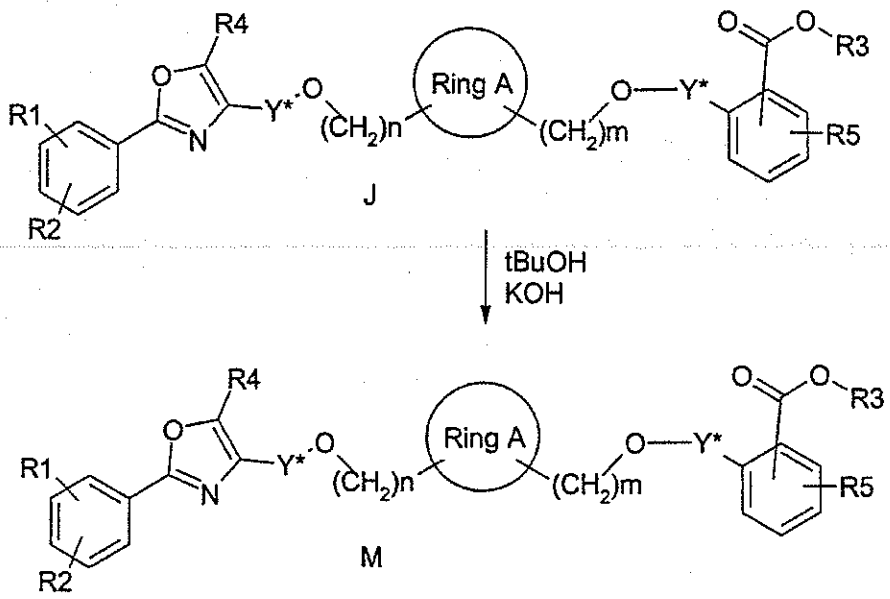
	R1	R2	Ring B	R4	X	Ring A	Y	R3	R5
XI	4-Me	H	Ph	Ph	CH2O	cis 1,3 Cy	CH2O	H	6-Me
XII	3-OMe	H	Ph	Ph	CH2O	cis 1,3 Cy	CH2O	H	6-Me
XIII	H	H		H	CH2O	cis 1,3 Cy	CH2O	H	6-Me

cis 1,3 cy means: cis-substituted cyclohexane-1,3-diyl

----: indicates the point of attachment

The compounds of the formulae I and Ia can be obtained in accordance with the reaction scheme below:





Compounds of the formula A in which R3, R5 and Y have the meanings given above are reacted with NBS in an inert solvent (e.g. CCl4), giving a compound of the formula B.

The compound of the formula B is reacted with a compound of the formula C in which n and m are each 0-5, giving a compound of the formula D in which R1, R2, R4, m, n and Y have the meanings described above, at the same time component C is initially heated with dibutyltin oxide in toluene on a water separator for a number of hours and then, with addition of dimethylformamide, cesium fluoride and bromide B, converted into D by stirring at room temperature for a number of hours.

The compound of the formula E is reacted with an aldehyde of the formula W (for example benzaldehyde, thiophene- or furancarbaldehyde) to give a compound of the formula F in which R1, R2, R4 and X are as defined above; to this end, components E and F are initially dissolved in acetic acid and HCl is introduced until the reaction has gone to completion, giving compounds of the formula F.

The compound of the formula F in which R1, R2, R4 and X are as defined above is heated under reflux with POCl3 in chloroform for a number of hours, giving compounds of the formula G.

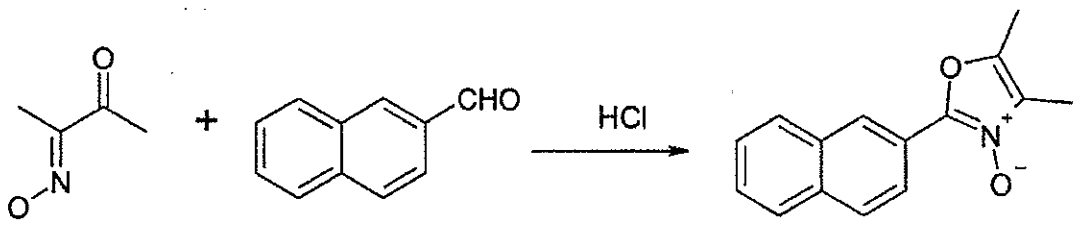
Compounds of the formula G in which R1, R2, R4 and X are as defined above are reacted with NaI in acetone under reflux for a number of hours, giving a compound of the formula H.

The compound of the formula D is reacted with a compound of formula H in which Y is as defined above, giving a compound of the formula J in which R1, R2, R4, R5, X and Y are as defined above. To establish an ether bond, D is deprotonated, for example, in a mixture of dimethylformamide and tetrahydrofuran using a strong base such as Na hydride, at room temperature, and then alkylated with component H.

The compound of the formula J is converted into compounds of the formula M in which R1, R2, R4, R5, X and Y are as defined above by hydrolyzing the ester function, for example by heating with potassium hydroxide and then alcohol (ethanol, tert-butanol), and releasing the carboxylic acid group of the formula I by acidification. This carboxylic acid group can be derivatized by customary methods into the group of the formula -(C=O)-OR3 in which R3 is as defined above.
Other compounds can be obtained accordingly or by known processes.

Example 1

4,5-Dimethyl-2-naphthalen-2-yloxazole 3-oxide

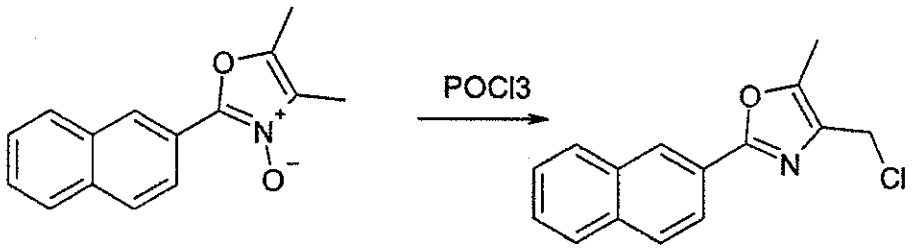


18.4 g of diacetyl monoxime and 31.2 g of 2-naphthaldehyde are added to 50 ml of glacial acetic acid, and HCl gas is introduced with ice-cooling for 30 minutes. The product is precipitated as the hydrochloride by addition of methyl tert-butyl ether

and filtered off with suction, and the precipitate is washed with methyl tert-butyl ether. The precipitate is suspended in a mixture of dichloromethane and water, and a basic pH is established using ammonia. The mixture is extracted three times with in each case 500 ml of dichloromethane and ethyl acetate, the combined organic phases are dried over MgSO4 and the solvent is then removed under reduced pressure. This gives 40.3 g of 4,5-dimethyl-2-naphthalen-2-yloxazole 3-oxide as a yellow solid.

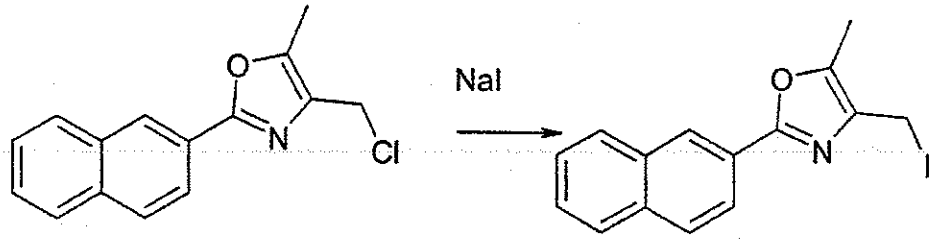
CF15H13NO2 (239.28), MS(ESI) = 240 ($M+H^+$).

4-Chloromethyl-5-methyl-2-naphthalen-2-yloxazole



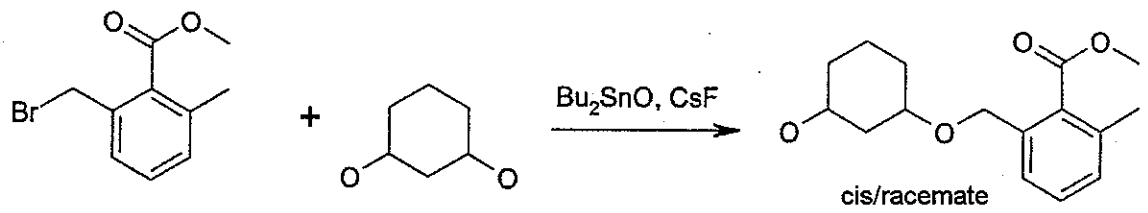
40 g of 4,5-dimethyl-2-naphthalen-2-yloxazole 3-oxide are dissolved in 200 ml of chloroform, 16.7 ml of phosphorus oxychloride are added and the mixture is heated under reflux for 30 minutes. The reaction mixture is cooled to 0°C, a slightly alkaline pH is established using ammonia and the mixture is extracted three times with in each case 500 ml of ethyl acetate. The combined organic phases are washed with water and dried over MgSO4 and the solvent is then removed under reduced pressure. The residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 80:1 => 5:1. This gives 10.6 g of 4-chloromethyl-5-methyl-2-naphthalen-2-yloxazole as a colorless solid. C15H12ClNO (257.72), MS(ESI): 258 ($M+H^+$).

4-Iodomethyl-5-methyl-2-naphthalen-2-yloxazole



1.8 g of 4-chloromethyl-5-methyl-2-naphthalen-2-yloxazole and 3 g of sodium iodide in 150 ml of acetone are heated under reflux for 2 hours. After the reaction mixture has been cooled, 300 ml of methyl tert-butyl ether are added, the mixture is washed three times with saturated Na2S2O3 solution and dried over MgSO4 and the solvents are then removed under reduced pressure. This gives 2.7 g of 4-iodomethyl-5-methyl-2-naphthalen-2-yloxazole as a light-yellow solid. C15H12INO (349.17), MS(ESI): 350 ($M+H^+$).

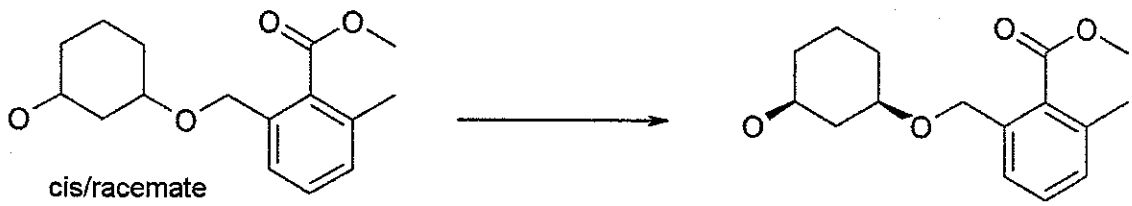
Methyl 2-(cis-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate



8.7 g of 1,3-cyclohexanediol and 12 g of dibutyltin oxide are dissolved in 600 ml of toluene and, in a water separator, heated under reflux. During the reaction, the reaction volume is reduced to half the original volume. After 4 hours, the reaction mixture is cooled to room temperature, and 300 ml of DMF, 9.0 g of methyl 2-bromomethyl-6-methylbenzoate and 9.4 g of cesium fluoride are added. The mixture is stirred at room temperature for 12 hours. The reaction mixture is diluted by addition of ethyl acetate and washed with saturated NaCl solution. The organic phase is dried over magnesium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel

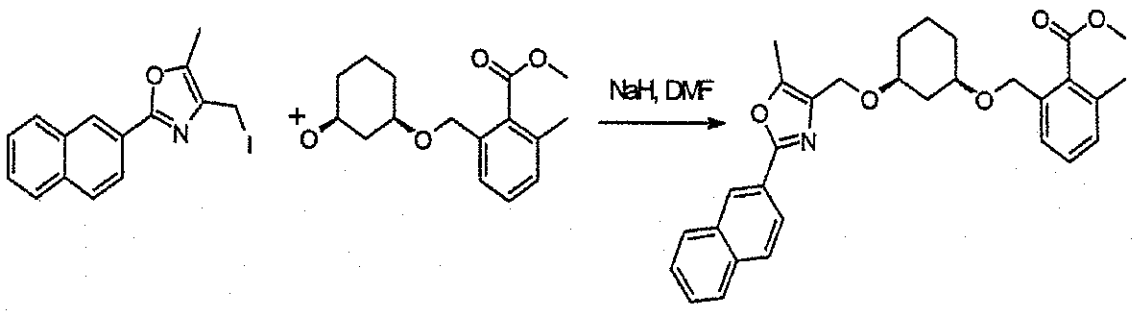
((n-heptane/ethyl acetate = 50:1 -> 1:2). This gives 6 g of methyl 2-(cis-3-hydroxy-cyclohexyloxymethyl)-6-methylbenzoate as an oil. $C_{16}H_{22}O_4$ (278.35), MS(ESI): 279 ($M + H^+$).

Methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate



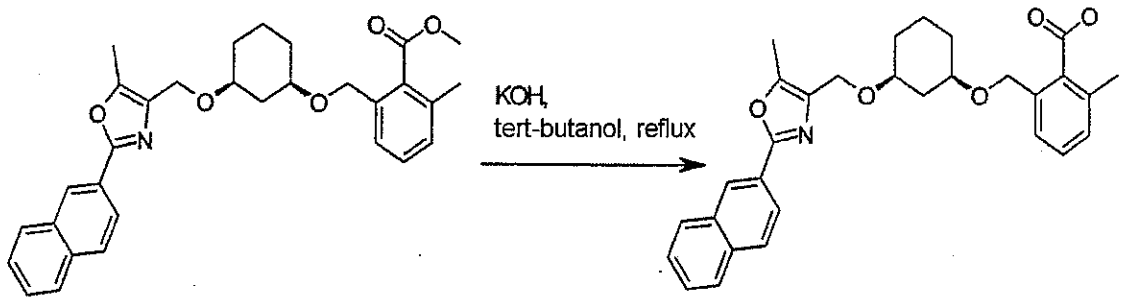
8 g of methyl 2-(cis-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate are dissolved in 100 ml of vinyl acetate, and 1 g of Candida antartika lipase B is added. The mixture is stirred at room temperature for seven hours and the enzyme is then filtered off and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel ((n-heptane/ethyl acetate = 10:1). This gives 3.9 g of the alcohol methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate as a colorless oil. $C_{16}H_{22}O_4$ (278.35), MS(ESI): 279 ($M + H^+$) ee = 98% ((Chiralpak AD/2 250x4.6; n-heptane:ethanol:methanol = 25:1:0.5 + 0.1% trifluoroacetic acid, R_t = 8.9 min; retention time of the enantiomer: R_t = 9.9 min.).

Methyl 2-methyl-6-[(1R,3S)-3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy)-cyclohexyloxymethyl]benzoate



At room temperature, 50 mg of a 60% strength suspension of sodium hydride are added to a solution of 200 mg of methyl 2-((1R,3S)-3-hydroxycyclohexyloxy-methyl)-6-methylbenzoate in 5 ml of dimethylformamide, and 380 mg of 4-iodo-methyl-5-methyl-2-naphthalen-2-yloxaxole are then added. After one hour, methyl tert-butyl ether is added and the mixture is extracted with water. The organic phase is dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by RP-HPLC. This gives 94 mg of methyl 2-methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclo-hexyloxymethyl]benzoate as a light-yellow oil.
C31H33NO5 (499.61), MS(ESI): 500 ($M + H^+$).

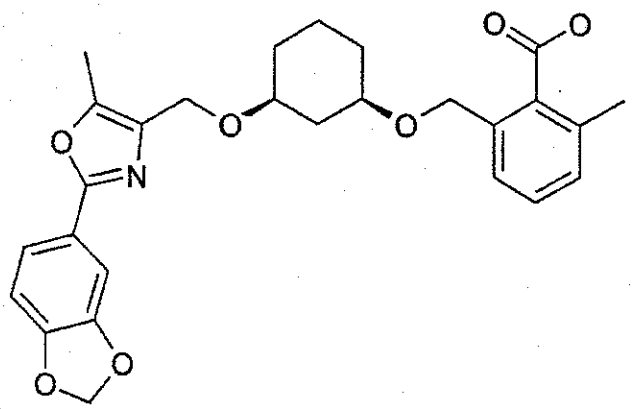
2-Methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclo-hexyloxymethyl]benzoic acid



94 mg of methyl 2-methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-yl-methoxy]cyclohexyloxymethyl]benzoate are stirred at 90°C in a mixture of 10 ml of tert-butanol and 1 ml of 10 N potassium hydroxide solution. After two days, the mixture is acidified with hydrochloric acid and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by RP-HPLC. This gives 72 mg of 2-methyl-6-[(1R,3S)3-(5-methyl-2-naphthalen-2-yloxazol-4-yl-methoxy)cyclohexyloxymethyl]benzoic acid as an amorphous solid. $C_{30}H_{31}NO_5$ (485.59), MS(ESI): 486 ($M + H^+$).

Example 2

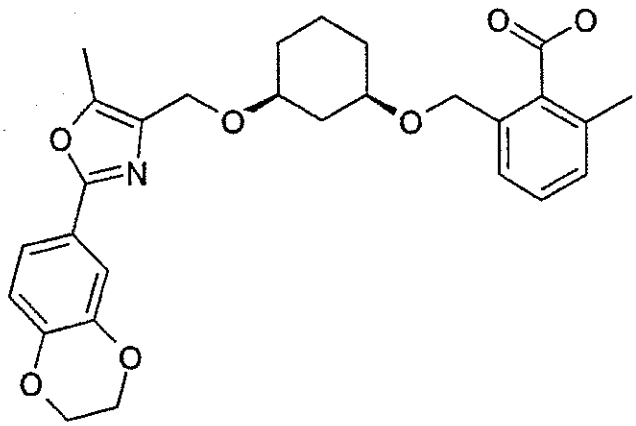
Analogously to **Example I**, diacetyl monoxime, benzo[1,3]dioxole-5-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-[(1R,3S)-3-(2-benzo[1,3]dioxol-5-yl-5-methyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-6-methylbenzoic acid.



$C_{27}H_{29}NO_7$(479.53), MS(ESI): 480 ($M + H^+$).

Example 3

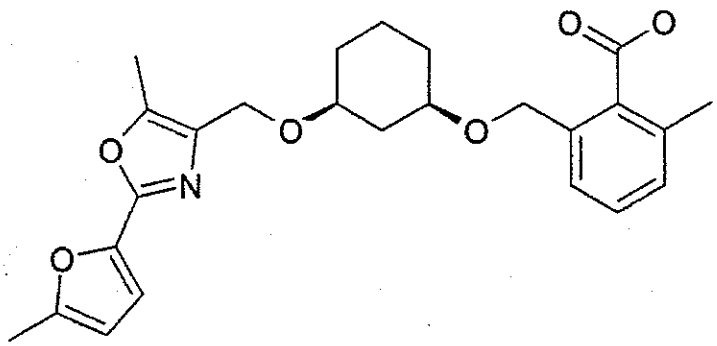
Analogously to **Example I**, diacetalymonoxime, 2,3-dihydrobenzo[1,4]dioxine-6-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-[(1R,3S)-3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-5-methyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-6-methylbenzoic acid.



$C_{28}H_{31}NO_7$(493.56), MS(ESI): 494 ($M + H^+$).

Example 4

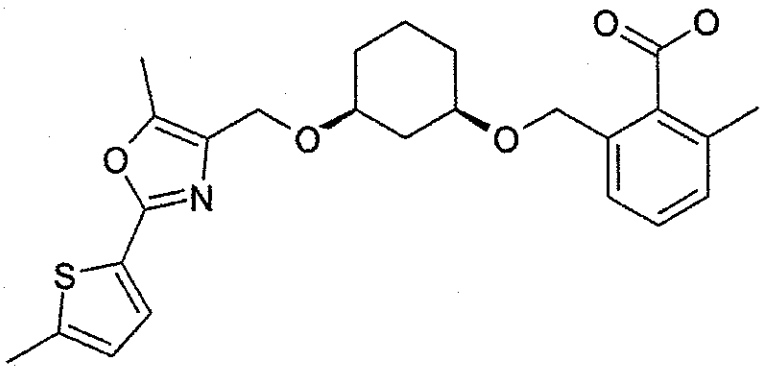
Analogously to **Example I**, diacetyl monoxime, furan-2-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-methyl-6-{(1R,3S)-3-[5-methyl-2-(5-methylfuran-2-yl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}benzoic acid.



$C_{25}H_{29}NO_6$(439.51), MS(ESI): 440 ($M + H^+$).

Example 5

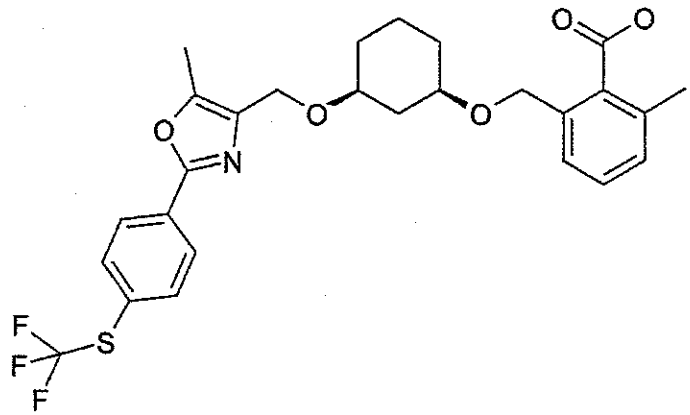
Analogously to **Example I**, diacetyl monoxime, 5-methylthiophene-2-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-methyl-6-{(1R,3S)-3-[5-methyl-2-(5-methylthiophen-2-yl)oxazol-4-ylmethoxy]-cyclohexyloxymethyl}benzoic acid.



$C_{25}H_{29}NO_5S$(455.58), MS(ESI): 456 ($M + H^+$).

Example 6

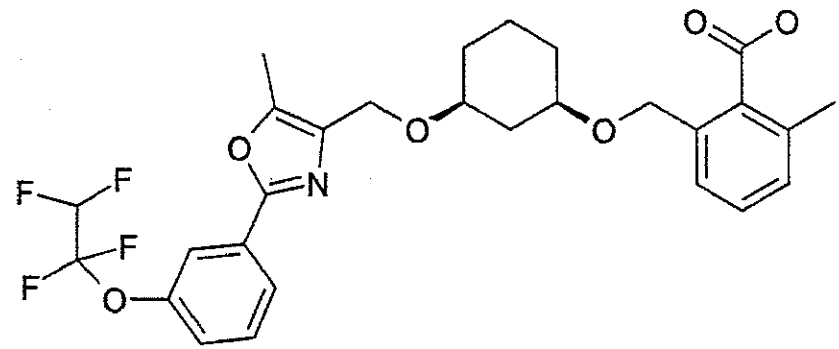
Analogously to **Example I**, diacetyl monoxime, 4-trifluoromethylsulfanyl-benzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methyl-benzoate gave 2-{(1R,3S)-methyl-6-{3-[5-methyl-2-(4-trifluoromethylsulfanyl-phenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}benzoic acid.



$C_{27}H_{28}F_3NO_5S$(535.58), MS(ESI): 536 ($M + H^+$).

Example 7

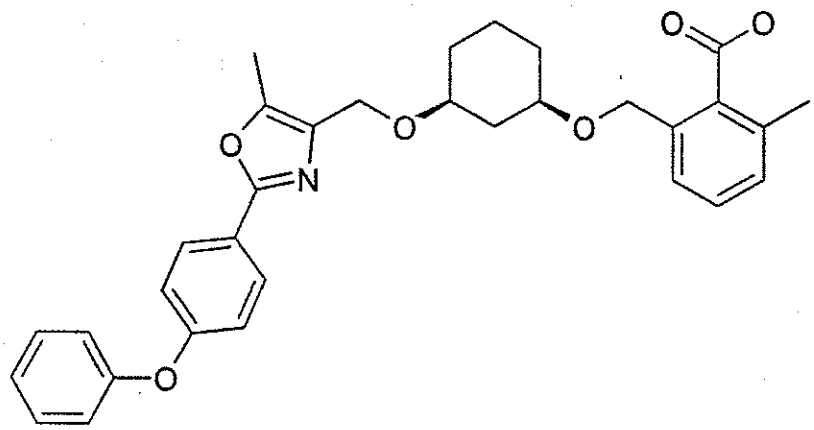
Analogously to **Example I**, diacetyl monoxime, 3-pentafluoroethyloxy-benzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methyl-benzoate gave 2-{(1R,3S)-methyl-6-(3-{5-methyl-2-[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]oxazol-4-ylmethoxy}cyclohexyloxymethyl)benzoic acid.



$C_{28}H_{29}F_4NO_6$(551.54), MS(ESI): 552 ($M + H^+$).

Example 8

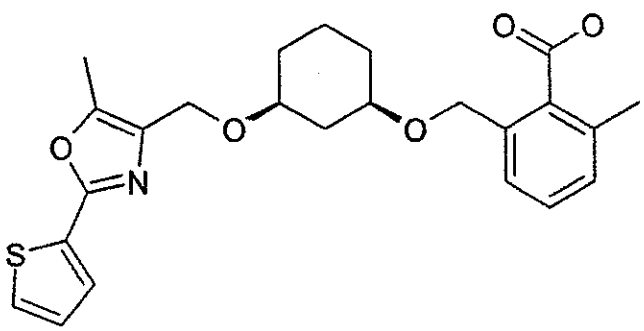
Analogously to **Example I**, diacetyl monoxime, 4-phenoxybenzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-{(1R,3S)-methyl-6-{3-[5-methyl-2-(4-phenoxyphenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}benzoic acid.



$C_{32}H_{33}NO_6$(527.62), MS(ESI): 528 ($M + H^+$).

Example 9

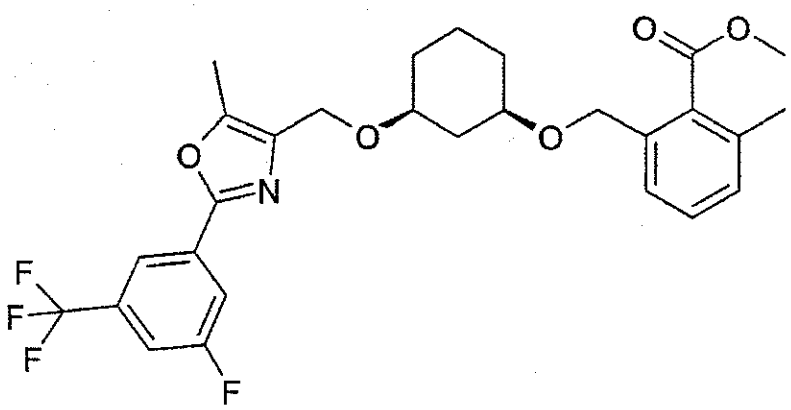
Analogously to **Example I**, diacetyl monoxime, thiophene-2-carbaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-{(1R,3S)-methyl-6-[3-(5-methyl-2-thiophen-2-yloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid.



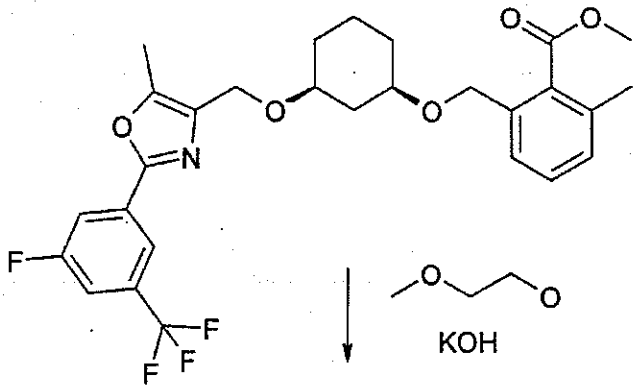
$C_{24}H_{27}NO_5S$(441.55), MS(ESI): 442 ($M + H^+$).

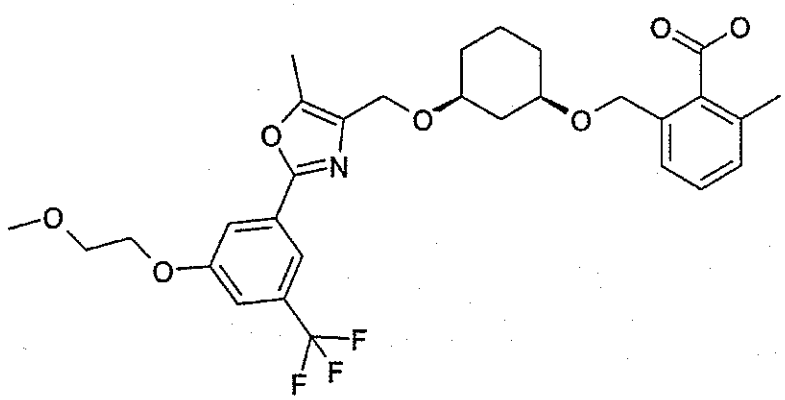
Example 10

Analogously to **Example I**, diacetyl monoxime, 3-fluoro-5-trifluoromethyl-benzaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methyl-benzoate gave methyl 2-{(1R,3S)-{3-[2-(3-fluoro-5-trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoate.



$C_{28}H_{29}F_4NO_5$ (535.54), MS(ESI): 536 ($M + H^+$).

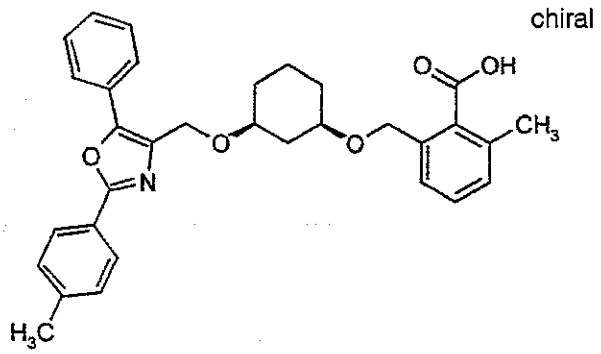




A mixture of 128 mg of methyl 2{(1R,3S)-{3-[2-(3-fluoro-5-trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoate, 5 ml of ethylene glycol monomethyl ether and 0.6 ml of 10N KOH were heated under reflux for 24. After cooling, the mixture is acidified with hydrochloric acid and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulphate, the solvent is removed under reduced pressure and the residue is purified by RP-HPLC. This gives 56 mg of 2-{(1R,3S)-(3-{2-[3-(2-methoxyethoxy)-5-trifluoromethylphenyl]-5-methyloxazol-4-ylmethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid as a colorless oil of molecular weight $C_{29}H_{32}F_3NO_7$ (563.58), MS(ESI): 564 ($M + H^+$).

Example 11

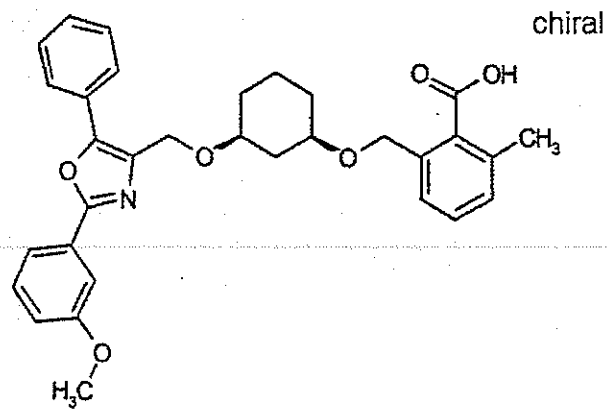
Analogously to **Example I**, 1-phenyl-1,2-propanedione 2-oxime, p-tolualdehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-methyl-6-[(1R,3S)-3-(5-phenyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid.



C32H33NO5 (511.62), MS(ESI) = 512 ($M+H^+$).

Example 12

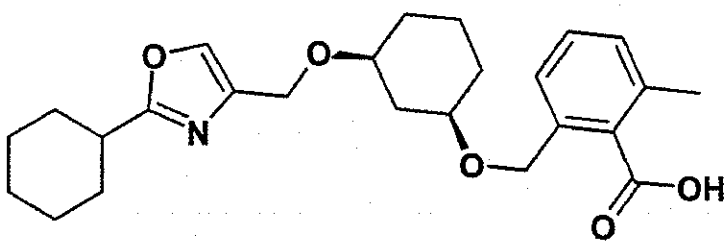
Analogously to **Example I**, 1-phenyl-1,2-propanedione 2-oxime, m-anisaldehyde and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-{(1R,3S)-3-[2-(3-methoxyphenyl)-5-phenyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.



C32H33NO6 (527.62), MS(ESI) = 528 ($M+H^+$).

Example 13

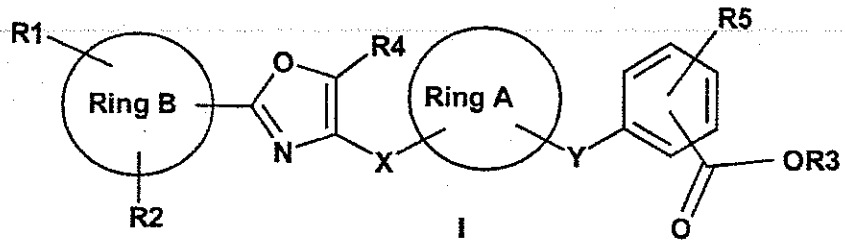
Analogously to **Example 1**, 2-cyclohexyl-4-iodomethyloxazole and methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate gave 2-[(1R,3S)-3-(2-cyclohexyloxazol-4-ylmethoxy)cyclohexyloxymethyl)-6-methylbenzoic acid.



$C_{25}H_{27}NO_5$(421.50); MS(ESI): 422 ($M+H^+$).

We claim:

1. A compound of the formula I



I

in which

Ring A is $(C_3$-$C_8)$-cycloalkanediyl or $(C_3$-$C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl; or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or $(C_3$-$C_8)$-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_3)$-alkyl;

c) in the case ring B = a) and R4 = phenyl:
$(C_1$-$C_6)$-alkyl or O-$(C_1$-$C_6)$-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

c) in the case ring B = a) and R1 = a):
$(C_1$-$C_6)$-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is $(C_1$-$C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

Y is $(C_1$-$C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;

and its physiologically acceptable salts.

2. A compound of the formula I as claimed in claim 1, wherein

Ring A is $(C_3$-$C_8)$-cycloalkanediyl or $(C_3$-$C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O

and S, an 8- to 14-membered aromatic ring or (C_3-C_8)-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1 = a):
(C_1-C_6)-alkyl;

R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

R3 is H or (C_1-C_6)-alkyl;

X is CH_2-O;

Y is (C_1-C_6)-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms.

3. A compound of the formula I as claimed in claim 1 or 2, wherein

Ring A is (C_3-C_8)-cycloalkanediyl in which one carbon atom may be replaced by an oxygen atom;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or (C_3-C_8)-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1 = a):
(C_1-C_6)-alkyl;

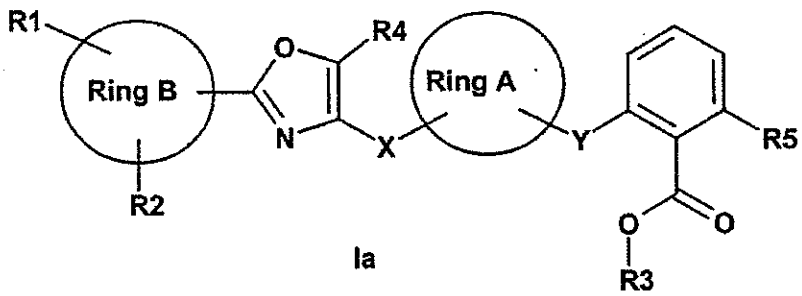
R5 is H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

X is CH_2-O;

Y is CH_2-O.

4. A compound of the formula Ia



Ia

in which ring A, ring B, R1, R2, R3, R4, R5, X and Y are as defined in claims 1 to 3.

5. A compound of the formula 1a as claimed in claim 4 in which

R3 is H and

R5 is methyl.

6. A compound of the formula Ia as claimed in claim 4 or 5, in which

Ring A is $(C_5$-$C_7)$-cycloalkanediyl;

Ring B is a) phenyl, or

b) a 5- to 12-membered heteroaromatic ring which may contain

one to four heteroatoms selected from the group consisting of N, O and S, an 8- to 14-membered aromatic ring or (C_3-C_8)-cycloalkyl;

R1 is a) in the case ring B = a):
SCF_3, OCF_2-CHF_2, O-phenyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, OCF_2-CF_3, SCF_3, OCF_2-CHF_2, O-phenyl, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl-O-(C_1-C_3)-alkyl;

c) in the case ring B = a) and R4 = phenyl:
(C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R2 is H or CF_3;

R4 is a) in the case ring B = a):
phenyl;

b) in the case ring B = b):
H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl;

c) in the case ring B = a) and R1/R2 = a):
(C_1-C_6)-alkyl;

R5 is methyl;

R3 is H;

X is CH_2-O;

Y is CH_2-O.

7. A compound of the formula I or Ia as claimed in any of claims 1 to 6, wherein the central cycloalkanediyl ring is attached 1,3-cis.

8. A pharmaceutical, comprising one or more compounds as claimed in one or more of claims 1 to 7.

9. A pharmaceutical comprising one or more of the compounds I as claimed in one or more of claims 1 to 7 and one or more active compounds which have favorable effects on metabolic disorders or associated diseases.

10. A pharmaceutical comprising one or more of the compounds I as claimed in one or more of claims 1 to 7 and one or more antidiabetics.

11. A pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 7 and one or more lipid modulators.

12. The use of the compounds as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

13. The use of the compounds as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of disorders in which insulin resistance plays a role.

14. The use of the compounds as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of diabetes mellitus and the associated sequelae.

15. The use of the compounds as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of dyslipidemias and their consequences.

16. The use of the compounds as claimed in one or more of claims 1 to 7 for the treatment and/or prevention of states which are associated with metabolic syndrome.

17. The use of the compounds as claimed in one or more of claims 1 to 7 in combination with at least one further active compound for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

18. The use of the compounds as claimed in one or more of claims 1 to 7 in combination with at least one further active compound for the treatment and/or prevention of disorders in which insulin resistance plays a role.

19. A process for preparing a pharmaceutical comprising one or more compounds as claimed in one or more of claims 1 to 7, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.