

Description

- 5 Arylcycloalkyl derivatives with branched side chains as PPAR receptor modulators, method for their production and their use as medicaments

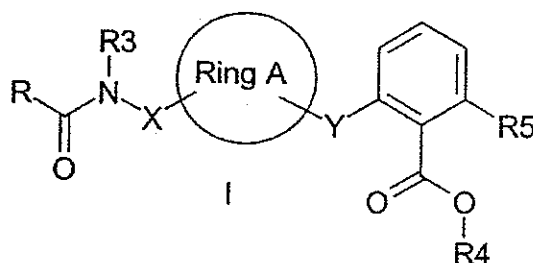
The invention relates to arylcycloalkyl derivatives having branched side chains and to their physiologically acceptable salts and physiologically
10 functional derivatives.

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

- 15 It was an object of the invention to provide compounds allowing a therapeutically exploitable modulation of the lipid and/or carbohydrate metabolism, and thereby being suitable for the prevention and/or treatment of diseases such as type II diabetes and atherosclerosis and of the various sequelae associated therewith.

20 Surprisingly, a series of compounds was found which modulate the activity of PPAR receptors. The compounds are particularly suitable for activating PPAR alpha and PPAR gamma, it being possible for the extent of the relative activation to vary depending on the compounds.

- 25 Accordingly, the invention relates to compounds of the formula I



- 30 in which

ring A is (C3-C8)-cycloalkanediyl or (C3-C8)-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

R is NR₁R₂ or OR₁, (C₆-C₁₀)-aryl or (C₅-C₁₂)-heteroaryl, where heteroaryl may contain one to three identical or different heteroatoms selected from the group consisting of N, O and S;

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R₁, R₂ independently of one another are H, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl or (C₆-C₁₀)-aryl, where aryl may be unsubstituted or substituted by F, Cl or (C₁-C₄)-alkyl;

10 R₃ is (C₃-C₆)-cycloalkyl or (C₁-C₁₀)-alkyl which are unsubstituted or substituted by phenyl, pyridyl, morpholinyl, (C₃-C₆)-cycloalkyl, where phenyl for its part may be substituted by chlorine or (C₁-C₄)-alkyl;

15 X is (C₁-C₆)-alkanediyl, where one or more carbon atoms in the alkanediyl group may be replaced by oxygen atoms;

Y is (C₁-C₆)-alkanediyl, where one or more carbon atoms in the alkanediyl group may be replaced by oxygen atoms;

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R₄ is H, (C₁-C₄)-alkyl;

R₅ is (C₁-C₄)-alkyl;

25 and their physiologically acceptable salts.

Preference is given to compounds of the formula I whose substituents X, and Y are linked to ring A in position 1,3 (X-ring A-Y).

30 Preference is furthermore given to compounds of the formula I in which ring A is (C₃-C₈)-cycloalkane-1,3-diyl or (C₃-C₈)-cycloalkene-1,3-diyl;

R is NR₁R₂ or (C₆-C₁₀)-aryl;

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R₁, R₂ independently of one another are H, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl or (C₆-C₁₀)-aryl, where aryl may be unsubstituted or substituted by F, Cl or (C₁-C₄)-alkyl;

- R3 is (C3-C6)-cycloalkyl or (C1-C8)-alkyl which is unsubstituted or substituted by phenyl, pyridyl, morpholinyl, (C3-C6)-cycloalkyl, where phenyl for its part may be substituted by chlorine or methyl;
- 5 X is (C1-C3)-alkanediyl, where one carbon atom in the alkanediyl group may be replaced by an oxygen atom;
- Y is (C1-C3)-alkanediyl, where the carbon atom adjacent to the ring A in the alkanediyl group may be replaced by an oxygen atom;
- 10 R4 is H;
- R5 is methyl;
- 15 and their physiologically acceptable salts.

Particular preference is given to compounds of the formula I in which

- ring A is cyclohexane-1,3-diyl;
- 20 R is NR₁R₂ or phenyl;
- R₁ is H;
- 25 R₂ is (C1-C6)-alkyl, cyclohexyl or phenyl, where phenyl may be unsubstituted or substituted by F, Cl or (C1-C4)-alkyl;
- R3 is (C3-C6)-cycloalkyl or (C1-C8)-alkyl which is unsubstituted or substituted by phenyl, pyridyl, morpholinyl, cyclopropyl, cyclopentyl, cyclohexyl, where phenyl for its part may be substituted by chlorine or methyl;
- 30 X is O-CH₂-CH₂;
- 35 Y is OCH₂;
- R4 is H;
- R5 is methyl;

and their physiologically acceptable salts.

Very particular preference is given to compounds of the formula I in which

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ring A is cyclohexane-1,3-diyl;

R is NR₁R₂ or phenyl;

10 R₁ is H;

R₂ is (C₁-C₄)-alkyl, cyclohexyl, phenyl, where phenyl may be unsubstituted or substituted by F, Cl or methyl;

15 R₃ is (C₃-C₆)-cycloalkyl or (C₁-C₈)-alkyl which is unsubstituted or substituted by phenyl, pyridyl, morpholinyl, cyclopropyl, cyclopentyl, cyclohexyl, where phenyl for its part may be substituted by chlorine or methyl;20 X is O-CH₂-CH₂;

Y is OCH₂;

R₄ is H;

25

R₅ is methyl;

and their physiologically acceptable salts.

30 The link to ring A can be either cis or trans and is preferably cis.

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

35 The alkyl, alkenyl and alkynyl 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 6 to 10 atoms in the ring or in the rings.

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

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The compounds of the formula I contain at least two centers of asymmetry and may additionally contain more. Accordingly, the compounds of the formula I may be present in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and diastereomer mixtures. The present invention encompasses all these isomeric forms of the compounds of the formula I. These isomeric forms may, even if this is not always described *expressis verbis*, be obtained by known methods.

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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 tromethanol (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 PPAR receptor activity.

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, PPAR alpha, PPAR gamma and PPAR delta, 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 are two variants of PPAR gamma, PPAR gamma₁ and gamma₂, which are the result of alternative use of promoters and differentiation mRNA splicing (Vidal-Puig et al. J. Clin. Invest., 97:2553-2561, 1996). Different PPAR receptors have different tissue distribution and modulate different physiological functions. The PPAR receptors play a key role in various aspects of the regulation of a large number of genes, the products of which genes are directly or indirectly critically involved in lipid and carbohydrate metabolism. Thus, for example, the PPAR alpha receptors play an important part in the regulation of fatty acid catabolism or lipoprotein metabolism in the liver, while PPAR gamma is critically involved,

for example, in regulating adipose cell differentiation. In addition, however, PPAR receptors are also involved in the regulation of many other physiological processes, including those which are not directly connected with carbohydrate or lipid metabolism. The activity of different PPAR
 5 receptors can be modulated by various fatty acids, fatty acid derivatives and synthetic compounds to varying extents. For relevant reviews about 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
 10 Res. 2001; 56: 239-63.

The present invention relates to compounds of the formula I suitable for modulating the activity of PPAR receptors, especially the activity of PPAR alpha and PPAR gamma. Depending on the modulation profile, the compounds of the formula I are suitable for the treatment, control and
 15 prophylaxis of the indications described hereinafter, and for a number of other pharmaceutical applications thereto (see, for example, 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; Jean-Charles Fruchart, Bart Staels and
 20 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, 421-4; Ines Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome
 25 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
 30 - disorders in which insulin resistance is involved.
2. Diabetes mellitus, in particular type 2 diabetes, including the prevention of the sequelae associated therewith.
 35 Particular aspects in this connection are:
 - hyperglycemia,
 - improvement in insulin resistance,
 - improvement in glucose tolerance,
 - protection of the pancreatic beta cells,

- prevention of macro- and microvascular disorders
3. Dyslipidermia and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebral vascular disorders, etc., especially those (but not restricted thereto) 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 the metabolic syndrome, such as:
- obesity (excess weight), including central obesity
 - thrombosis, hypercoagulability and prothrombotic stages (arterial and venous)
 - high blood pressure
 - heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy.
5. Further diseases or conditions in which, for example, inflammatory processes or cell differentiation processes are involved:
- atherosclerosis such as, for example (but not restricted thereto), 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 conditions
 - retinopathy
 - adipose cell tumors
 - adipose cell carcinomas such as, for example, liposarcomas
 - solid tumors and neoplasms, such as, for example, (but not restricted thereto), 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 disorders
 - 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
- 5 - acute respiratory distress syndrome (ARDS) ("shock lung")

Formulations

10 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

15 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

20 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

25 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

30 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,

35 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, hydroxypropyl-methylcellulose 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.

The 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.
- 10 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.
- 15 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 20 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 diverse sequelae associated therewith.

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 disturbances or disorders frequently associated therewith. Examples of such medicaments are

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

20 They can be combined with the compounds of the invention of the formula I in particular for a synergistic improvement in the effect. Administration of the active ingredient combination can take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present

25 in one pharmaceutical preparation.

Examples which may be mentioned are:

Antidiabetics

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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

35 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 effective hypoglycemic active ingredients 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 blood lipid composition, compounds which reduce food intake or food absorption, PPAR and PXR modulators and active ingredients which act on the ATP-dependent potassium channel of the beta cells.

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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 in combination with substances which influence hepatic glucose production such as, for example, glycogen phosphorylase inhibitors (see: 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 one embodiment, the compounds of the formula I are administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with a biguanide such as, for example, metformin.

In a further 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 are administered 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-pentan ammonium 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).

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

- 10 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.

- 15 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.

- 20 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

- 25 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.

- 30 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).

- 35 In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorbent 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.

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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).

- 10 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
- 15 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
- 20 products or muesli bars.

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

- 25 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)-
- 30 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.

- 35 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, e.g. CP- 529, 414 (torcetrapib).

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

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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.

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

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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.

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

Antiobesity agents

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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.

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In one embodiment, the further active ingredient 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, e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}-amide hydrochloride (CGP 71683A)), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]amide; (WO 01/91752)), orexin antagonists (e.g. 1-(2-methyl-benzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A)), H3 agonists (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 (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (e.g. urocortin), urocortin agonists, β 3 agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethyl-amino]ethanol hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (e.g. {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 (e.g. dexfenfluramine), mixed serotonergic and noradrenergic compounds (e.g. WO 00/71549), 5HT agonists e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), bombesin agonists, galanin antagonists, growth hormone (e.g. human growth hormone), growth hormone-releasing compounds (6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tertiary butyl ester (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), uncoupling 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 (bromocriptine, Doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR modulators or TR- β agonists).

35

In one embodiment of the invention, the further active ingredient is leptin.

In one embodiment, the further active ingredient is dexamphetamine, amphetamine, mazindole or phentermine.

In one embodiment, the compounds of the formula I are as 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 other 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 PPAR alpha assay

Principle

To analyze the effectiveness of substances which bind to human PPARalpha, activating it in agonistic manner, a stable transfected HEK cell line (HEK = human embryo kidney) designated here as "PPARalpha reporter cell line" is used. 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 stably 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 assay. 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.

5

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
 10 HEK cells. For this purpose, five binding sites of the yeast transcription factor GAL4 (in each case 5'-CGGAGTACTGTCCTCCGAG-3') were cloned in 5'-upstream of a 68 bp-long minimal MMTV promoter (Genbank Accession # V01175). The minimal MMTV promoter section contains a CCAAT box and a TATA element in order to enable efficient transcription
 15 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 (Genbank Accession # M15077) was cloned in 3'-downstream of the GAL4-MMTV element. After
 20 sequencing, the luciferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene was recloned into a plasmid which confers zeocin 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
 25 biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Then zeocin-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
 30 described. For this purpose, initially the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Genbank Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386). The cDNA of the ligand-binding domain of the human PPARalpha receptor
 35 (amino acids S167-Y468; Genbank Accession # S74349) was cloned in at the 3' end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPARalpha-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 zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

Assay procedure

- The activity of PPARalpha agonists is determined in a 3-day assay which is described below:

Day 1

- The PPARalpha reporter cell line is cultivated to 80% confluence in DMEM medium (# 41965-039, Invitrogen) which is mixed with the following additions: 10% cs-FCS (fetal calf serum; # SH-30068.03, Hyclone), 0.5 mg/ml zeocin (# R250-01, Invitrogen), 0.5 mg/ml G418 (# 10131-027, Invitrogen), 1% penicillin-streptomycin solution (# 15140-122, Invitrogen) and 2 mM L-glutamine (# 25030-024, Invitrogen). The cultivation takes place in standard cell culture bottles (# 353112, Becton Dickinson) in a cell culture incubator at 37°C in the presence of 5% CO₂. 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, 35 000 cells 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% CO₂ for 24 h.

Day 2

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

Test substances are tested in 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 or between 100 nM and 1 pM.

The medium of the PPARalpha reporter cell line 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 μ l per well of a 96 well microtiter plate. The DMSO concentration in the assay is less than 0.1% v/v in order to avoid cytotoxic effects of the solvent.

Each plate was charged with a standard PPARalpha agonist, which was likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO₂ 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 lysed by pipetting 50 μ l 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.

20

Evaluation

The raw data from the luminometer are transferred into a Microsoft Excel file. Dose-effect plots and EC50 values of PPAR agonists are calculated using the XL.Fit program as specified by the manufacturer (IDBS).

25

In this assay, the PPARalpha-EC50 values for the compounds of examples 1 to 62 are in the range from 0.01 nM to > 10 nM.

30 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	1.9
II	4.9
VII	1.7
VIII	96
IX	0.13
XII	0.07
XV	31
XVI	38
XVII	84
XXII	3.3
XXXIX	0.17
XLV	90

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 assay

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 assay the two components (luciferase reporter
 5 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

10

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'),
 15 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
 20 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-humanPPAR γ LBD was prepared by first cloning the cDNA coding for amino acids 1-147 of the
 25 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 PPAR γ receptor (amino acids I152-Y475; Accession # g1480099) 3'-downstream of the GAL4 DNA binding domain. Cloning and
 30 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 PPAR γ expression plasmid pcDNA3-GAL4-
 35 humanPPARgammaLBD, also used for the cellular PPARgamma assay 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.

Assay procedure

5 The activity of PPAR γ agonists is determined in a 4-day assay 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).

10

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 an assay: 2622 μ l of antibiotic- and serum-free DMEM (#41965-039, Invitrogen), 100 μ l of reference plasmid pRL-CMV (1 ng/ μ l), 100 μ l of luciferase reporter plasmid pGL3basic-5xGAL4-TK (10 ng/ μ l), 100 μ l of PPAR γ expression plasmid pcDNA3-GAL4-humanPPAR γ LBD (100 ng/ μ l) and 78 μ l of plasmid pBluescript-SK(+) (500 ng/ μ l). Then 2 ml of solution B are prepared by mixing 1.9 ml of DMEM (#41965-039, Invitrogen) with 100 μ l 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.

25 80%-confluent HEK cells from a cell culture bottle with a capacity of 175 cm² 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 μ l 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% CO₂ for 24 h.

35

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% Ultrosor (#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 μ M to 100 pM. More potent compounds are tested in concentration ranges from 1 μ M 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 μ l per well of a 96 well microtiter plate. Each plate is charged with a standard PPAR γ agonist, which is likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO₂ for 48 h.

Day 4

After removal of the medium by aspiration, 50 μ l of Dual-GloTM reagent (Dual-GloTM Luciferase Assay System; Promega) are added to each well in accordance with the manufacturer's instructions in order to lyse 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 μ l of the Dual-GloTM Stop & Glo reagent (Dual-GloTM 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

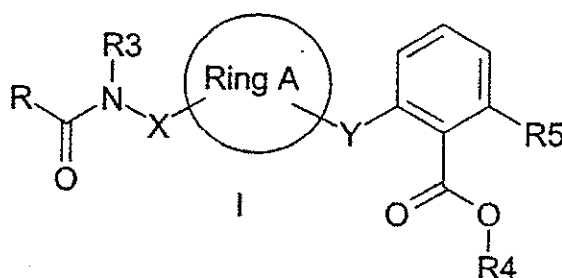
The crude data from the luminometer are transferred into a Microsoft Excel file. The firefly/Renilla luciferase activity ratio is determined for each measurement derived from one well of the microtiter plate. The dose-effect

plots and EC50 values of PPAR agonists are calculated from the ratios by the XL.Fit program as specified by the manufacturer (IDBS).

- 5 PPARgamma EC50 values in the range from 50 nM to >10 μ M were measured for the PPAR agonists described in this application.

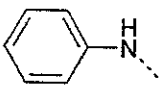
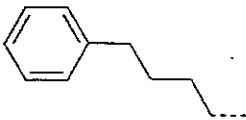
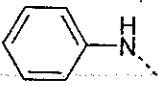
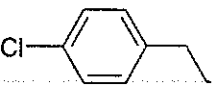
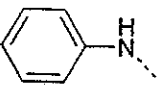
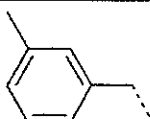
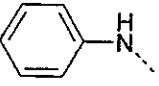
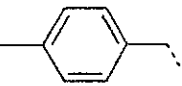
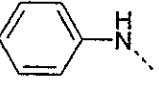
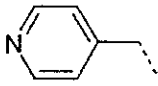
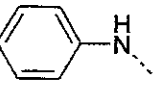
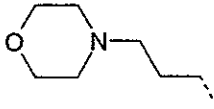
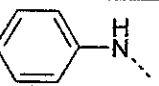
The examples given in Table II serve to illustrate the invention, but without limiting it.

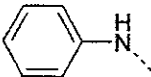
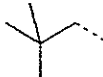
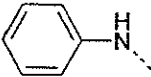
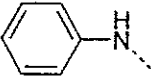
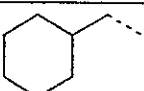
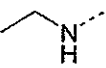
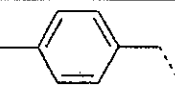
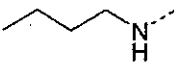
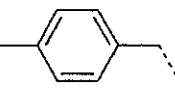
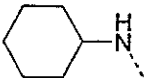
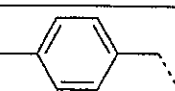
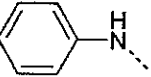
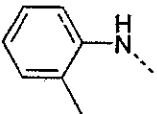
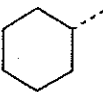
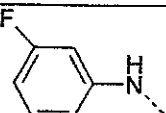
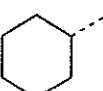
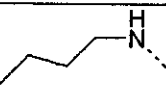
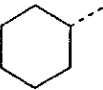
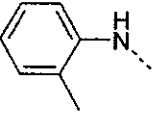
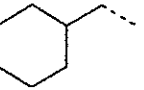
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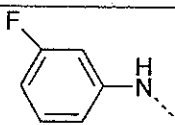
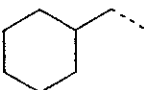
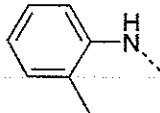
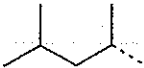
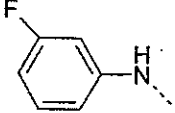
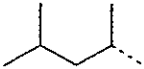
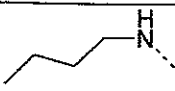
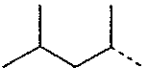
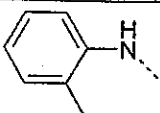
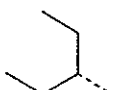
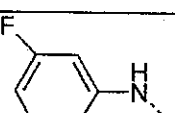
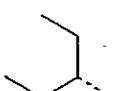
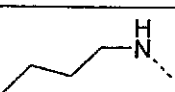
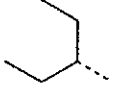
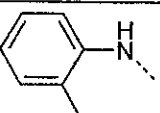
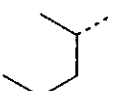
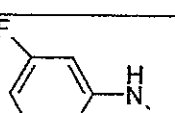
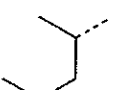
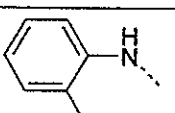
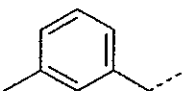


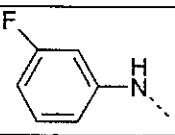
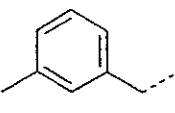
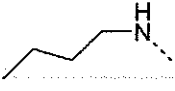
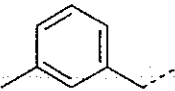
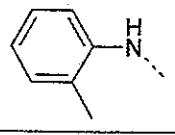
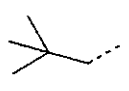
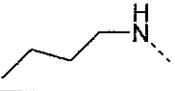
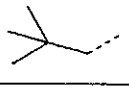
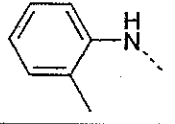
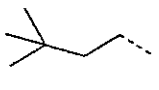
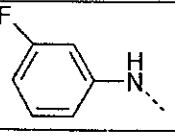
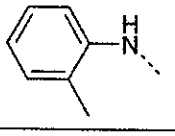
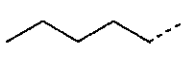
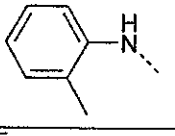
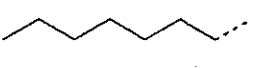
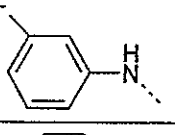
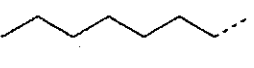
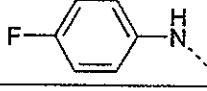
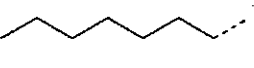
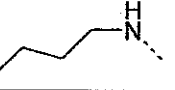
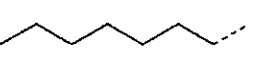
In the examples, ring A = cis-cyclohexane-1,3-diyl, R5 = methyl, R4 = H, X = O(CH₂)₂ and Y = OCH₂.

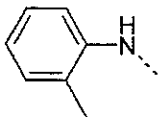
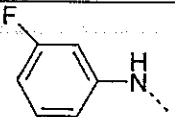
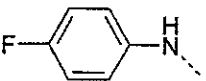
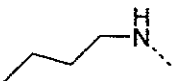
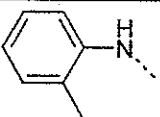
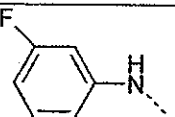
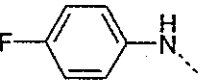
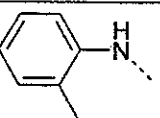
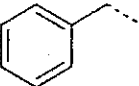
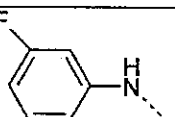
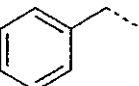
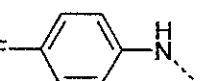
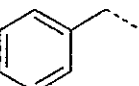
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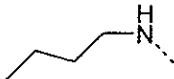
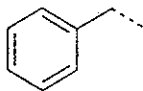
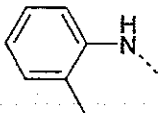
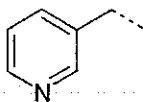
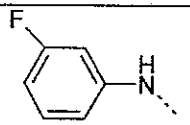
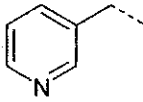
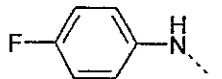
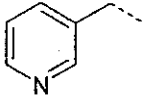
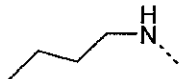
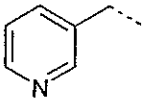
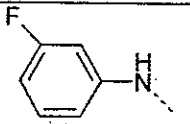
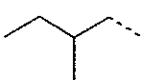
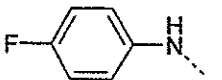
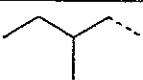
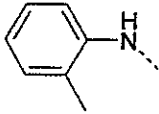
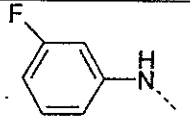
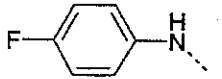
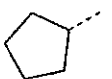
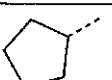
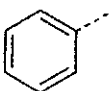
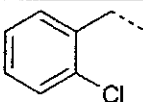
Ex.	R- Ex	R3-
I		
II		
III		
IV		
V		
VI		
VII		

Ex.	R-	R3-
VIII		
IX		
X		
XI		
XII		
XIII		
XIV		
XV		
XVI		
XVII		
XVIII		

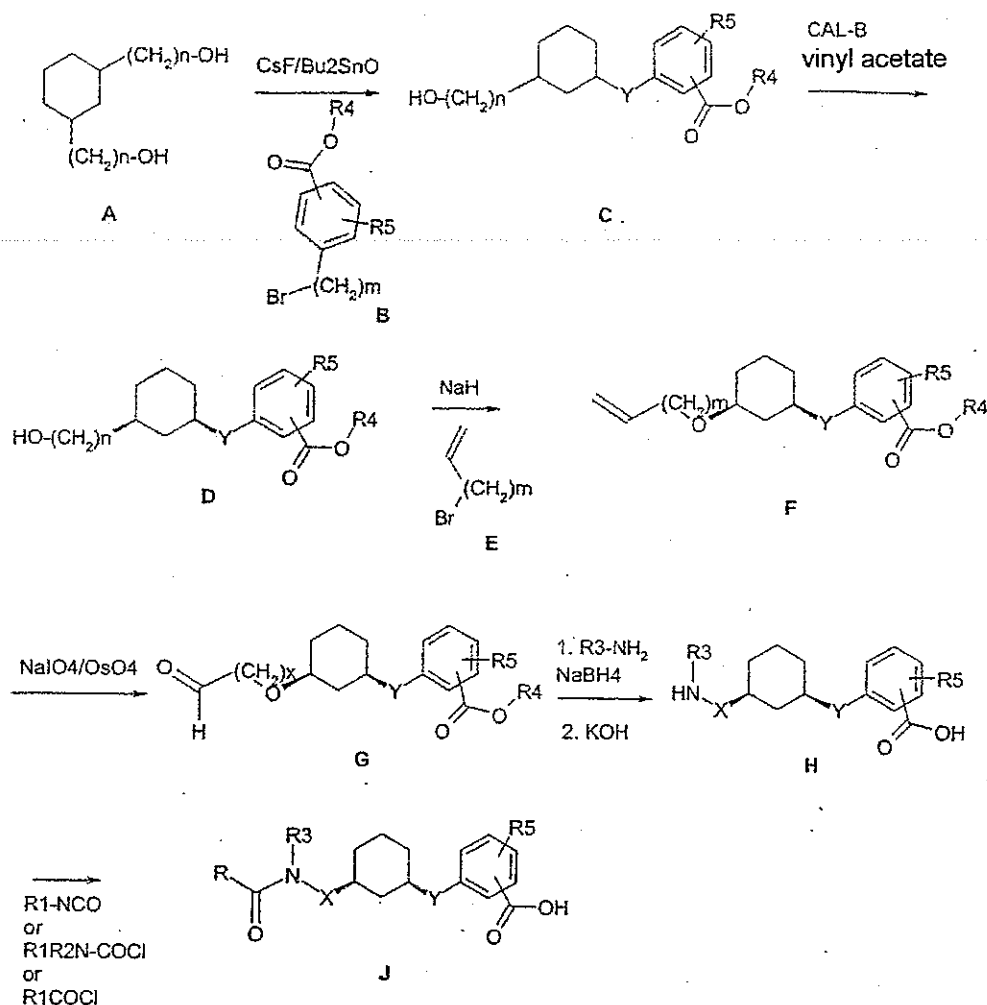
Ex.	R-	R3-
XIX		
XX		
XXI		
XXII		
XXIII		
XXIV		
XXV		
XXVI		
XXVII		
XXVIII		

Ex.	R-	R3-
XXIX		
XXX		
XXXI		
XXXII		
XXXIII		
XXXIV		
XXXV		
XXXVI		
XXXVII		
XXXVIII		
XXXIX		

Ex.	R-	R3-
XL		
XLI		
XLII		
XLIII		
XLIV		
XLV		
XLVI		
XLVII		
XLVIII		
XLIX		
L		

Ex.	R-	R3-
LI		
LII		
LIII		
LIV		
LV		
LVI		
LVII		
LVIII		
LIX		
LX		
LXI		
LXII		

The compounds of the formula I according to the invention can be obtained in accordance with the reaction scheme below:



- The compound of the formula A in which $n = 0-2$ and dibutyltin oxide are heated in toluene under reflux on a water separator. After addition of cesium fluoride and dimethylformamide, the mixture is reacted with a compound of the formula B in which R_4 and R_5 are as defined above and in which $x = 1-4$, to give a compound of the formula C in which Y , R_4 and R_5 are as defined above.
- 5
 - 10 By stirring with *Candida antarctica* lipase B in vinyl acetate at room temperature, the compound of the formula C is converted into the enantiomerically pure product of the formula D. The corresponding other enantiomer is removed chromatographically, by known methods.
 - 15 The compound of formula C or D is deprotonated with sodium hydride in dimethylformamide or tetrahydrofuran and reacted at room temperature with an alkenyl bromide of the formula E in which $m = 0-2$ to give the

racemic (starting with C) or enantiomerically pure (starting with D) compound of the formula F.

- 5 The respective racemic or enantiomerically pure compound of the formula F is reacted with sodium periodate and osmium tetroxide in diethyl ether at 0°C to give the racemic or enantiomerically pure aldehyde of the formula G.

- 10 The compound of the formula G is reacted at room temperature with primary amines R₃-NH₂ in which R₃ is as defined above with addition of sodium borohydride in methanol. The ester is cleaved by reacting the substance in a tertiary alcohol (for example tert-butanol) with potassium hydroxide, to give the racemic or enantiomerically pure compound of the formula H in which X is as defined above.

- 15 The compound of the formula H is reacted with isocyanates R₁-NCO or carbamoyl chlorides R₁R₂N-COCl or carbonyl chlorides R₁-COCl in which R₁ and R₂ are as defined above, to give racemic or enantiomerically pure urea derivatives or carboxamides of the formula J in which R, R₃, R₅, X and Y are as defined above, by stirring both starting materials in an aprotic solvent (for example dimethylformamide) at room temperature in the presence of a base (for example pyridine) for a number of hours.
- 20

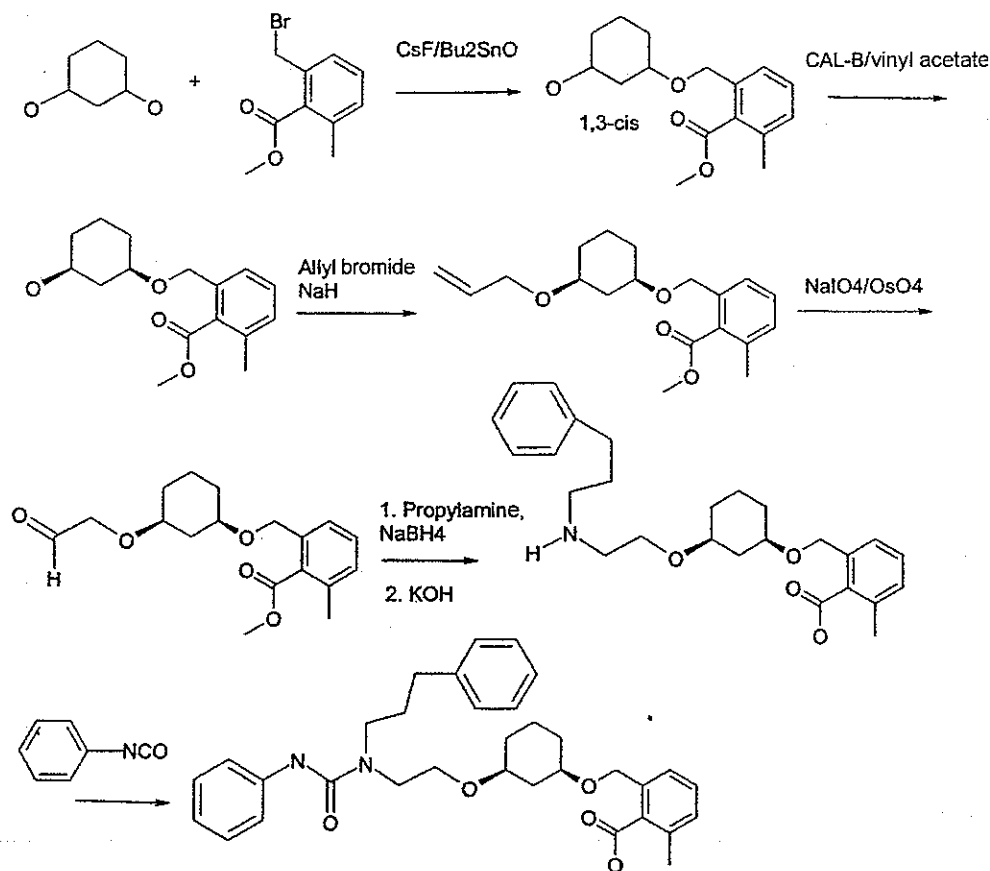
Further compounds of the formula I can be prepared analogously or by known processes.

The experimental procedures for preparing the examples mentioned above are described below:

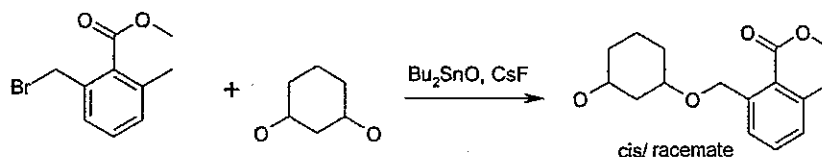
Examples I-XIV were prepared and tested in enantiomerically pure form.

5

Example I



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



8.7 g of 1,3-cyclohexanediol and 12 g of dibutyltin oxide are dissolved in 15 600 ml of toluene and heated to the boil under reflux on a water separator. 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 dimethylformamide, 9.0 g of methyl 2-bromomethyl-6-

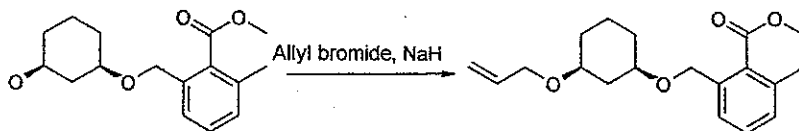
- methylbenzoate and 9.4 g of cesium fluoride are added. The mixture is stirred at room temperature for 12 hours. The reaction mixture is diluted by addition of ethyl acetate and washed with saturated sodium chloride solution. The organic phase is dried over magnesium sulfate, the solvent is reduced 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-hydroxycyclohexyloxymethyl)-6-methylbenzoate as an oil. C₁₆H₂₂O₄ (278.35), MS(ESI): 279 (M+H⁺).

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



- 13.1 g of methyl cis-2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate are dissolved in 100 ml of vinyl acetate and 1.6 g of *Candida antarctica* lipase B are added. After eight hours of stirring at room temperature, the enzyme is 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 → ethyl acetate). This gives 4.3 g of methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate as a colorless oil. C₁₆H₂₂O₄ (278.35), MS(ESI): 279 (M+H⁺), ee = 99% (Chiralpak AD/2 250x4.6; n-heptane:ethanol:methanol = 25:1:0.5 + 0.1% trifluoroacetic acid, Rt = 8.9 min)

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



- 4.3 g of methyl 2-((1R,3S)-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate are dissolved in 40 ml of dimethylformamide and 1.3 g of sodium hydride (60% strength suspension in paraffin oil) are added. After 40 minutes of stirring, 4 ml of allyl bromide, dissolved in 20 ml of tetrahydrofuran, are added. After 3 hours, 300 ml of ethyl acetate are

added and the mixture is washed three times with saturated sodium chloride solution. The combined organic phases are dried over sodium sulfate and the solvents are then removed under reduced pressure. The resulting residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 50:1 → 5:1. This gives 2.1 g of methyl 2-((1R,3S)-3-allyloxycyclohexyloxymethyl)-6-methylbenzoate as a yellow oil. C₁₉H₂₆O₄ (318.42), MS(ESI): 319 (M+H⁺).

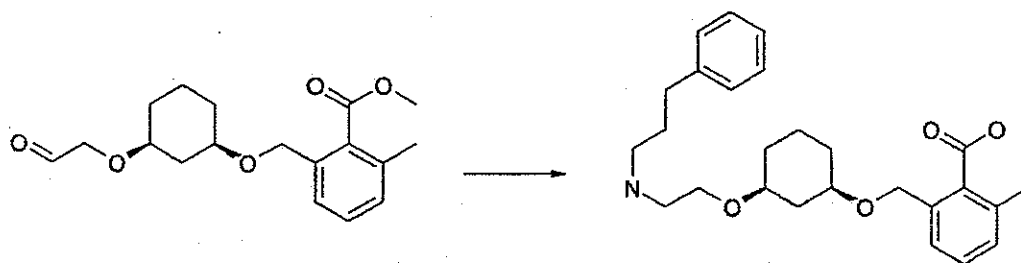
10 Methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate



1.0 g of methyl 2-((1R,3S)-3-allyloxycyclohexyloxymethyl)-6-methylbenzoate is dissolved in 30 ml of diethyl ether, and 2.0 g of sodium periodate, dissolved in 30 ml of water, are added. At 0°C, 2 ml of a solution of 2.5% by weight of osmium tetroxide and tert-butanol are added. The reaction mixture is stirred vigorously for three hours. The mixture is then cooled to 0°C, and 50 ml of a saturated sodium thiosulfate solution are added. The organic phase is removed. The aqueous phase is extracted three times with in each case 20 ml of diethyl ether. The combined organic phases are dried over magnesium sulfate and the solvent is then removed under reduced pressure. This gives 1.0 g of methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate as a yellow oil C₁₈H₂₄O₅ (320.39), MS(ESI): 321 (M+H⁺), R_f = 0.23 (n-heptane:ethyl acetate = 1:1).

25

2-Methyl-6-[(1R,3S)-3-[2-(3-phenylpropylamino)ethoxy]cyclohexyloxymethyl]benzoic acid

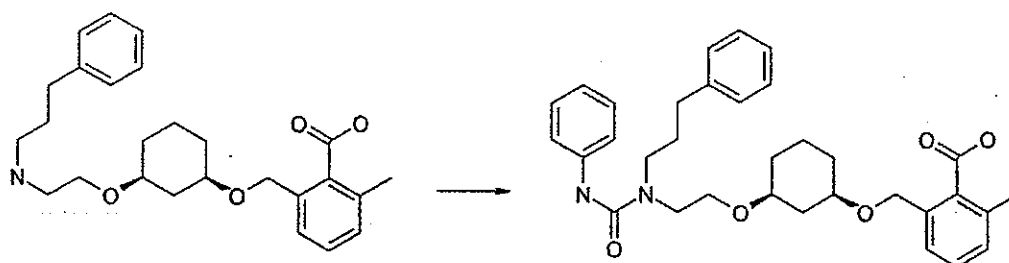


30

- 200 mg of methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)cyclohexyloxy-methyl]benzoate and 90 μ l of 3-phenylpropylamine are dissolved in 5 ml of methanol. 300 mg of 4 Å molecular sieve, which had been dried by heating, are added, and the mixture is stirred at room temperature for two hours.
- 5 25 mg of sodium borohydride are then added to the reaction mixture. After 30 minutes, 50 ml of ethyl acetate are added and the molecular sieve is removed from the mixture by filtration through celite. The filtrate is concentrated under reduced pressure, the residue is dissolved in 5 ml of tert-butanol and 0.5 ml of 10 N potassium hydroxide solution are added.
- 10 The mixture is refluxed for 1 day. After addition of 2 ml of water, the organic phase is removed and the aqueous phase is extracted three times with in each case 20 ml of ethyl acetate. The combined organic phases are dried over magnesium sulfate and the solvents are then removed under reduced pressure. This gives 160 mg of 2-methyl-6-[(1R,3S)-3-[2-(3-phenylpropylamino)ethoxy]cyclohexyloxymethyl]benzoic acid as a yellow oil. C₂₆H₂₅NO₄ (425.57), MS(ESI): 426 (M+H⁺).
- 15

2-[(1R,3S)-3-[2-(1-[3-Phenylpropyl]-3-phenylureido)ethoxy]cyclohexyloxymethyl]-6-methylbenzoic acid

20



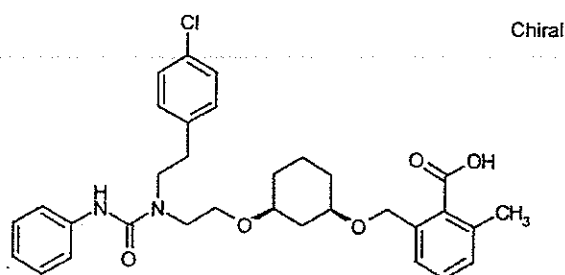
- 160 mg of 2-methyl-6-[(1R,3S)-3-[2-(3-phenylpropylamino)ethoxy]cyclohexyloxymethyl]benzoic acid are dissolved in 2 ml of dimethylformamide, and 0.1 ml of phenyl isocyanate is added. After 30 minutes, the reaction mixture is purified by RP-HPLC. This gives 54 mg of 2-[(1R,3S)-3-[2-(1-[3-phenylpropyl]-3-phenylureido)ethoxy]cyclohexyloxymethyl]-6-methylbenzoic acid as a white lyophilizate. C₃₃H₄₀N₂O₅ (544.70), MS(ESI): 545 (M+H⁺).
- 25

30

Example II

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-

cyclohexyloxymethyl]benzoate, 2-(4-chlorophenyl)ethylamine and phenyl isocyanate gave 2-((1R,3S)-3-[2-(1-[2-(4-chlorophenyl)ethyl]-3-phenylureido)ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid.

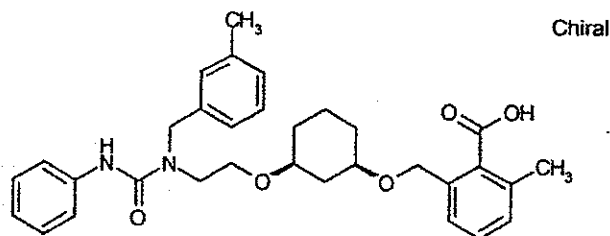


C₃₂H₃₇ClN₂O₅ (565.11), MS(ESI): 565 (M+H⁺).

5

Example III

Analogously to Example I, methyl 2-methyl-6-((1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, 3-methylbenzylamine and phenyl isocyanate gave 2-((1R,3S)-3-[2-(1-(3-methylbenzyl)-3-phenylureido)-ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid.

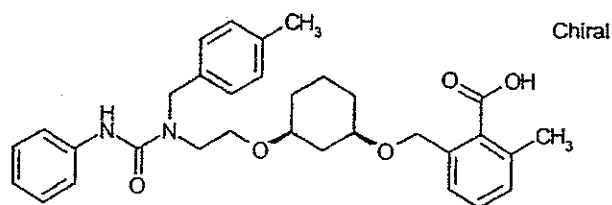


C₃₂ H₃₈ N₂ O₅ (530.66), MS(ESI): 531.

15 Example IV

Analogously to Example I, methyl 2-methyl-6-((1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, 4-methylbenzylamine and phenyl isocyanate gave 2-((1R,3S)-3-[2-(1-(4-methylbenzyl)-3-phenylureido)-ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid.

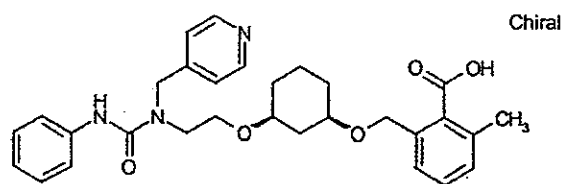
20



C32 H38 N2 O5 (530.66), MS(ESI): 531.

Example V

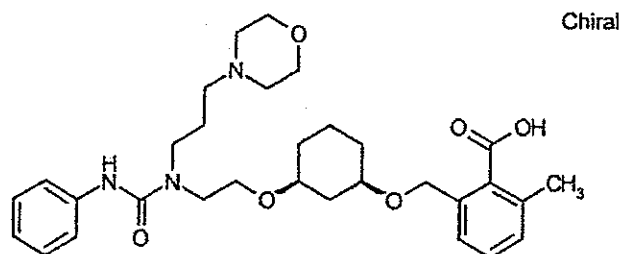
- 5 Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, pyridin-4-ylmethylamine and phenyl isocyanate gave 2-[(1R,3S)-3-[2-(1-pyridin-4-ylmethyl-3-phenylureido)-ethoxy]cyclohexyloxymethyl]-6-methylbenzoic acid.



C30 H35 N3 O5 (517.62), MS(ESI): 518.

Example VI

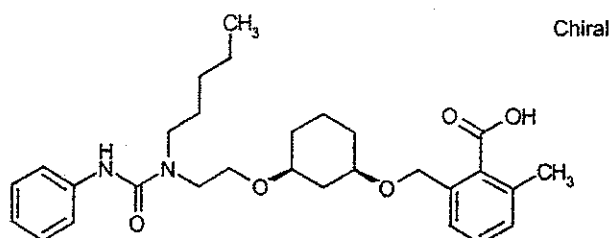
- 15 Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, 3-morpholin-4-ylpropylamine and phenyl isocyanate gave 2-[(1R,3S)-3-[2-(1-(3-morpholin-4-ylpropyl)-3-phenylureido)ethoxy]cyclohexyloxymethyl]-6-methylbenzoic acid.



C31 H43 N3 O6 (553.70), MS(ESI): 554.

Example VII

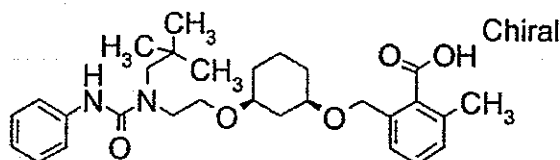
Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-
 cyclohexyloxymethyl]benzoate, pentylamine and phenyl isocyanate gave
 5 2-[(1R,3S)-3-[2-(1-pentyl-3-phenylureido)ethoxy]cyclohexyloxymethyl]-6-
 methylbenzoic acid.



C₂₉H₄₀N₂O₅ (496.64), MS(ESI): 497.

Example VIII

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-
 oxoethoxy)cyclohexyloxymethyl]benzoate, 2,2-dimethylpropylamine and
 phenyl isocyanate gave 2-[(1R,3S)-3-[2-[1-(2,2-dimethylpropyl)-3-
 15 phenylureido]ethoxy]cyclohexyloxymethyl]-6-methylbenzoic acid.



C₂₉H₄₀N₂O₅ (496.65), MS(ESI): 497.

Example IX

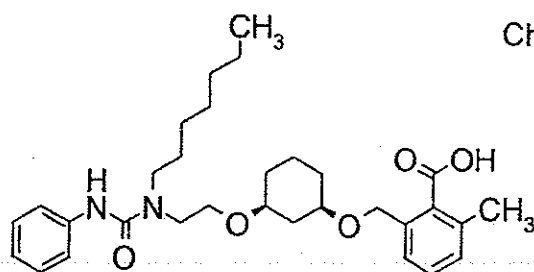
20

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-
 cyclohexyloxymethyl]benzoate, heptylamine and phenyl isocyanate gave 2-
 {(1R,3S)-3-[2-(1-heptyl-3-phenylureido)ethoxy]cyclohexyloxymethyl}-6-
 methylbenzoic acid.

25

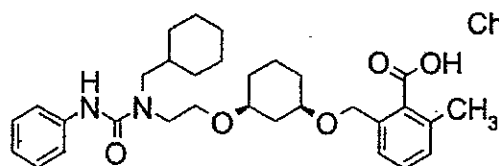
A002609939

Chiral

C₃₁H₄₄N₂O₅ (524.71), MS(ESI): 525.**Example X**

- 5 Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, cyclohexylmethylamine and phenyl isocyanate gave 2-[(1R,3S)-3-[2-(1-cyclohexylmethyl-3-phenylureido)-ethoxy]cyclohexyloxymethyl]-6-methylbenzoic acid.

Chiral

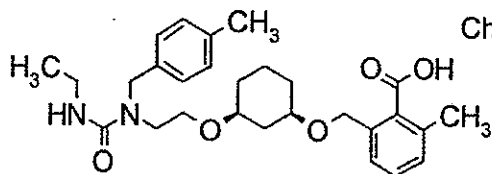
C₃₁H₄₂N₂O₅ (522.69), MS(ESI): 523.

10

Example XI

- 15 Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 4-methylbenzylamine and ethyl isocyanate gave 2-[(1R,3S)-3-{2-[3-ethyl-1-(4-methylbenzyl)ureido]ethoxy}-cyclohexyloxymethyl]-6-methyl benzoic acid.

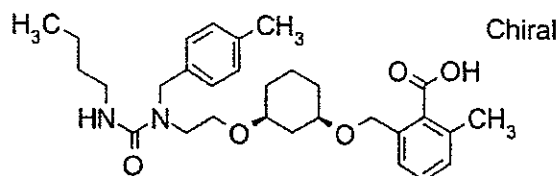
Chiral

C₂₈H₃₈N₂O₅ (482.63), MS(ESI): 483.

20

Example XII

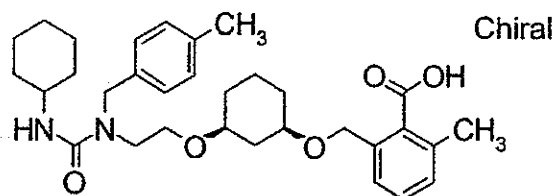
Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, 4-methylbenzylamine and butyl isocyanate
 5 gave 2-((1R,3S)-3-{2-[3-butyl-1-(4-methylbenzyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



C₃₀H₄₂N₂O₅ (510.68), MS(ESI): 511.

Example XIII

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, 4-methylbenzylamine and cyclohexyl
 15 isocyanate gave 2-((1R,3S)-3-{2-[3-cyclohexyl-1-(4-methylbenzyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



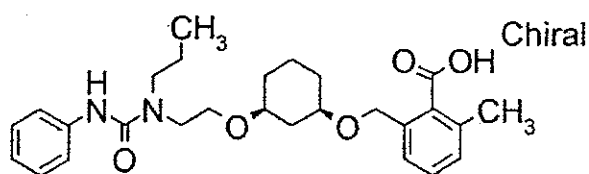
C₃₂H₄₄N₂O₅ (536.72), MS(ESI): 537.

Example XIV

20

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, propylamine and phenyl isocyanate gave
 2-methyl-6-[(1R,3S)-3-{2-[3-phenyl-1-propylureido]ethoxy}cyclohexyloxymethyl]benzoic acid.

25



C₂₇H₃₆N₂O₅ (468.60), MS(ESI): 469.

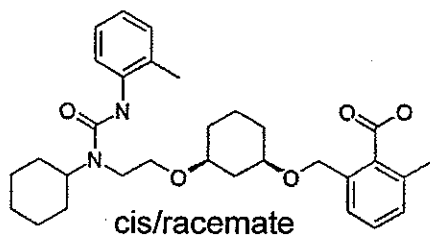
Examples XV-LXII were prepared and tested as racemic compounds having cis configuration of the two substituents on the cyclohexane ring.

5

Example XV

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, cyclohexylamine and 2-methylphenyl isocyanate gave 2-[cis-3-[2-(1-cyclohexyl-3-o-tolylureido)ethoxy]-cyclohexyloxymethyl]-6-methylbenzoic acid.

10

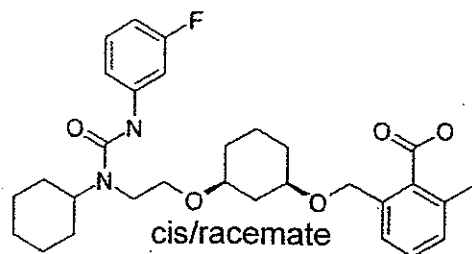


C₃₁H₄₂N₂O₅ (522.69), MS(ESI): 523 (M+H⁺).

15 Example XVI

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclohexylamine and 3-fluorophenylisocyanate gave 2-(cis-3-[2-[1-cyclohexyl-3-(3-fluorophenyl)-ureido]ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid.

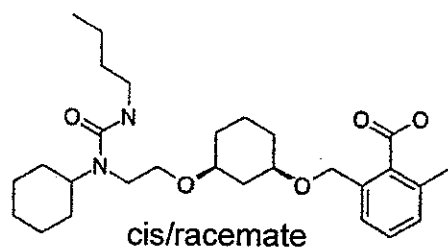
20



C30H39FN2O5 (526.65), MS(ESI): 527 (M+H+).

Example XVII

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclohexylamine and butyl isocyanate gave 2-{cis-3-[2-(3-butyl-1-cyclohexylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.

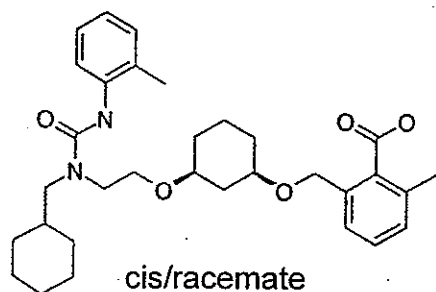


C28H44N2O5 (488.67), MS(ESI): 489 (M+H+).

10

Example XVIII

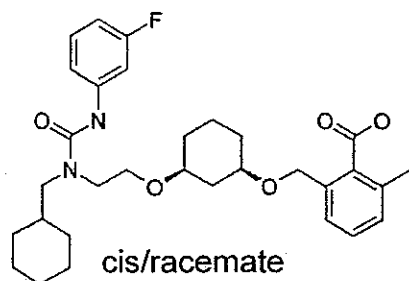
- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclohexylmethylamine and 2-methyl phenyl isocyanate gave 2-{cis-3-[2-(1-cyclohexylmethyl-3-o-tolylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.



C32H44N2O5 (536.72), MS(ESI): 537 (M+H+).

Example XIX

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)-
 5 cyclohexyloxymethyl]benzoate, cyclohexylmethylamine and 3-fluorophenyl-
 isocyanate gave 2-(cis-3-{2-[1-cyclohexylmethyl-3-(3-fluorophenyl)ureido]-
 ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

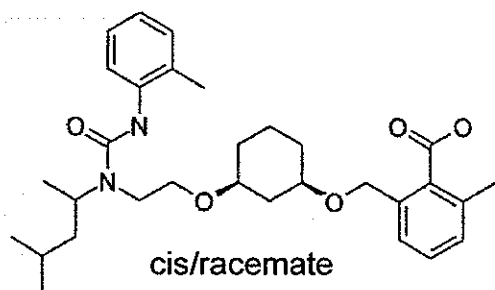


C₃₁H₄₁FN₂O₅ (540.68), MS(ESI): 541 (M+H⁺).

10

Example XX

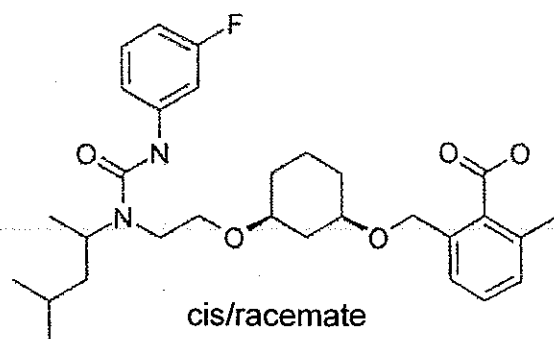
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1,3-dimethylbutylamine and
 15 2-methyl phenyl isocyanate gave 2-(cis-3-{2-[1-((1R)/(1S),3-dimethylbutyl)-
 3-o-tolylureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



C₃₁H₄₄N₂O₅ (524.71), MS(ESI): 525 (M+H⁺).

Example XXI

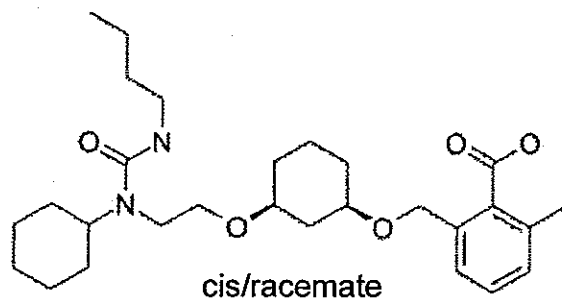
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1,3-dimethylbutylamine and
 3-fluorophenyl isocyanate gave (cis-3-{2-[1-((1S)/(1R),3-dimethylbutyl)-3-
 25 (3-fluorophenyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



C₃₀H₄₁FN₂O₅ (528.67), MS(ESI): 529 (M+H⁺).

5 Example XXII

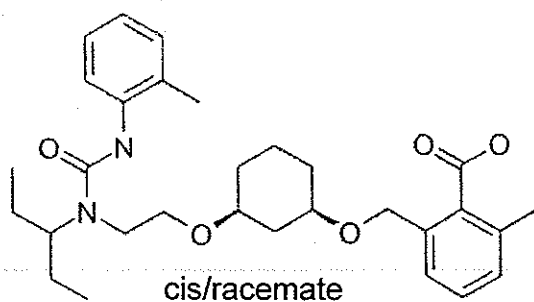
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, 1,3-dimethylbutylamine and butyl isocyanate gave 2-(cis-3-{2-[3-butyl-1-((1S)/(1R),3-dimethylbutyl)ureido]-ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



C₂₈H₄₆N₂O₅ (490.69), MS(ESI): 491 (M+H⁺).

15 Example XXIII

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1-ethylpropylamine and 2-methylphenyl isocyanate gave 2-(cis-3-{2-[1-(1-ethylpropyl)-3-o-tolylureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



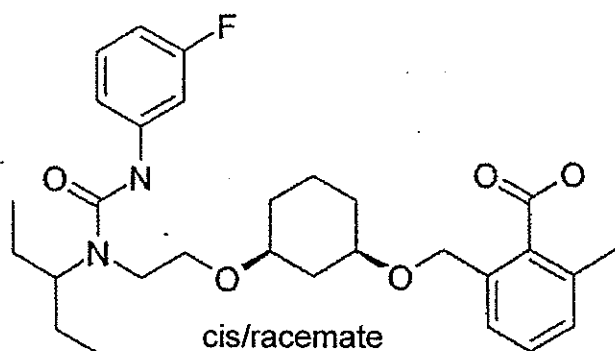
C₃₀H₄₂N₂O₅ (510.68) MS(ESI): 511.

Example XXIV

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1-ethylpropylamine and 3-fluorophenyl isocyanate gave 2-(cis-3-{2-[1-(1-ethylpropyl)-3-(3-fluorophenyl)-ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

10

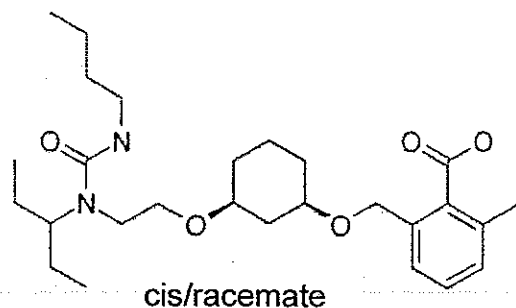


C₂₉H₃₉FN₂O₅ (514.64), MS(ESI): 515 (M+H⁺).

Example XXV

15

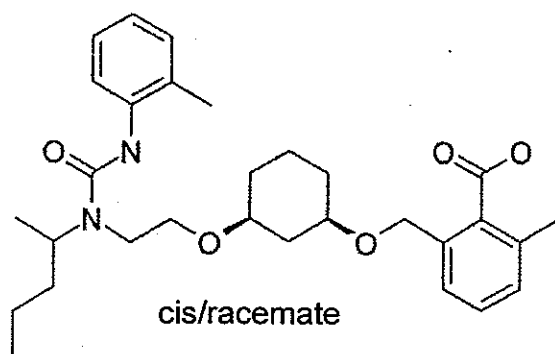
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1-ethylpropylamine and butyl isocyanate gave 2-(cis-3-{2-[3-butyl-1-(1-ethylpropyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



C₂₇H₄₄N₂O₅ (476.66), MS(ESI): 477 (M+H⁺).

Example XXVI

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1-methylbutylamine and 2-methylphenyl isocyanate gave 2-methyl-6-(cis-3-{2-[1-(methylbutyl)-3-oxotolylureido]ethoxy}cyclohexyloxymethyl)benzoic acid.

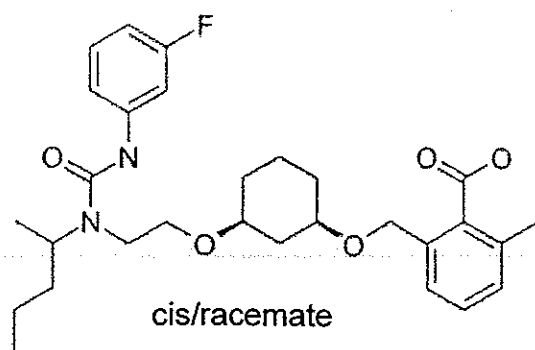


10

C₃₀H₄₂N₂O₅ (510.68), MS(ESI): 511 (M+H⁺).

Example XXVII

- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1-methylbutylamine and 3-fluorophenylisocyanate gave 2-(cis-3-{2-[3-(3-fluorophenyl)-1-(methylbutyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



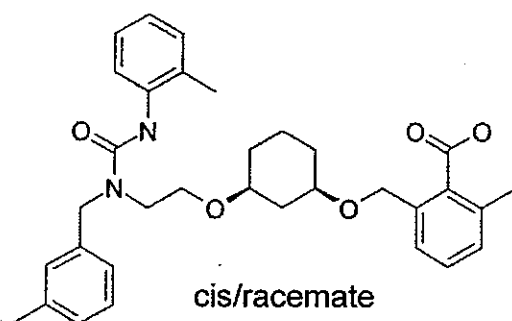
C₂₉H₃₉FN₂O₅ (514.64), MS(ESI): 515 (M+H⁺).

Example XXVIII

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 3-methylbenzylamine and 2-methylphenyl isocyanate gave 2-methyl-6-(cis-3-{2-[1-(3-methylbenzyl)-3-o-tolylureido]ethoxy}cyclohexyloxymethyl)benzoic acid.

10



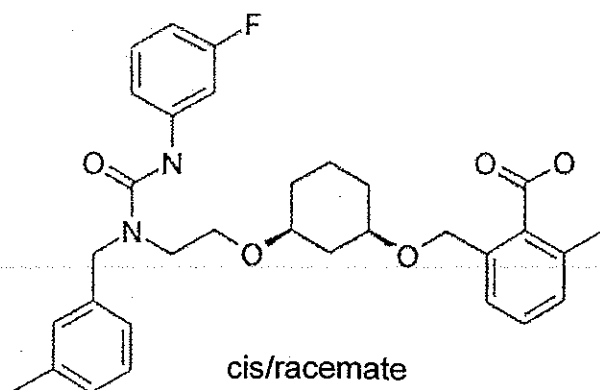
C₃₃H₄₀N₂O₅ (544.70), MS(ESI): 545 (M+H⁺).

544.2937

Example XXIX

15

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 3-methylbenzylamine and 3-fluorophenyl isocyanate gave 2-(cis-3-{2-[3-(3-fluorophenyl)-1-(3-methylbenzyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



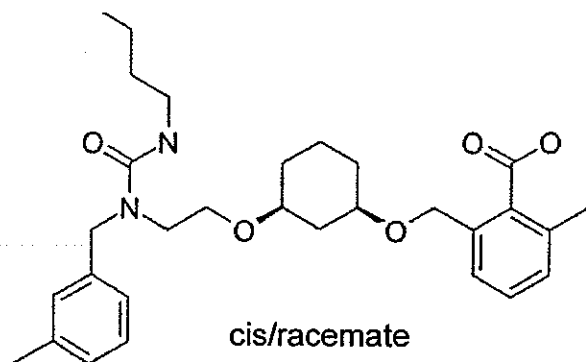
C₃₂H₃₇FN₂O₅ (548.66), MS(ESI): 549 (M+H⁺).
548.2687

Example XXX

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 3-methylbenzylamine and butyl isocyanate gave 2-(cis-3-{2-[3-butyl-1-(3-methylbenzyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

10

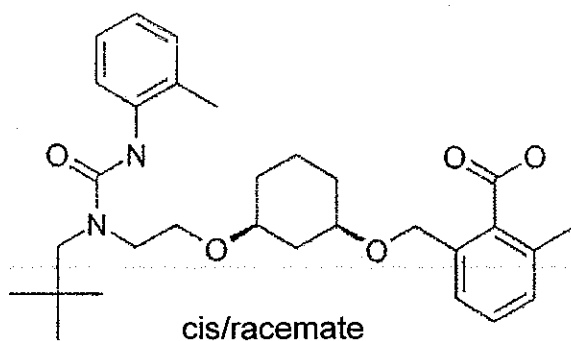


C₃₀H₄₂N₂O₅ (510.68), MS(ESI): 511 (M+H⁺).

Example XXXI

15

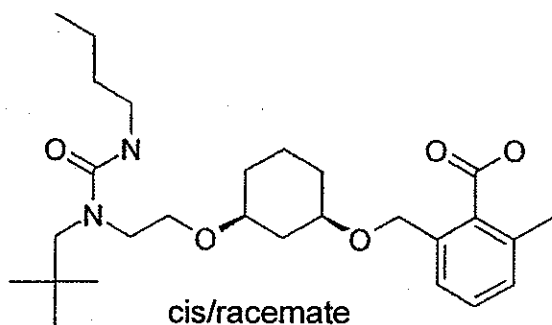
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 2,2-dimethylpropylamine and 2-methylphenylisocyanate gave 2-(cis-3-{2-[1-(2,2-dimethylpropyl)-3-o-tolylureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



C₃₀H₄₂N₂O₅ (510.68), MS(ESI): 511 (M+H⁺).

Example XXXII

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 2,2-dimethylpropylamine and butyl isocyanate gave 2-(cis-3-{2-[3-butyl-1-(2,2-dimethylpropyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

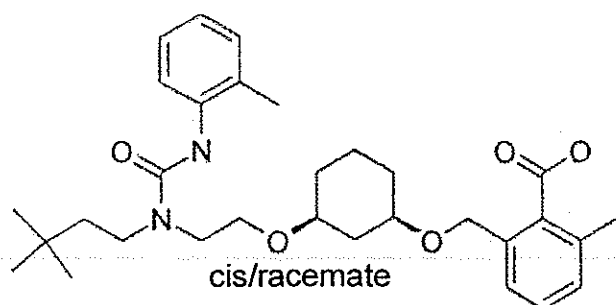


10

C₂₇H₄₄N₂O₅ (476.66), MS(ESI): 477 (M+H⁺).

Example XXXIII

- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 3,3-dimethylbutylamine and 2-methylphenylisocyanate gave 2-(cis-3-{2-[1-(3,3-dimethylbutyl)-3-*o*-tolylureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



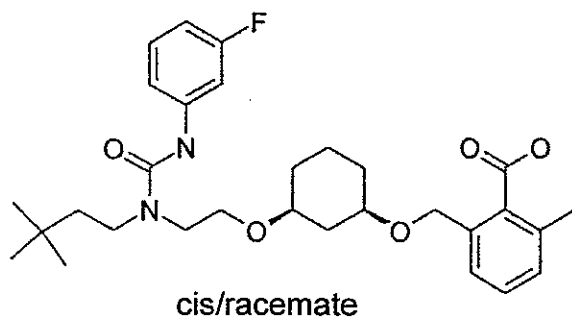
C₃₁H₄₄N₂O₅ (524.71), MS(ESI): 525 (M+H⁺).

Example XXXIV

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, 3,3-dimethylbutylamine and 3-fluorophenyl-isocyanate gave 2-(cis-3-{2-[1-(3,3-dimethylbutyl)-3-(3-fluorophenyl)-ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

10

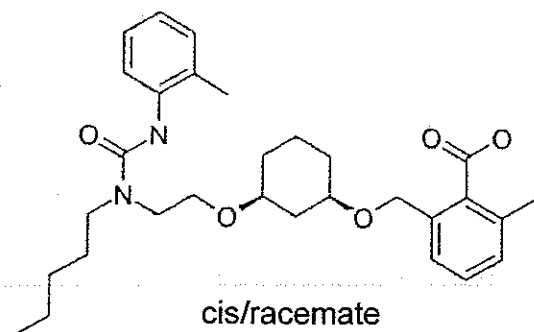


C₃₀H₄₁FN₂O₅ (528.67), MS(ESI): 529 (M+H⁺).

Example XXXV

15

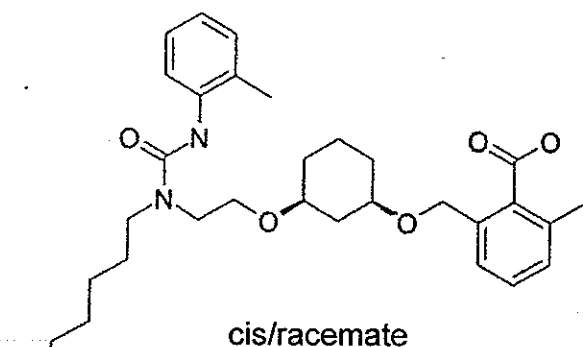
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, pentylamine and 2-methylphenyl isocyanate gave 2-methyl-6-{cis-3-[2-(1-pentyl-3-o-tolylureido)ethoxy]cyclohexyloxymethyl}benzoic acid.



C₃₀H₄₂N₂O₅ (510.68), MS(ESI): 511 (M+H⁺).

Example XXXVI

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, heptylamine and 2-methylphenyl isocyanate gave 2-{cis-3-[2-(1-heptyl-3-o-tolylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.

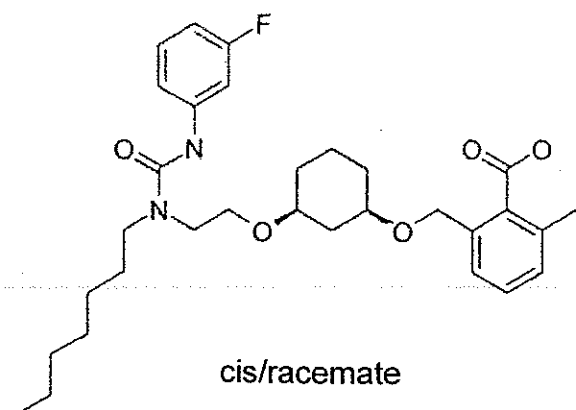


10

C₃₂H₄₆N₂O₅ (538.73), MS(ESI): 539 (M+H⁺).

Example XXXVII

- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, heptylamine and 3-fluorophenyl isocyanate gave 2-(cis-3-[2-[3-(3-fluorophenyl)-1-heptylureido]ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid.



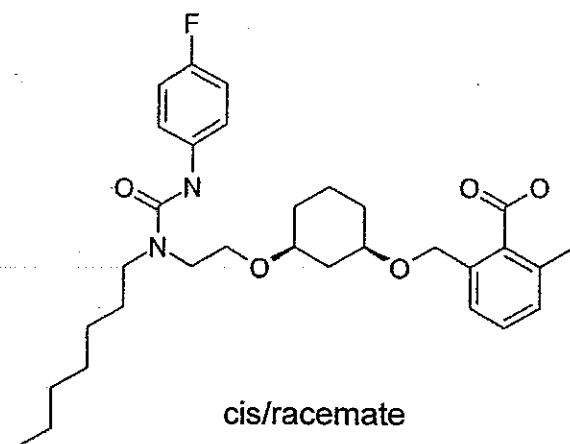
C₃₁H₄₃FN₂O₅ (542.70), MS(ESI): 543 (M+H⁺).

Example XXXVIII

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, heptylamine and 4-fluorophenyl isocyanate gave 2-(cis-3-{2-[3-(4-fluorophenyl)-1-heptylureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

10



C₃₁H₄₃FN₂O₅ (542.70), MS(ESI): 542 (M+H⁺).

Example XXXIX

15

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, heptylamine and butyl isocyanate gave 2-{cis-3-[2-(3-butyl-1-heptylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.



C₂₉H₄₈N₂O₅ (504.72), MS(ESI): 505 (M+H⁺).

Example XL

- 5 Analogously to Example 1, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1,2-dimethylpropylamine and 2-methylphenylisocyanate gave 2-(cis-3-{2-[1-((1R)/(1S),2-dimethylpropyl)-3-o-tolylureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

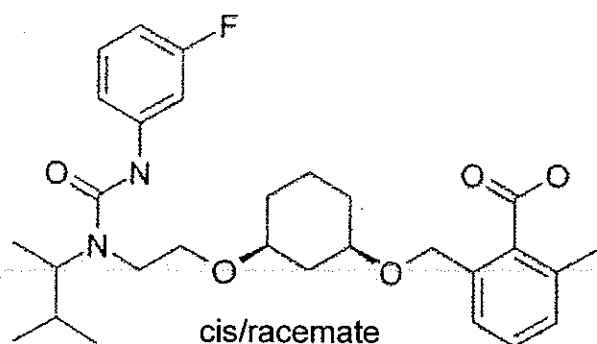


10

C₃₀H₄₂N₂O₅ (510.68), MS(ESI): 567 (M+H⁺).

Example XLI

- 15 Analogously to Example 1, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1,2-dimethylpropylamine and 3-fluorophenylisocyanate gave 2-(cis-3-{2-[1-(2-dimethylpropyl)-3-(3-fluorophenyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



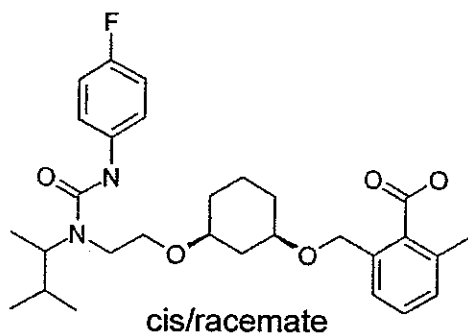
C₂₉H₃₉FN₂O₅ (514.64), MS(ESI): 515 (M+H⁺).

Example XLII

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1,2-dimethylpropylamine and 4-fluorophenylisocyanate gave 2-(cis-3-{2-[1-(2-dimethylpropyl)-3-(4-fluorophenyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

10

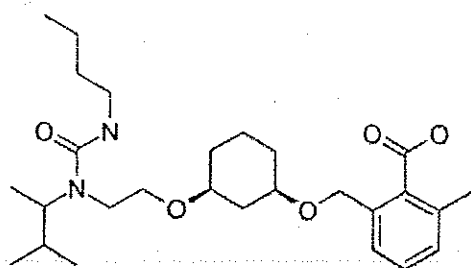


C₂₉H₃₉FN₂O₅ (514.64), MS(ESI): 515 (M+H⁺).

Example XLIII

15

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 1,2-dimethylpropylamine and butyl isocyanate gave 2-(cis-3-{2-[3-butyl-1-(2-dimethylpropyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

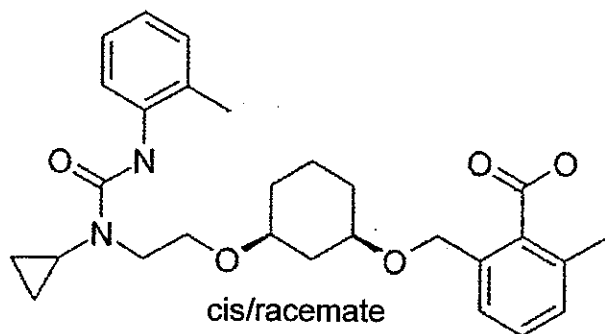


cis/racemate

C₂₇H₄₄N₂O₅ (476.66), MS(ESI): 477 (M+H⁺).

Example XLIV

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, cyclopropylamine and 2-methylphenyl isocyanate gave 2-{cis-3-[2-(1-cyclopropyl-3-o-tolylureido)ethoxy]-cyclohexyloxymethyl}-6-methylbenzoic acid.



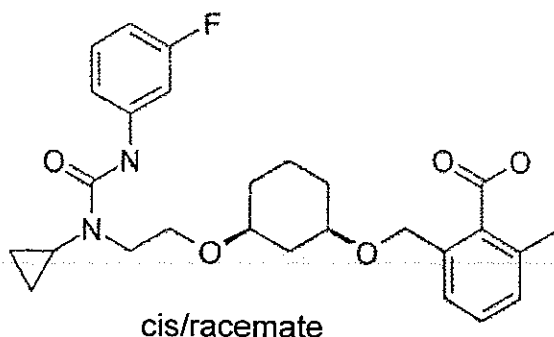
cis/racemate

10

C₂₈H₃₆N₂O₅ (480.61), MS(ESI): 481 (M+H⁺).

Example XLV

- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclopropylamine and 3-fluorophenyl isocyanate gave 2-(cis-3-{2-[1-cyclopropyl-3-(3-fluorophenyl)-ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



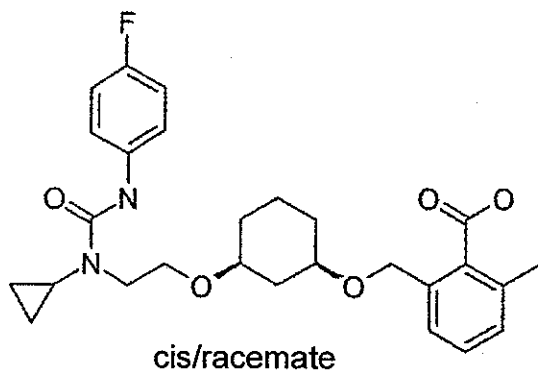
C₂₇H₃₃FN₂O₅ (484.57), MS(ESI): 485 (M+H⁺).

Example XLVI

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)-cyclohexyloxymethyl]benzoate, cyclopropylamine and 4-fluorophenyl isocyanate gave 2-(cis-3-{2-[1-cyclopropyl-3-(4-fluorophenyl)ureido]-ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

10

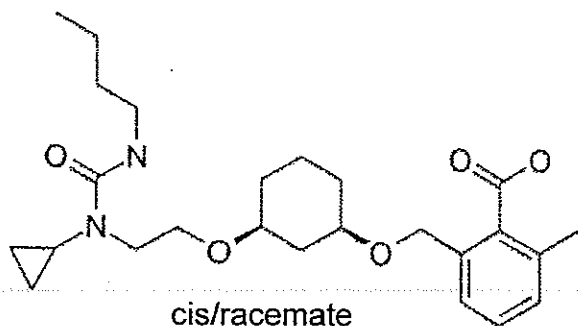


C₂₇H₃₃FN₂O₅ (484.57), MS(ESI): 485 (M+H⁺).

Example XLVII

15

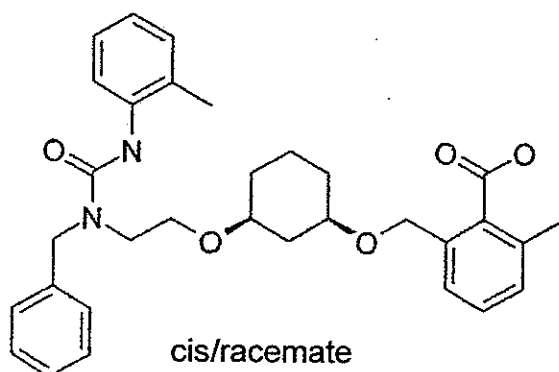
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclopropylamine and butyl isocyanate gave 2-{cis-3-[2-(3-butyl-1-cyclopropylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.



C₂₅H₃₈N₂O₅ (446.59), MS(ESI): 447 (M+H⁺).

Example XLVIII

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, benzylamine and 2-methylphenylisocyanate gave 2-[cis-3-[2-(1-benzyl-3-o-tolylureido)ethoxy]cyclohexyloxymethyl]-6-methylbenzoic acid.

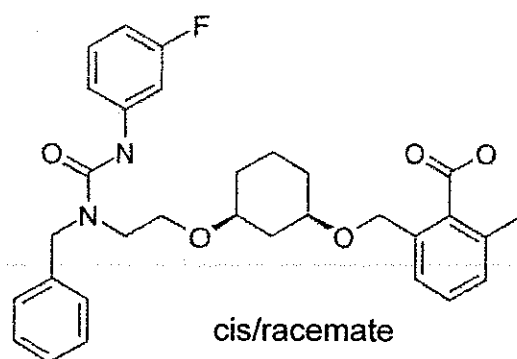


10

C₃₂H₃₈N₂O₅ (530.67), MS(ESI): 531 (M+H⁺).

Example XLIX

- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, benzylamine and 3-fluorophenyl isocyanate gave 2-(cis-3-[2-[1-benzyl-3-(3-fluorophenyl)ureido]ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid.



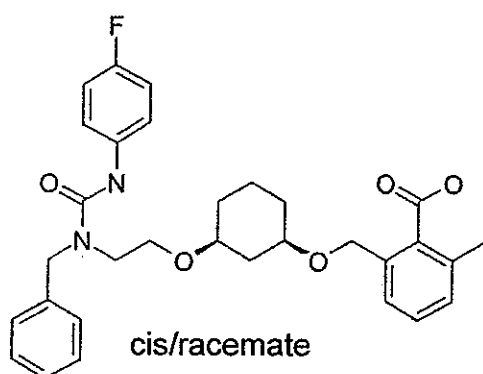
C₃₁H₃₅FN₂O₅ (534.63), MS(ESI): 535 (M+H⁺).

Example L

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, benzylamine and 4-fluorophenyl isocyanate gave 2-(cis-3-{2-[1-benzyl-3-(4-fluorophenyl)ureido]ethoxy}-cyclohexyloxymethyl)-6-methylbenzoic acid.

10

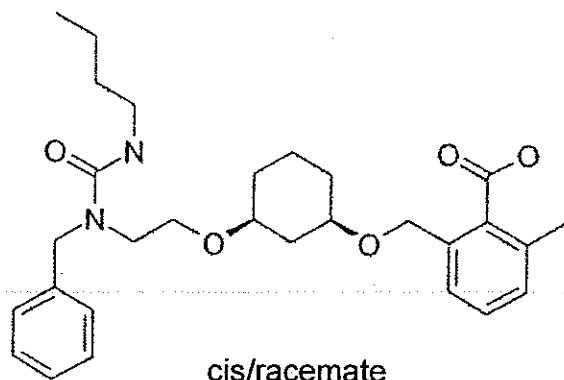


C₃₁H₃₅FN₂O₅ (534.63), MS(ESI): 535 (M+H⁺).

Example LI

15

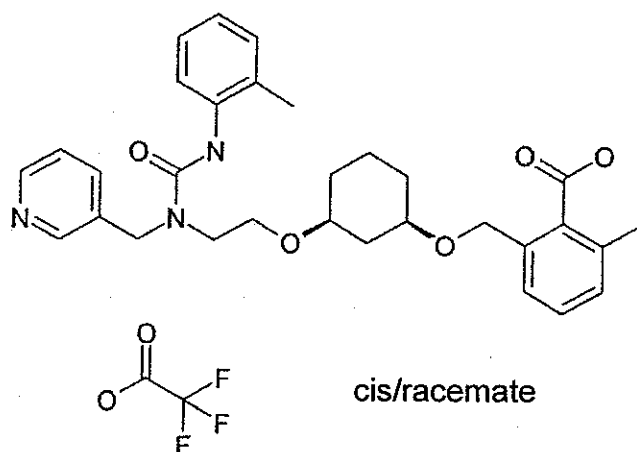
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, benzylamine and butyl isocyanate gave 2-{cis-3-[2-(1-benzyl-3-butylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.



C₂₉H₄₀N₂O₅ (496.65), MS(ESI): 497 (M+H⁺).

Example LII

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, pyridin-4-ylmethylamine and 2-methylphenyl isocyanate gave 2-methyl-6-[cis-3-[2-(1-pyridin-3-ylmethyl-3-o-tolylureido)ethoxy]cyclohexyloxymethyl]benzoic acid trifluoroacetate.

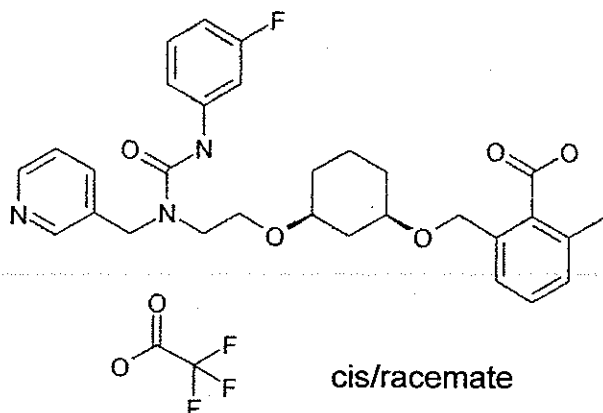


10

C₃₁H₃₇N₃O₅.C₂HF₃O₂ (645.68), MS(ESI): 532 (M+H⁺).

Example LIII

- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, pyridin-4-ylmethylamine and 3-fluorophenylisocyanate gave 2-(cis-3-[2-[3-(3-fluorophenyl)-1-pyridin-3-ylmethylureido]ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid trifluoroacetate.

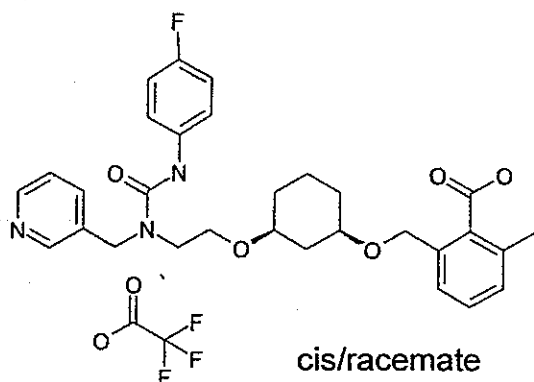


C₃₀H₃₅N₃O₅.C₂HF₂3O₂ (649.64), MS(ESI): 536 (M+H⁺).

Example LIV

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, pyridin-4-ylmethylamine and 4-fluorophenylisocyanate gave 2-(cis-3-{2-[3-(4-fluorophenyl)-1-pyridin-3-ylmethylureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid trifluoroacetate.

10

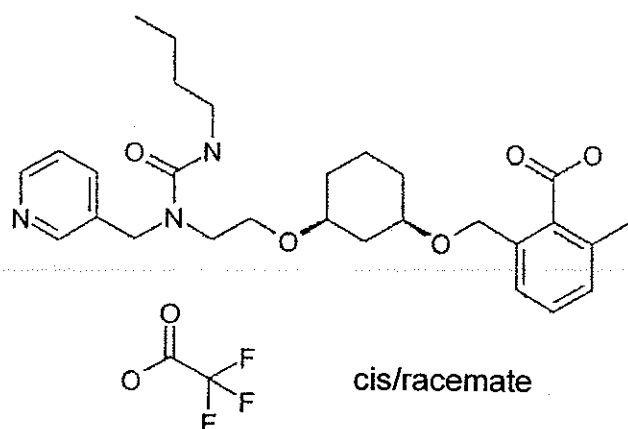


C₃₀H₃₄FN₃O₅.C₂HF₃O₂ (649.64); MS(ESI): 536 (M+H⁺).

Example LV

15

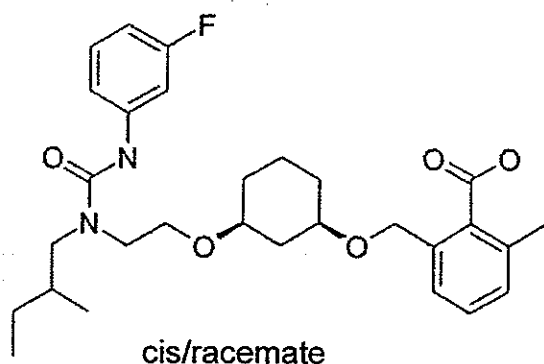
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, pyridin-4-ylmethylamine and butyl isocyanate gave 2-{cis-3-[2-(3-butyl-1-pyridin-3-ylmethylureido)-ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid trifluoroacetate.



C₂₈H₃₉N₃O₅.C₂HF₃O₂ (611.66), MS(ESI): 498 (M+H⁺).

Example LVI

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 2-methylbutylamine and 3-fluorophenyl isocyanate gave 2-(cis-3-{2-[3-(3-fluorophenyl)-1-(2-methylbutyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

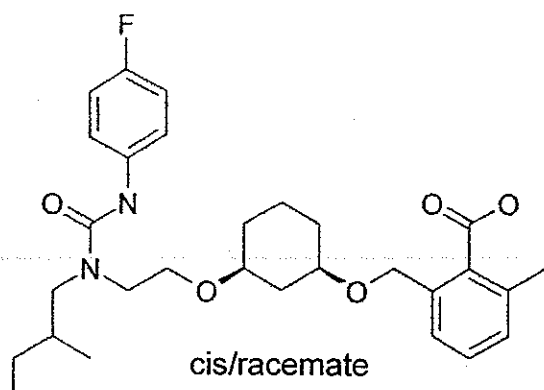


10

C₂₉H₃₉FN₂O₅ (514.643), MS(ESI): 515 (M+H⁺).

Example LVII

- 15 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 2-methylbutylamine and 4-fluorophenyl isocyanate gave 2-(cis-3-{2-[3-(4-fluorophenyl)-1-(2-methylbutyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



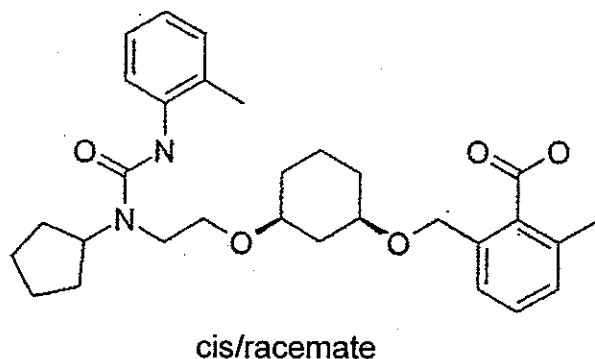
C₂₉H₃₉FN₂O₅ (514.64), MS(ESI): 515 (M+H⁺).

Example LVIII

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclopentylamine and 2-methylphenyl isocyanate gave 2-{cis-3-[2-(1-cyclopentyl-3-o-tolylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.

10

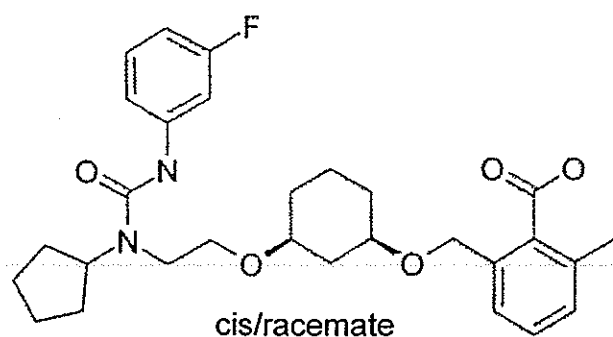


C₃₀H₄₀N₂O₅ (508.66), MS(ESI): 509 (M+H⁺).

15 Example LIX

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclopentylamine and 3-fluorophenyl isocyanate gave 2-(cis-3-[2-[1-cyclopentyl-3-(3-fluorophenyl)ureido]ethoxy]cyclohexyloxymethyl)-6-methylbenzoic acid.

20



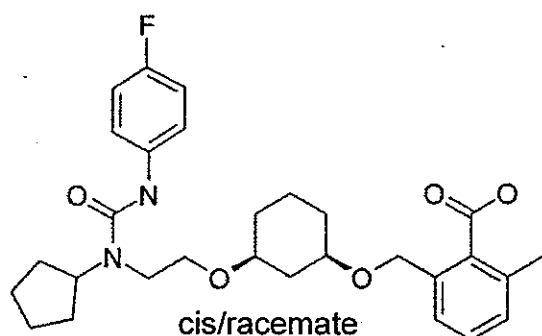
C₂₉H₃₇FN₂O₅ (512.62), MS(ESI): 513 (M+H⁺).

Example LX

5

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclopentylamine and 4-fluorophenyl isocyanate gave 2-(cis-3-{2-[1-cyclopentyl-3-(4-fluorophenyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

10

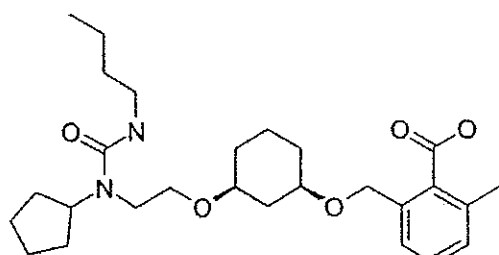


C₂₉H₃₇FN₂O₅ (512.62), MS(ESI): 513 (M+H⁺).

Example LXI

15

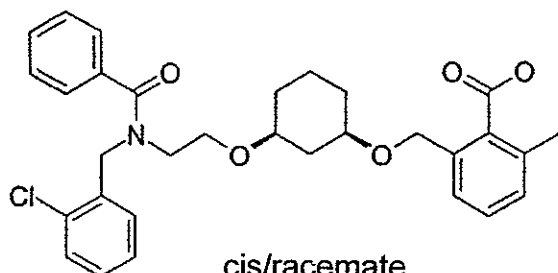
Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, cyclopentylamine and butyl isocyanate gave 2-{cis-3-[2-(3-butyl-1-cyclopentylureido)ethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid.



cis/racemate

C₂₇H₄₂N₂O₅ (474.65), MS(ESI): 475 (M+H⁺).**Example LXII**

- 5 Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, 2-chlorobenzylamine and benzoyl chloride gave 2-(cis-3-{2-[benzoyl-(2-chlorobenzyl)amino]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.



cis/racemate

10

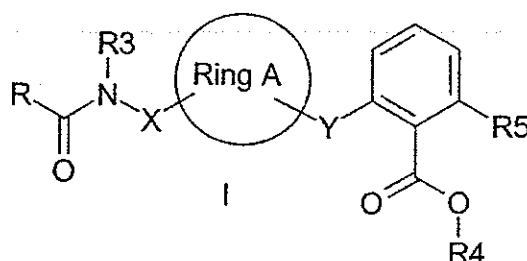
C₃₁H₃₄ClNO₅ (536.07), MS(ESI): 536 (M+H⁺).

We claim:

DEAV2003/0016

Dr.WI

1. A compound of the formula I



5

in which

10 ring A is (C3-C8)-cycloalkanediyl or (C3-C8)-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;

15 R is NR₁R₂ or OR₁, (C6-C10)-aryl or (C5-C12)-heteroaryl, where heteroaryl may contain one to three identical or different heteroatoms selected from the group consisting of N, O and S;

20 R₁, R₂ independently of one another are H, (C1-C6)-alkyl, (C3-C8)-cycloalkyl or (C6-C10)-aryl, where aryl may be unsubstituted or substituted by F, Cl or (C1-C4)-alkyl;

25 R₃ is (C3-C6)-cycloalkyl or (C1-C10)-alkyl which are unsubstituted or substituted by phenyl, pyridyl, morpholinyl, (C3-C6)-cycloalkyl, where phenyl for its part may be substituted by chlorine or (C1-C4)-alkyl;

30 X is (C1-C6)-alkanediyl, where one or more carbon atoms in the alkanediyl group may be replaced by oxygen atoms;

Y is (C1-C6)-alkanediyl, where one or more carbon atoms in the alkanediyl group may be replaced by oxygen atoms;

R₄ is H, (C1-C4)-alkyl;

R5 is (C1-C4)-alkyl;

and its physiologically acceptable salts.

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

ring A is (C3-C8)-cycloalkane-1,3-diyl or (C3-C8)-cycloalkene-1,3-diyl;

R is NR₁R₂ or (C6-C10)-aryl;

10

R₁, R₂ independently of one another are H, (C1-C6)-alkyl, (C3-C8)-cycloalkyl or (C6-C10)-aryl, where aryl may be unsubstituted or substituted by F, Cl or (C1-C4)-alkyl;

15 R₃ is (C3-C6)-cycloalkyl or (C1-C8)-alkyl which is unsubstituted or substituted by phenyl, pyridyl, morpholinyl, (C3-C6)-cycloalkyl, where phenyl for its part may be substituted by chlorine or methyl;

20 X is (C1-C3)-alkanediyl, where one carbon atom in the alkanediyl group may be replaced by an oxygen atom;

Y is (C1-C3)-alkanediyl, where the carbon atom adjacent to the ring A in the alkanediyl group may be replaced by an oxygen atom;

25 R₄ is H;

R₅ is methyl;

and its physiologically acceptable salts.

30

3. A compound of the formula I as claimed in claims 1 or 2, in which

ring A is cyclohexane-1,3-diyl;

35 R is NR₁R₂ or phenyl;

R₁ is H;

R₂ is (C1-C6)-alkyl, (C3-C8)-cycloalkyl or (C6-C10)-aryl, where aryl

may be unsubstituted or substituted by F, Cl or (C1-C4)-alkyl;

5 R3 is (C3-C6)-cycloalkyl or (C1-C8)-alkyl which is unsubstituted or substituted by phenyl, pyridyl, morpholinyl, cyclopropyl, cyclopentyl, cyclohexyl, where phenyl for its part may be substituted by chlorine or methyl;

10 X is (C1-C3)-alkanediyl, where the carbon atom adjacent to the ring A in the alkanediyl group may be replaced by an oxygen atom;

Y is OCH₂;

R4 is H;

15 R5 is methyl;

and its physiologically acceptable salts.

4. A compound of the formula I as claimed in claims 1 to 3, in which

20

ring A is cyclohexane-1,3-diyl;

R is NR₁R₂ or phenyl;

25 R1 is H;

R2 is (C1-C4)-alkyl, cyclohexyl, phenyl, where phenyl may be unsubstituted or substituted by F, Cl or methyl;

30 R3 is (C3-C6)-cycloalkyl or (C1-C8)-alkyl which is unsubstituted or substituted by phenyl, pyridyl, morpholinyl, cyclopropyl, cyclopentyl, cyclohexyl, where phenyl for its part may be substituted by chlorine or methyl;

35 X is O-CH₂-CH₂;

Y is OCH₂;

R4 is H;

R5 is methyl;

and its physiologically acceptable salts.

5

5. A compound of the formula I as claimed in claims 1 to 4 where the link of X and Y to ring A is cis-configured.

6. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 5.

7. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 5 and one or more active compounds which act favorably on metabolic disorders or diseases associated therewith.

8. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 5 and one or more antidiabetics.

9. A pharmaceutical comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 5 and one or more lipid modulators.

10. The use of the compounds of the formula I as claimed in one or more of claims 1 to 5 for the treatment and/or prevention of disorders of the fatty acid metabolism and glucose utilization disorders.

11. The use of the compounds of the formula I as claimed in one or more of claims 1 to 5 for the treatment and/or prevention of disorders in which insulin resistance plays a part.

12. The use of the compounds of the formula I as claimed in one or more of claims 1 to 5 for the treatment and/or prevention of diabetes mellitus and sequelae associated therewith.

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13. The use of the compounds of the formula I as claimed in one or more of claims 1 to 5 for the treatment and/or prevention of dyslipidemia and sequelae associated therewith.

14. The use of the compounds of the formula I as claimed in one or more of claims 1 to 5 for the treatment and/or prevention of conditions associated with the metabolic syndrome.
- 5 15. The use of compounds as claimed in one or more of claims 1 to 5 in combination with at least one further active compound for the treatment and/or prevention of disorders of the fatty acid metabolism and glucose utilization disorders.
- 10 16. The use of compounds as claimed in one or more of claims 1 to 5 in combination with at least one further active compound for the treatment and/or prevention of disorders in which insulin resistance plays a part.
- 15 17. A process for preparing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 5, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.