The invention relates to arylcycloalkyl derivatives with branched side chains, in addition to their physiologically compatible salts and physiologically functional derivatives. The invention relates to compounds of formula (I), in which the groups are defined as cited in the description, in addition to their physiologically compatible salts and to a method for their production. The compounds are suitable for treating and/or preventing disorders of the fatty acid metabolism and disorders of glucose utilisation in addition to disorders, in which insulin resistance plays a part.
Inventors (continued): KEIL, STEFANIE, DE; SCHAEFER, HANS-LUDWIG, DE; WENDLER, WOLFGANG, DE
Title: ARLCYCLOALKYL DERIVATIVES WITH BRANCHED SIDE CHAINS AS PPAR RECEPTOR MODULATORS, METHOD FOR THEIR PRODUCTION AND THEIR USE AS MEDICAMENTS

Bezeichnung: ARLCYCLOALKYLDERIVATE MIT VERZWIEGTEITEN SEITENKETTEN ALS PPAR REZEPTOR MODULATOREN, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE ANWENDUNG ALS ARZNEIMITTEL

Abstract: The invention relates to arylcycloalkyl derivatives with branched side chains, in addition to their physiologically compatible salts and physiologically functional derivatives. The invention relates to compounds of formula (I), in which the groups are defined as cited in the description, in addition to their physiologically compatible salts and to a method for their production. The compounds are suitable for treating and/or preventing disorders of the fatty acid metabolism and disorders of glucose utilisation in addition to disorders, in which insulin resistance plays a part.

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.
Description

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 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).

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.

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.

Accordingly, the invention relates to compounds of the formula I

\[
\begin{align*}
\text{Ring A} & \\
\text{R} & \\
\text{R3} & \\
\text{N} & \\
\text{X} & \\
\text{R} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]

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;

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-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;

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 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).

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;

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;

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;

R4 is H;

R5 is methyl;

and their physiologically acceptable salts.

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

ring A is cyclohexane-1,3-diyi;

R is NR1R2 or phenyl;

R1 is H;

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;

X is O-CH2-CH2;

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

5
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.

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.

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 gamma\textsubscript{1} and gamma\textsubscript{2}, 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 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 Res. 2001; 56: 239-63.


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

1. disorders of fatty acid metabolism and glucose utilization disorders
2. disorders in which insulin resistance is involved.

2. Diabetes mellitus, in particular type 2 diabetes, including the prevention of the sequelae associated therewith.

Particular aspects in this connection are:
- hyperglycemia,
- improvement in insulin resistance,
- improvement in glucose tolerance,
- protection of the pancreatic beta cells,
3. Dyslipidemia 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 of 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

6. 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
- erythematous-squamous dermatoses such as, for example,
psoriasis
- acne vulgaris
- other skin disorders and dermatological conditions which are
modulated by PPAR
- eczemas and neurodermatitis
- dermatitis such as, for example, seborrheic dermatitis or
photodermatitis
- keratitis and keratoses such as, for example, seborrheic
keratoses, senile keratoses, actinic keratosis, photo-induced
keratoses or keratosis follicularis
- keloids and keloid prophylaxis
- warts, including condylomata or condylomata acuminata
- human papilloma virus (HPV) infections, such as, for
example, venereal papillomata, viral warts such as, for
example, molluscum contagiosum, leukoplakia
- papular dermatoses such as, for example, lichen planus
- skin cancer such as, for example, basal-cell carcinomas,
melanomas or cutaneous T-cell lymphomas
- localized benign epidermal tumors such as, for example,
keratoderma, epidermal naevi
- chilblains
- high blood pressure
- syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic
disorders such as, for example, rheumatoid arthritis
- vasculitis
- wasting (cachexia)
- gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS) ("shock lung")

Formulations

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.001 mg to 100 mg (typically from 0.01 mg to 50 mg) per day and per kilogram of body weight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active compound. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 0.05 to 1000 mg, typically from 0.5 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active compound. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

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

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

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

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.

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

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

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active compound in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active compound concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active compound to be released by electrotreatment 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,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors
7. antithrombotic active ingredients
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.

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 in one pharmaceutical preparation.

Examples which may be mentioned are:

Antidiabetics

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

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-pentanammonium chloride), P-31/98, LAF237 (1-[2-[3-
hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2-(S)-carbonitrile), TS021
((2S, 4S)-4-fluoro-1-[[2-hydroxy-1,1-dimethyllethyl]amino]acetyl]pyrrolidine-
2-carbonitrile monobenzenesulfonate).

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.

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,

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

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

Lipid modulators

In one embodiment of the invention, the compounds of the formula I are
administered in combination with an HMGC0A reductase inhibitor such as
lovastatin, fluvastatin, pravastatin, simvastatin, ivastatin, itavastatin,
atorvastatin, rosuvastatin.

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

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

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

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

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate such as, for example, fenofibrate, gemfibrozil, clofibrate, bezafibrate.

In one embodiment of the invention, the compounds of the formula I are administered in combination with nicotinic acid or niacin.
In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, e.g. CP-529, 414 (torcetrapib).

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

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

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

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

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

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

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

**Antiobesity agents**

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

In one embodiment, the further active ingredient is fenfluramine or dextfenfluramine. 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-methylbenzoxazol-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. uro cortin), urocortin agonists, β3 agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yl)oxy]ethylamino]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-ylcarbamoylel]-5,7-dimethylindol-1-yl]acetic acid trifluoroacetic acid salt (WO 99/15525)), serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed sertoninergic 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).

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.

Construction of the cell line

The PPARalpha reporter cell line was prepared in two steps: Firstly, the luciferase reporter element was constructed and stably transfected into HEK cells. For this purpose, five binding sites of the yeast transcription factor GAL4 (in each case 5'-CGGAGTACTGTCTCCCGAG-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 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 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 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 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 (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 nM. 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 μl 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 μl of Bright Glo reagent (from Promega) into each well of a 96 well microtiter plate. After incubation at room temperature in the dark for 10 minutes, the microtiter plates are measured in the luminometer (Trilux from Wallac). The measuring time for each well of a microtiter plate is 1 sec.

Evaluation

The 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).

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.

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

Table I

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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 plasmid and PPARgamma expression plasmid) are transiently transfected into HEK cells because stable and permanent expression of the PPARgamma fusion protein is cytotoxic.

Construction of the plasmids

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

The PPARgamma expression plasmid pcDNA3-GAL4-humanPPARγLBD was prepared by first cloning the cDNA coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386) into the plasmid pcDNA3 (from Invitrogen) 3'-downstream of the cytomegalovirus promoter. Subsequently, the cDNA of the ligand-binding domain (LBD) of the human PPARγ receptor (amino acids 1152-Y475; Accession # g1480099) 3'-downstream of the GAL4 DNA binding domain. Cloning and sequencing of the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD again took place in analogy to the description in Sambrook J. et al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Besides the luciferase reporter plasmid pGL3basic-5xGAL4-TK and the PPARγ expression plasmid pcDNA3-GAL4-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

The activity of PPARgamma 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).

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 μl of antibiotic- and serum-free DMEM (#41965-039, Invitrogen), 100 μl of reference plasmid pRL-CMV (1 ng/μl), 100 μl of luciferase reporter plasmid pGL3basic-5xGAL4-TK (10 ng/μl), 100 μl of PPARγ expression plasmid pcDNA3-GAL4-humanPPARγLBD (100 ng/μl) and 78 μl of plasmid pBluescript SK(+) (500 ng/μl). Then 2 ml of solution B are prepared by mixing 1.9 ml of DMEM (#41965-039, Invitrogen) with 100 μl of PolyFect transfection reagent (from Qiagen) for each 96 well microtiter plate. Subsequently, 3 ml of solution A are mixed with 2 ml of solution B to give 5 ml of solution C, which is thoroughly mixed by multiple pipetting and incubated at room temperature for 10 min.

80%-confluent HEK cells from a cell culture bottle with a capacity of 175 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 each microtiter plate. 200 μl of the suspension are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in a cell culture incubator at 37°C and 5% CO₂ for 24 h.
Day 2
PPAR agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (#41965-039, Invitrogen) which is mixed with 2% Ultroser (#12039-012, Biosepra), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). Test substances are tested in a total of 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM. The medium of the HEK cells transfected and seeded on day 1 is completely removed by aspiration, and the test substances diluted in medium are immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 µl per well of a 96 well microtiter plate. Each plate is charged with a standard PPARγ 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 µl of Dual-Glo™ reagent (Dual-Glo™ Luciferase Assay System; Promega) are added to each well in accordance with the manufacturer's instructions in order to lyze the cells and provide the substrate for the firefly luciferase (Photinus pyralis) formed in the cells. After incubation at room temperature in the dark for 10 minutes, the firefly luciferase-mediated chemiluminescence is measured in a measuring instrument (measuring time/well 1 sec; Trilux from Wallac). Then 50 µl of the Dual-Glo™ Stop & Glo reagent (Dual-Glo™ Luciferase Assay System; Promega) is added to each well in order to stop the activity of the firefly luciferase and provide the substrate for the Renilla luciferase expressed by the reference plasmid pRL-CMV. After incubation at room temperature in the dark for a further 10 minutes, a chemiluminescence mediated by the Renilla luciferase is again measured for 1 sec/well in the measuring instrument.

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

PPARgamma EC50 values in the range from 50 nM to >10 μM 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.

Table II

![Chemical Structure](image)

In the examples, ring A = cis-cyclohexane-1,3-diy1, R5 = methyl, R4 = H, X = O(CH2)2 and Y = OCH2.

Broken lines indicate the point of attachment of the substituent.
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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 dibutylltin 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.

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.

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.

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.

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.

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.

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.

**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 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+).

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 antartika 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)

Methyl 2-((1R,3S)-3-allyloxydicyclohexyloxymethyl)-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-\((1R,3S)-3\)-allyloxy-cyclohexyloxymethyl\)-6-methylbenzoate as a yellow oil. C19H26O4 (318.42), MS(ESI): 319 (M+H+).

Methyl 2-methyl-6-\((1R,3S)-3\)-(2-oxoethoxy)cyclohexyloxymethyl\)benzoate

1.0 g of methyl 2-\((1R,3S)-3\)-allyloxy-cyclohexyloxymethyl\)-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+), Rf = 023 (n-heptane:ethyl acetate = 1:1).

2-Methyl-6-\((1R,3S)-3\)-[2-(3-phenylpropylamino)ethoxy]cyclohexyloxymethyl\)benzoic acid
200 mg of methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)cyclohexyloxy-methyl]benzoate and 90 µl 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. 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. 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]cyclohexyloxy(methyl)]benzoic acid as a yellow oil. C26H25NO4 (425.57), MS(ESI): 426 (M+H+).

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

160 mg of 2-methyl-6-[(1R,3S)-3-[2-(3-phenylpropylamino)ethoxy]cyclohexyloxy(methyl)]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]cyclohexyloxy(methyl)]-6-methyl-benzoic acid as a white lyophilizate. C33H40N2O5 (544.70), MS(ESI): 545 (M+H+).

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-\{(1R,3S)-3-[2-(4-chlorophenyl)ethyl]-3-phenylureido)ethoxy]cyclohexyloxymethyl\}-6-methylbenzoic acid.

C32H37CIN2O5 (565.11), MS(ESI): 565 (M+H+).

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.

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.
Example V

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

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

Example VI

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

Example VIII

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

Example IX

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

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.

Example XI

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.
Example XII

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-
cyclohexyloxy)methyl]benzoate, 4-methylbenzylamine and butyl isocyanate
gave 2-((1R,3S)-3-([2-[3-buty1-1-(4-methylbenzyl)ureido]ethoxy]cyclohexyl-
oxymethyl)-6-methylbenzoic acid.

C30H42N2O5 (510.68), MS(ESI): 511.

Example XIII

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-
cyclohexyloxy)methyl]benzoate, 4-methylbenzylamine and cyclohexyl
isocyanate gave 2-((1R,3S)-3-[2-[3-cyclohexyl-1-(4-methylbenzyl)-

C32H44N2O5 (536.72), MS(ESI): 537.

Example XIV

Analogously to Example I, methyl 2-methyl-6-[(1R,3S)-3-(2-oxoethoxy)-
cyclohexyloxy)methyl]benzoate, propylamine and phenyl isocyanate gave
2-methyl-6-[(1R,3S)-3-[2-(3-phenyl-1-propylureido)ethoxy]cyclohexyloxy-
methyl]benzoic acid.
Examples XV-LXII were prepared and tested as racemic compounds having cis configuration of the two substituents on the cyclohexane ring.

**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.

**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.
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+).

Example XVIII

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-otolylureido)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)cyclohexyloxymethyl]benzoate, cyclohexylmethylamine and 3-fluorophenylisocyanate gave 2-(cis-3-{2-[1-cyclohexylmethyl-3-(3-fluorophenyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

![Chemical structure diagram]

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

Example XX

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

![Chemical structure diagram]

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-(3-fluorophenyl)ureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.
5 Example XXII

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

15 Example XXIII

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

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-otolylureido]ethoxy}cyclohexyloxymethyl)benzoic acid.

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.
Example XXVIII

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

Example XXIX

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

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.

Example XXXI

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-otolyureido]ethoxy)cyclohexyloxymethyl)-6-methylbenzoic acid.
Example XXXII

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

Example XXXIII

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxy)methyl]benzoate, 3,3-dimethylbutylamine and 2-methylphenylisocyanate gave 2-(cis-3-[2-[1-(3,3-dimethylbutyl)-3-otolyureido]ethoxy]cyclohexyloxy)methyl)-6-methylbenzoic acid.
Example XXXIV

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

Example XXXV

Analogously to Example I, racemic methyl 2-methyl-6-[cis-3-(2-oxoethoxy)cyclohexyloxymethyl]benzoate, pentyamine and 2-methylphenylisocyanate gave 2-methyl-6-[cis-3-[2-(1-pentyl-3-o-tolylureido)ethoxy)cyclohexyloxymethyl]benzoic acid.
Example XXXVI

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]cyclohexyloxy-methyl]-6-methylbenzoic acid.

Example XXXVII

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]cyclo-hexyloxymethyl)-6-methylbenzoic acid.
Example XXXVIII

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

Example XXXIX

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

Analogously to Example I, 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-tolyureido]ethoxy}cyclohexyloxymethyl)-6-methylbenzoic acid.

Example XLI

Analogously to Example I, 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.
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.

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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.

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.
Example XLVI

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

Example XLVII

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

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.

Example XLIX

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

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.

Example LI

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]cyclohexyloxy-methyl]-6-methylbenzoic acid.
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.

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.
Example LIV

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

Example LV

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

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

Example LVII

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

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.

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

Example LIX

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

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.

Example LXI

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.
Example LXII

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.

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

1. A compound of the formula I

\[
\begin{align*}
\text{Ring A} & \quad \text{Y} \\
\text{R} & \quad \text{R1} \\
\text{R3} & \quad \text{R2} \\
\text{R4} & \quad \text{R5}
\end{align*}
\]

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;
- 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-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;
- 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;

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

20 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;

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

\[ \text{X is (C1-C3)-alkanediyl, where the carbon atom adjacent to the ring A in the alkanediyl group may be replaced by an oxygen atom;} \]

\[ \text{Y is OCH_2;} \]

\[ \text{R4 is H;} \]

\[ \text{R5 is methyl;} \]

and its physiologically acceptable salts.

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

\[ \text{ring A is cyclohexane-1,3-diyl;} \]

\[ \text{R is NR1R2 or phenyl;} \]

\[ \text{R1 is H;} \]

\[ \text{R2 is (C1-C4)-alkyl, cyclohexyl, phenyl, where phenyl may be unsubstituted or substituted by F, Cl or methyl;} \]

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

\[ \text{X is O-CH_2-CH_2;} \]

\[ \text{Y is OCH_2;} \]

\[ \text{R4 is H;} \]
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.

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.

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.

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.

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.