

Description

2-{-3,2-(PHENYL)-OXAZOL-4-YLMETHOXYL-CYCLOHEXYL METHOXY}-
 5 PROPIONIC ACID DERIVATIVES USED AS PPAR LIGANDS (PEROXISOME
 PROLIFERATOR-ACTIVATED RECEPTORS) FOR THE TREATMENT OF
 HYPERLIPIDAEMIE AND DIABETES

The invention relates to acetic acid derivatives with cyclohexylmethoxy substituents,
 10 process for their preparation and their use as medicaments, and to their physiologically
 tolerated salts and physiologically functional derivatives.

Compounds of similar structure have been described in the art for the treatment of
 hyperlipidemia and diabetes (WO 2004/076427).

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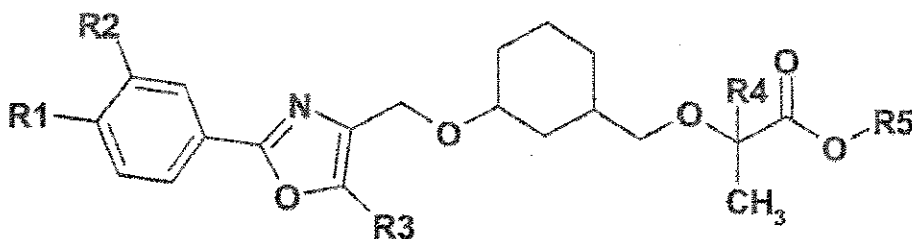
The invention was based on the object of finding particularly effective compounds
 allowing a therapeutically useable modulation of lipid and/or carbohydrate metabolism
 and thus being suitable for the prevention and/or treatment of diseases such as type 2
 diabetes and atherosclerosis, and the diverse sequelae thereof.

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This has been achieved by a selection of the compounds described below, which
 surprisingly show besides a particularly good PPARalpha effect also a correspondingly
 good PPARgamma effect.

25 Summary of Invention

In a first aspect, there is provided a compound of the formula I



in which the meanings are:

- 5 R1 H, (C1-C6)-alkyl;
 R2 H, O-(C1-C3)-alkyl, CF₃; or
 R1 and R2 are together with the phenyl ring fused naphthyl;
 10 R3 (C1-C6)-alkyl;
 R4 (C1-C6)-alkyl, benzyl;
 R5 H, (C1-C6)-alkyl;
 15 wherein the following compounds are disclaimed:
 2-[cis-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-2-methylpropionic acid,
 2-[(1R, 3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-2-methylpropionic
 acid,
 2-[(1S, 3R)-cis-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexylmethoxy]-
 20 2-methylpropionic acid,
 2-[(1S, 3R)-3-[2-(cis-3-trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexylmethoxy]-
 2-methylpropionic acid, and
 2-methyl-2-[(1R,3S)-cis-3-(5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy)
 cyclohexylmethoxy]propionic acid.
 25 and the physiologically tolerated salts and solvates thereof.

In a second aspect, there is provided a medicament comprising one or more of the compounds of the formula I according to the first aspect.

30 In a third aspect, there is provided a medicament comprising one or more of the compounds of the formula I according to the first aspect and one or more active ingredients which have favorable effects on metabolic disturbances or disorders associated therewith.

35 In a fourth aspect, there is provided a medicament comprising one or more of the compounds of the formula I according to the first aspect and one or more antidiabetics.

In a fifth aspect, there is provided a medicament comprising one or more of the compounds of the formula I according to the first aspect and one or more lipid modulators.

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In a sixth aspect, there is provided the use of the compounds of the formula I according to the first aspect in the manufacture of a medicament for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

- 10 In a seventh aspect, there is provided the use of the compounds of the formula I according to the first aspect in the manufacture of a medicament for the treatment and/or prevention of disorders in which insulin resistance is involved.

- 15 In an eighth aspect, there is provided the use of the compounds of the formula I according to the first aspect in the manufacture of a medicament for the treatment and/or prevention of diabetes mellitus and the sequelae associated therewith.

- 20 In a ninth aspect, there is provided the use of the compounds of the formula I according to the first aspect in the manufacture of a medicament for the treatment and/or prevention of dyslipidemias and their sequelae.

- In a tenth aspect, there is provided the use of the compounds of the formula I according to the first aspect in the manufacture of a medicament for the treatment and/or prevention of conditions associated with the metabolic syndrome.

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In an eleventh aspect, there is provided the use of the compounds according to the first aspect in combination with at least one further active ingredient in the manufacture of a medicament for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

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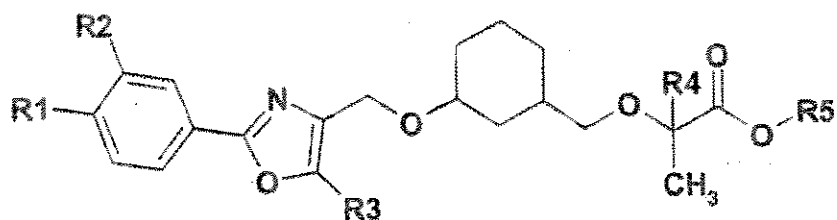
In a twelfth aspect, there is provided the use of the compounds according to the first aspect in combination with at least one further active ingredient in the manufacture of a medicament

for the treatment and/or prevention of disorders in which insulin resistance is involved.

In a thirteenth aspect, there is provided a process for producing a medicament comprising one or more of the compounds according to the first aspect, which comprises mixing the active
5 ingredient with a pharmaceutically suitable carrier, and bringing this mixture into a form suitable for administration.

Compound

10 The invention relates to compounds of the formula I



I

in which the meanings are:

R1 H, (C1-C6)-alkyl;

5 R2 H, O-(C1-C3)-alkyl, CF₃; or

R1 and R2 are together with the phenyl ring fused naphthyl;

R3 (C1-C6)-alkyl;

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R4 (C1-C6)-alkyl, benzyl;

R5 H, (C1-C6)-alkyl;

15 and the physiologically tolerated salts, solvates and physiologically functional derivatives thereof.

Preferred compounds of the formula I are those in which

20 R1 is H, methyl, propyl or butyl;

R2 is H, methoxy, CF₃; or

R1 and R2 are together with the phenyl ring fused naphthyl;

25

R3 is methyl, ethyl or propyl;

R4 is methyl, propyl or benzyl; and

30 R5 is H.

Particularly preferred compounds of the formula 1 are those in which

R1 or R2 is H;

or those in which

5

R4 is methyl.

The alkyl radicals in the substituents R1, R2, R3, R4 and R5 may be either straight-chain or branched.

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The compounds of the formula I comprise at least two centers of asymmetry and may comprise more in addition. The compounds of the formula I may therefore be in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and diastereomeric mixtures. The present invention includes all these isomeric forms of the
15 compounds of the formula I. These isomeric forms can be obtained by known methods even if not expressly described in some cases.

Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications.

20 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 acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic,
25 isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

30

Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework 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 on administration to a mammal such as, for example, a human is able 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 be active 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 framework of the invention and are a further aspect of the invention.

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

Use

This invention relates further to the use of compounds of the formulae 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, PPARalpha, PPARgamma and PPARdelta, which are encoded by different genes (Peroxisome proliferator-activated receptor (PPAR): structure, mechanisms of activation and diverse functions: Motojima K, Cell Struct Funct., 1993 Oct, 18(5), 267-77).

Two variants of PPARgamma exist, PPARgamma₁ and gamma₂, which are the result of an alternative use of promoters and differential 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 crucially involved in lipid and carbohydrate metabolism. Thus, for example, PPARalpha receptors play an important part in the regulation of fatty acid catabolism or lipoprotein metabolism in the liver, while
5 PPARgamma is crucially 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
10 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.

The present invention relates to compounds of the formula I suitable for modulating the
15 activity of PPAR receptors, especially the activity of PPARalpha and PPARgamma. Depending on the modulation profile, the compounds of the formula I are suitable for the treatment, control and prophylaxis of the indications described hereinafter, and for a number of other pharmaceutical applications connected thereto (see, for example, Joel Berger et al., Annu. Rev. Med., 2002, 53, 409 – 435; Timothy Wilson et al. J. Med.
20 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 Patrick Duriez: PPARS, Metabolic Disease and Arteriosclerosis, Pharmacological Research, Vol. 44, No. 5, 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000; Ines Pineda Torra, Giulia Chinetti,
25 Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

Compounds of this type are particularly suitable for the treatment and/or prevention of
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1. - disorders of fatty acid metabolism and glucose utilization disorders
- disorders in which insulin resistance is involved
2. Diabetes mellitus, especially type 2 diabetes, including the prevention of the
35 sequelae associated therewith.

Particular aspects in this connection are

- hyperglycemia,
 - improvement in insulin resistance,
 - improvement in glucose tolerance,
 - protection of the pancreatic β cells
- 5 - prevention of macro- and microvascular disorders
3. Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors:
- 10 - high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations,
- low HDL cholesterol concentration
- low ApoA lipoprotein concentrations
- high LDL cholesterol concentrations
- 15 - small dense LDL cholesterol particles
- high ApoB lipoprotein concentrations
4. Various other conditions which may be associated with the metabolic syndrome, such as:
- 20 - obesity (excess weight), including central obesity
- thromboses, hypercoagulable 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
- 25
5. Further disorders or conditions in which for example inflammatory reactions or cell differentiation are involved:
- atherosclerosis such as, for example (but not restricted thereto), coronary sclerosis including angina pectoris or myocardial infarction, stroke
- 30 - vascular restenosis or reocclusion
- chronic inflammatory bowel diseases such as, for example, Crohn's disease and ulcerative colitis
- pancreatitis
- other inflammatory states
- 35 - retinopathy
- adipose cell tumors

- lipomatous 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 viral (HPV) infections such as, for example, venereal warts, 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)

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 of 0.01 mg and 50 mg) per day and per kilogram of bodyweight, for example 0.1-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.001 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. 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 to 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 ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I.

30 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, cachets, 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 ingredient 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 ingredient 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 agents in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

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

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

preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

- 5 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.
- 10 Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, cream, 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 ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.
- 15 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 ingredient in an aqueous solution which is buffered where appropriate, dissolved
 20 and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active ingredient to be released by electrotransport or iontophoresis as described, for example, in *Pharmaceutical Research*, 2(6): 318 (1986).
- 25 The compounds of the formula I are distinguished by favorable effects on metabolic disorders. They beneficially influence lipid and sugar metabolism, in particular they lower the triglyceride level and are suitable for the prevention and treatment of type II diabetes and arteriosclerosis and the diverse sequelae thereof.

30 **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
 35 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
- 5 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
- 10 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:

20 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, 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.

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

5 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
10 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
15 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
20 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-
25 thiazolidinedione.

In one embodiment, the compounds of the formula I are 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-
30 hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2-(S)-carbonitrile), TS021 ((2S, 4S)-4-fluoro-1-[[[(2-hydroxy-1,1-dimethylethyl)amino]acetyl]pyrrolidine-2-carbonitrile monobenzenesulfonate).

In one embodiment of the invention, the compounds of the formula I are administered
35 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 WO 2004/007517, WO 2004/052902 and WO 2004/052903.

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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
10 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

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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.

20 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
25 in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine, colessevelam.

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
30 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).

35 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
 5 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.

- 10 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
 15 (Tesaglitazar, (S)-3-(4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl)-2-ethoxypropionic acid), BMS 298585 (N-[(4-methoxyphenoxy)carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine) or as described in WO 99/62872, WO 99/62871, WO 01/40171, WO 01/40169, WO96/38428, WO 01/81327, WO 01/21602, WO 03/020269, WO 00/64888 or WO 00/64876.

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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.

- 25 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.

- In one embodiment of the invention, the compounds of the formula I are administered
 35 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
5 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.

10 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.

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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.

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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
25 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-
30 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
35 (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, $\beta 3$ agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)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-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 tert-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.

20

In one embodiment, the further active ingredient is dexamphatamine, 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.

30

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 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

35

conferred by the present invention.

The activity of the compounds was tested as follows:

5 **Determination of EC50 values of PPAR agonists in the cellular PPARalpha assay**

Principle

The potency of substances which bind to human PPARalpha and activate it in an agonistic manner is analyzed using a stably transfected HEK cell line (HEK= human embryo kidney) which is referred to here as PPARalpha reporter cell line. It contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) which mediates expression of the luciferase reporter element depending on a PPARalpha ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARalpha-LBD binds in the cell nucleus of the PPARalpha reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is 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.

25 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'-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 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 subcloned into a plasmid which confers zeozin resistance in order to obtain the plasmid pdeltaM-GAL4-Luc-Zeo. This vector was transfected into HEK cells in accordance with the statements in Ausubel, F.M. et al. (Current protocols in molecular biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Then zeozin-containing medium (0.5 mg/ml) was used to select a suitable stable cell clone which showed very low basal expression of the luciferase gene.

In a second step, the PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) was introduced into the stable cell clone described. For this purpose, initially the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (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 subcloned 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-humanPPARalpha-LBD) was isolated by selection with zeozin (0.5 mg/ml) and G418 (0.5 mg/ml).

25 Assay procedure

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

30 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 zeozin (# 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 5 500 000 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

10 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 (zeozin, G418, penicillin and streptomycin).

15 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 20 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 25 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

30 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 Wallace). The measuring time for each well of 35 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
5 program as specified by the manufacturer (IDBS).

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

10

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
15 (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
20 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
25 transfected into HEK cells because stable and permanent expression of the PPARgamma fusion protein is cytotoxic.

Construction of the plasmids

30 The luciferase reporter plasmid pGL3basic-5xGAL4-TK is based on the vector pGL3basic from Promega. The reporter plasmid is prepared by cloning five binding sites of the yeast transcription factor GAL4 (each binding site with the sequence

5'-CTCGGAGGACAGTACTCCG-3'), together with a 160 bp-long thymidine kinase promoter section (Genbank Accession # AF027128) 5'-upstream into pGL3basic. 3'-downstream of the thymidine kinase promoter is the complete luciferase gene from *Photinus pyralis* (Genbank Accession # M15077), which is already a constituent of the plasmid pGL3basic used. The cloning and sequencing of the reporter plasmid pGL3basic-5xGAL4-TK took place in analogy to the description in Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989).

The PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD was prepared by first cloning the cDNA coding for amino acids 1-147 of the yeast

transcription factor GAL4 (Genbank Accession # P04386) into the plasmid pcDNA3 (from Invitrogen) 3'-downstream of the cytomegalovirus promoter. Subsequently, the cDNA of the ligand-binding domain (LBD) of the human PPARgamma receptor (amino acids I152-Y475; Accession # g1480099) 3'-downstream of the GAL4 DNA binding domain was cloned. Cloning and sequencing of the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD again took place in analogy to the description in Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Besides the luciferase reporter plasmid pGL3basic-5xGAL4-TK and the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD, also used for the cellular PPARgamma 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

25

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 medium (# 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).

30

Day 1

Firstly, solution A, a transfection mixture which contains all four plasmids previously described in addition to DMEM medium, 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 medium (# 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 PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD (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 medium (# 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.

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 medium (# 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.

25

Day 2

PPAR 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 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 µl per well of a 5 96-well microtiter plate. Each plate is charged with a standard PPARgamma agonist, which is likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO₂ for 48 h.

10 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 lyse the cells and provide the substrate for the firefly luciferase (*Photinus pyralis*) formed in the cells. After incubation at room 15 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 20 expressed by the reference plasmid pRL-CMV. After incubation at room temperature in the dark for a further 10 minutes, the chemiluminescence mediated by the Renilla luciferase is again measured for 1 sec/well in the measuring instrument.

Evaluation

25

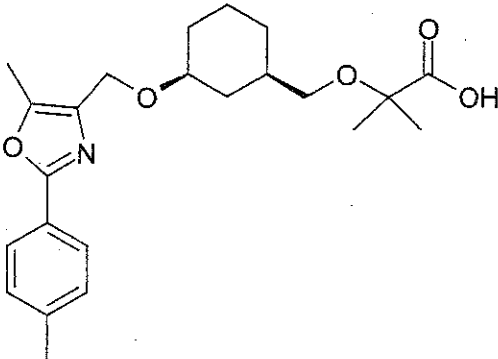
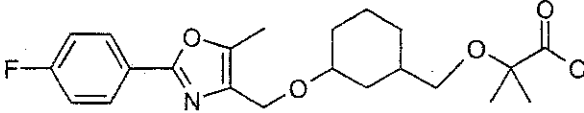
The raw data from the luminometer are transferred into a Microsoft Excel file. The firefly/Renilla luciferase activity ratio is determined for each measurement derived from one well of the microtiter plate. The dose-effect plots and EC50 values of PPAR agonists are calculated from the ratios by the XL.Fit program as specified by the 30 manufacturer (IDBS).

The results for the activity of some compounds of the invention of the formula I are indicated in Table I below:

Table I

5

Example No.	Formula	EC50 PPARalpha [μM]	EC50 PPARgamma [μM]
1		0.045	0.93
2		0.0035	2.9
3		0.019	0.67
4		0.0020	1.1
5		0.012	1.5
7		0.0012	2.6
9		0.32	0.39
10		0.054	0.13
11		0.0041	0.87
12		0.012	0.075
13		0.0066	0.13
14		0.00038	0.22
14		0.00053	0.056

15		0.00039	0.16
16		0.017	0.40
17		0.00016	0.51
18		0.0026	0.15
19		0.00038	0.54
20		0.00054	0.17
21		0.0058	0.60
*		0.0018	> 10 000
**	 cis/racemate	0.0045	> 10 000

* Example 8a from WO 2004/076427.

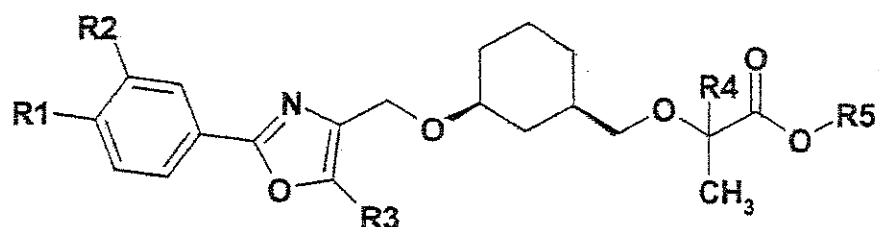
** Example 10 from WO 2004/076427.

It is evident from Table I that the compounds of the invention of the formula I activate
5 the PPARalpha receptor and the PPARgamma receptor and thus for example bring
about a lowering of triglycerides in the body in analogy to fibrates in clinical use (see,
for example, J.-Ch. Fruchard et al.,: PPARS, Metabolic Disease and Atherosclerosis,

Pharmacological Research, Vol. 44, No. 5, 2001; S. Kersten et al.: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000; I. Pineda et al.: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

5

The examples detailed below serve to illustrate the invention without, however, restricting it.



10 Table II:

1a

Ex.	R1	R2	R3	R4	R5
1	H	3-OCH3	C2H5	CH3	H
2	4-CH3	H	C2H5	CH3	H
3	4-i-C4H9	H	C2H5	CH3	H
4	2-Naphthyl		C2H5	CH3	H
5	H	3-CF3	C2H5	CH3	H
6	4-i-C3H7	H	C2H5	CH3	H
7	2-Naphthyl		CH3	CH3	H
8 ^a	H	3-OCH3	i-C3H7	CH3	H
9	H	3-OCH3	i-C3H7	CH3	H
10	H	3-OCH3	C2H5	n-C3H7	H
11	4-CH3	H	C2H5	n-C3H7	H
12	4-i-C4H9	H	C2H5	n-C3H7	H
13	2-Naphthyl		C2H5	n-C3H7	H
14	4-i-C3H7	H	C2H5	n-C3H7	H
15	2-Naphthyl		CH3	n-C3H7	H
16	H	3-OCH3	C2H5	CH2Ph	H
17	4-CH3	H	C2H5	CH2Ph	H
18	4-i-C4H9	H	C2H5	CH2Ph	H

Ex.	R1	R2	R3	R4	R5
19	2-Naphthyl		C2H5	CH2Ph	H
20	4-i-C3H7	H	C2H5	CH2Ph	H
21	2-Naphthyl		CH3	CH2Ph	H

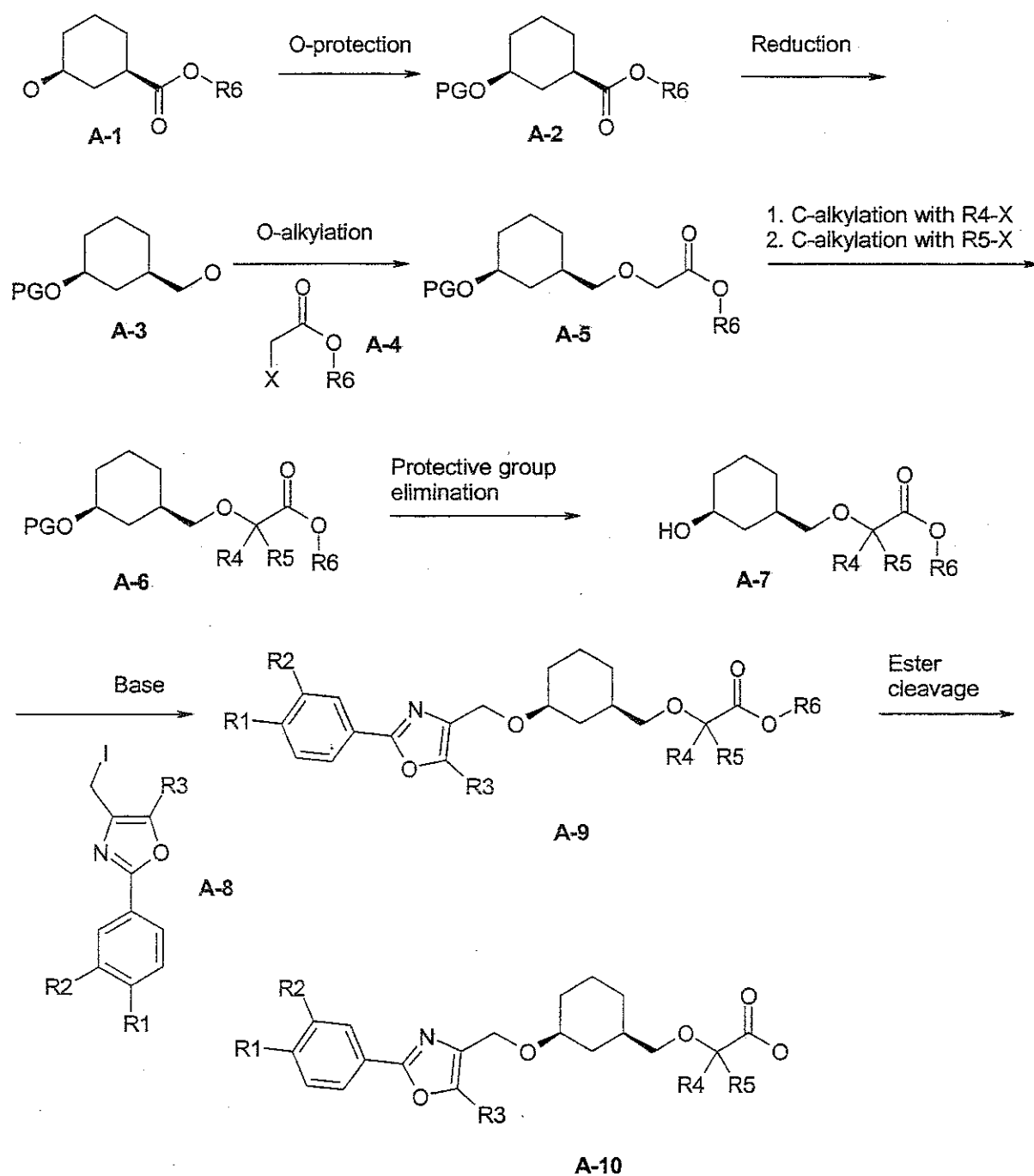
^aracemate

Processes

The compounds of the invention of the formula I can be obtained in accordance with the following reaction schemes:

5

Process A:



The compound A-1 is protected on the secondary hydroxyl group (for example for PG=TBDPS; by stirring with TBDPSCI and imidazole in DMF at RT or for PG = THP; by stirring with dihydropyran and toluenesulfonic acid in dichloromethane at RT),

5 resulting in the compound A-2, in which R6 has the meaning described above. A-2 is reduced with lithium aluminum hydride in an etheral solvent to the compound A-3. The compound A-3 is reacted with the compound A-4 – an ester of 2-haloacetic acid and of the alcohol R6-OH in which R6 has the meaning described above and halogen can be chlorine, bromine or iodine – to give the compound A-5. The compound A-5 is reacted
 10 with a lithium amide base (e.g. lithium diisopropylamide or lithium- 2,2,5,5-tetramethylpyrrolidide) and an alkyl halide of the general formula R4X, in which R4 has the meaning described above and halogen can be chlorine, bromine or iodine, in an etheral solvent at low temperature. The compound obtained in this way is then reacted with a lithium amide base (e.g. lithium diisopropylamide or lithium- 2,2,5,5-
 15 tetramethylpyrrolidide) and an alkyl halide of the general formula R5X, in which R5 has the meaning described above and halogen can be chlorine, bromine or iodine, in an etheral solvent at low temperature to give the compound A-6. The protective group is eliminated from A-6 (in the case of PG = TBDPS with tetrabutylammonium fluoride in THF or in the case of PG=THP with toluenesulfonic acid in methanol), resulting in the
 20 compound of the general formula A-7. The compound A-7 is reacted with a base (for example sodium hydride or potassium tert-butoxide) and the compound A-8 (see Process A) in which R1, R2 and R3 have the meanings described above in an etheral solvent to give the compound A-9. The compound A-9 is hydrolyzed to the acid A-10: in the case where R6 are primary or secondary alkyl radicals, with a base in methanol,
 25 or in the case where R6 is a tertiary alkyl radical, with anhydrous acid in an inert solvent (for example hydrogen chloride in dioxane or trifluoroacetic acid in dichloromethane).

Enantiomerically pure compounds are synthesized starting from the enantiomerically pure ester A-1.

30

Examples 1 to 21 can be synthesized by this process.

The abbreviations used stand for:

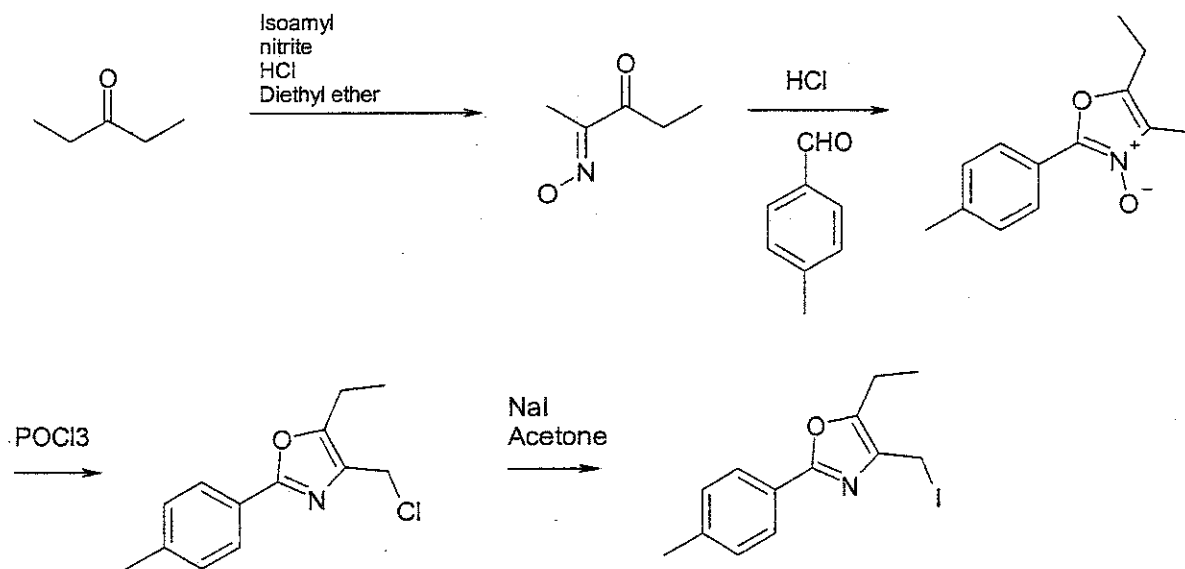
Ac	Acetyl
Bn	Benzyl
Bu	Butyl
iBu	Isobutyl
tBu	tert-Butyl
BuLi	n-Butyllithium
Bz	Benzoyl
Cy	Cyclohexyl
DCI	Direct chemical ionization (in MS)
DCM	Dichloromethane
DHP	2,3-Dihydropyran
DMAP	4-N,N-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
EA	Ethyl acetate
EDC	N'-(3-Dimethylaminopropyl)-N-ethylcarbodiimide x HCl
EI	Electron impact ionization (in MS)
equiv.	Equivalent
ESI	Electron spray ionization (in MS)
Et	Ethyl
h	Hour
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	1-Hydroxy-1H-benzotriazole x H ₂ O
HPLC	High pressure, high performance liquid chromatography
LC-MS	Coupled liquid chromatography – mass spectroscopy
Me	Methyl
MS	Mass spectroscopy
MsCl	Methanesulfonyl chloride

MTBE	tert-Butyl methyl ether
NMR	Nuclear magnetic resonance spectroscopy
Pd/C	Palladium on carbon
Ph	Phenyl
iPr	Isopropyl
nPr	n-Propyl
R _f	Retention ratio (in TLC)
RT	Room temperature
sat.	Saturated
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPSCI	tert-Butyldiphenylsilyl chloride
TBDMSCI	tert-Butyldimethylsilyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin layer chromatography
Tr	Trityl
TsOH	Toluene sulfonic acid

Other compounds can be prepared in accordance with the abovementioned processes.

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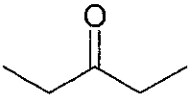
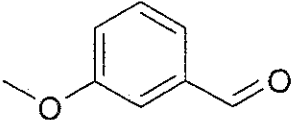
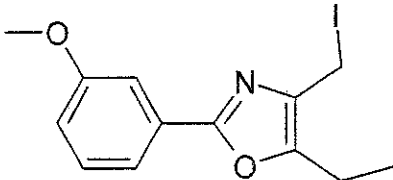
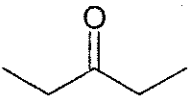
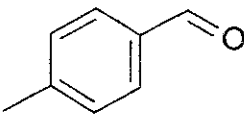
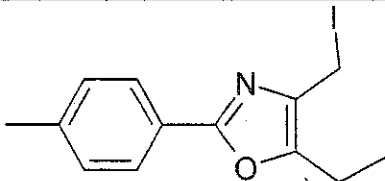
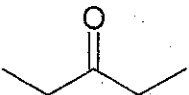
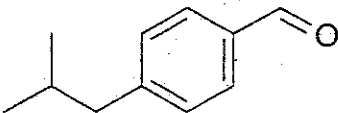
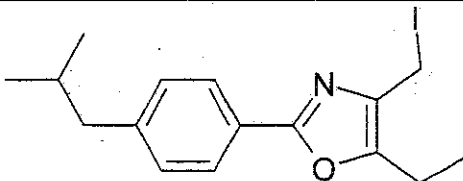
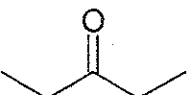
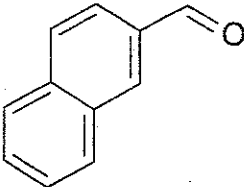
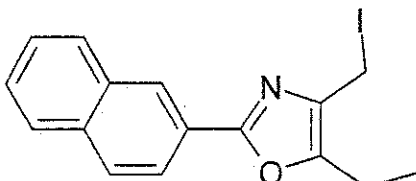
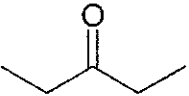
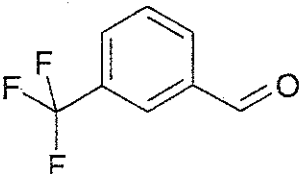
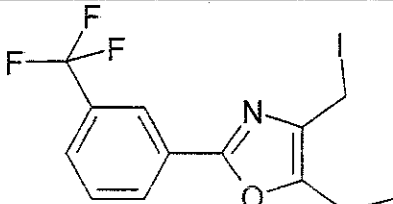
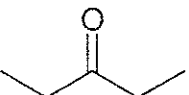
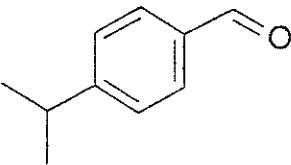
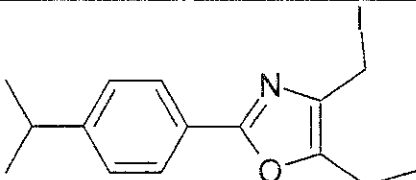
Building block synthesis of the compounds of the general formula A-8:

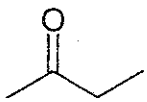
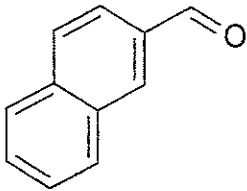
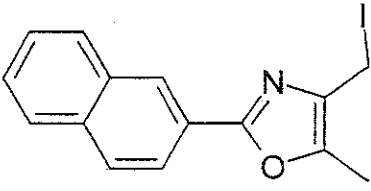
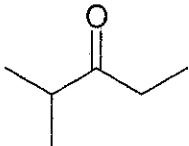
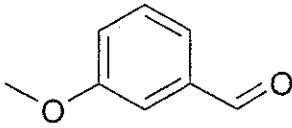
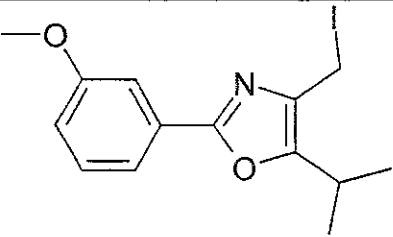


Diethyl ketone is reacted with isoamyl nitrite and HCl in diethyl ether, resulting in pentane-2,3-dione 2-oxime (G. Buechi, J. Galindo, J.Org.Chem. (1991) 56(8), 2605-2606). The latter is reacted with p-methylbenzaldehyde and HCl in acetic acid to give 5-ethyl-4-methyl-2-p-tolylloxazole 3-oxide (P. M. Weintraub, J. Med. Chem. (1972) 15(4), 419 – 420). Boiling this compound with phosphoryl chloride in chloroform results in 4-chloromethyl-5-ethyl-2-p-tolylloxazole (M. S. Malamas, R. P. Carlson, D. Grimes, R. Howell, K. Glaser, I. Gunawan, J. A. Nelson, M. Kanzelberger, U. Shah, D. A. Hartman, J. Med. Chem. (1996) 39(1), 237 – 245). This compound is heated with sodium iodide in acetone under reflux, resulting in 5-ethyl-4-iodomethyl-2-p-tolylloxazole (A., Zlatkov, P., Peikov, J., Rodriguez-Alvarez, N., Danchev, I., Nikolova, J., Mitkov, Eur.J.Med.Chem.Chim.Ther. (2000) 35(10), 941 – 948).

The following building blocks are obtained in analogy to the synthesis from the precursors depicted in Table III:

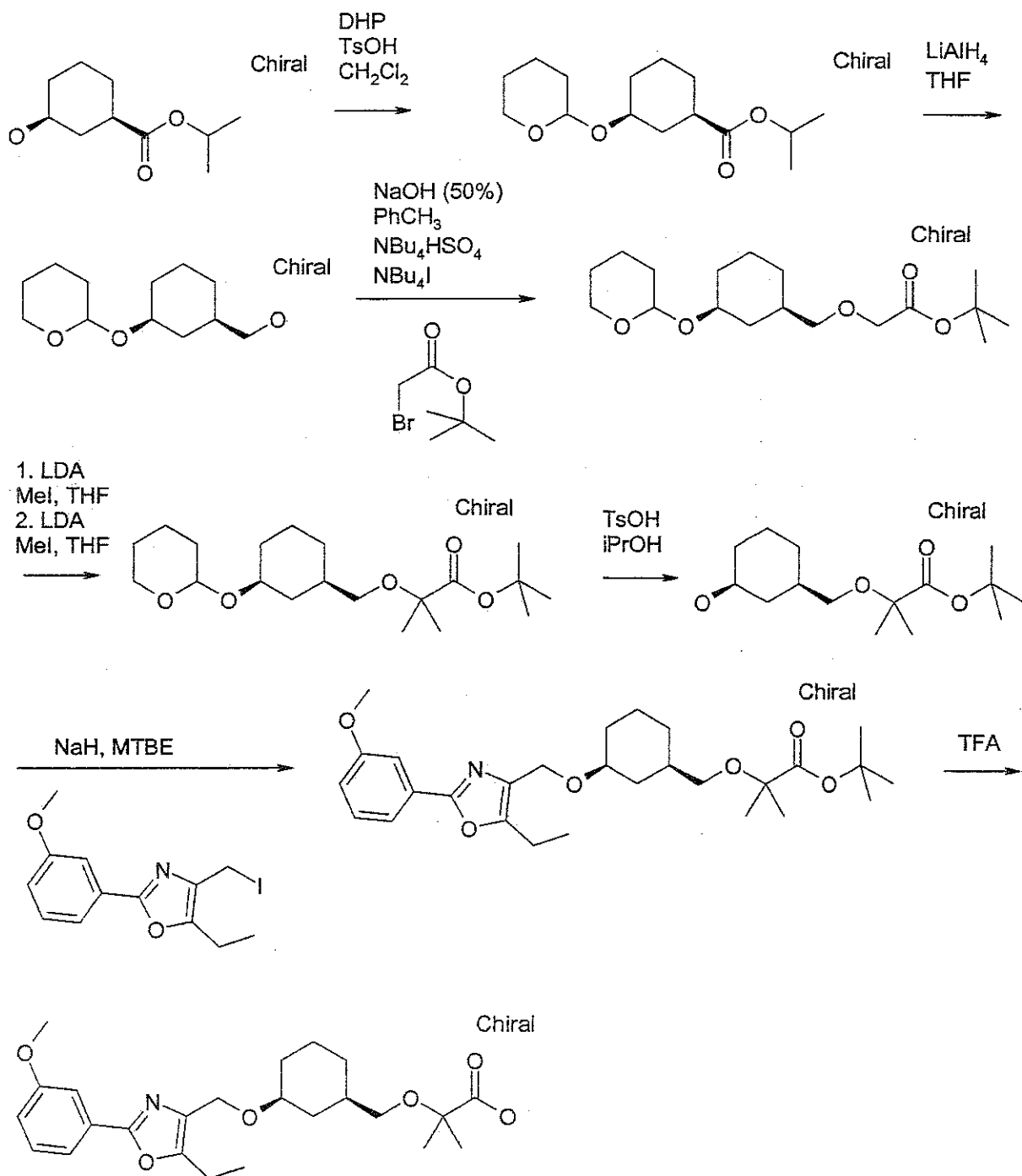
Table III:

No.	Ketone (Precursor 1)	Aldehyde (Precursor 2)	Product
1			
2			
3			
4			
5			
6			

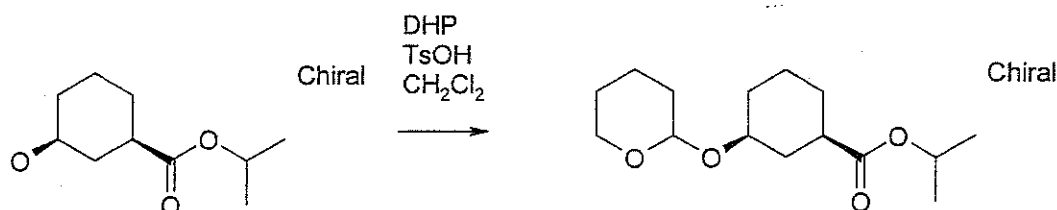
7			
8			

Example 1

2-((1R,3S)-3-[5-Ethyl-2-(4-methoxyphenyl)-oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid



Isopropyl (1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexanecarboxylate



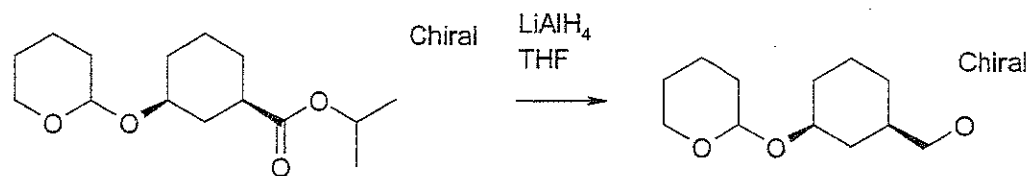
5 20.0 g of isopropyl (1R,3S)-3-hydroxycyclohexanecarboxylate and 9.94 g of dihydropyran are dissolved in 100 ml of dichloromethane and, at room temperature (RT), toluenesulfonic acid monohydrate is added. The solution is left to stand overnight at RT and then sat. sodium bicarbonate solution is added. The organic phase is separated off, washed once with sat. sodium bicarbonate solution and then with water, dried over MgSO₄ and concentrated, resulting in 28.0 g of isopropyl (1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexanecarboxylate as a brown oil.

The synthesis of isopropyl (1R,3S)-3-hydroxycyclohexanecarboxylate is described in: L. Fonteneau, S.Rosa, D. Buisson, Tetrahedron: Asymmetry (2002), 13(6), 579-585.

15 ¹H-NMR (500 MHz, DMSO): δ = 4.82-4.92 (m, 1H); 4.61-4.64 and 4.68-4.72 (m, 1H, THP-CH(OR)₂); 3.70-3.80 (m 1H); 3.49-3.58 (m, 1H); 3.35-3.46 (m, 1H); 2.20-2.36 (m 1H); 2.04-2.16 (m, 1H), 0.97-2.0 (m, 13H); 1.15-1.19 (2d, 6H).

[(1R,3S)-3-(Tetrahydropyran-2-yloxy)cyclohexyl]methanol

20



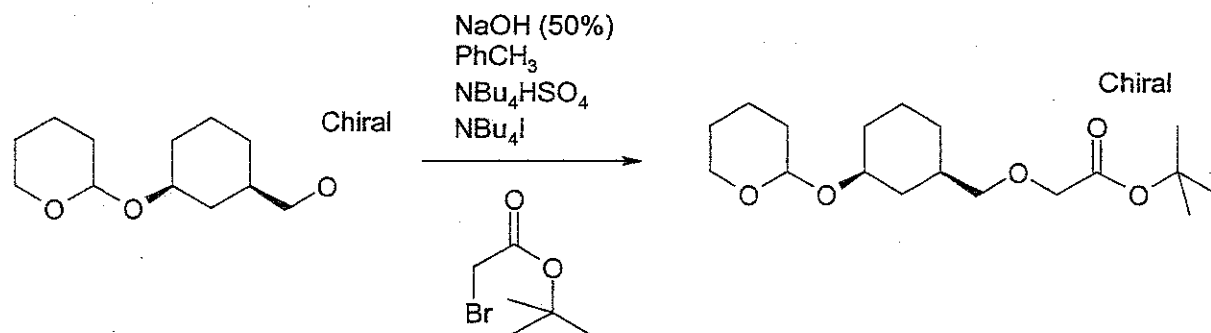
47 g of isopropyl (1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexanecarboxylate are, at 0°C, added dropwise to a suspension of 13.2 g of lithium aluminum hydride in THF.

25 The mixture is stirred at RT for 1 h, then, at 0°C, 68 ml of ethyl acetate and

subsequently 55.6 g of sodium hydroxide, dissolved in 62.6 ml of water, are added. Then 50 ml of methanol are added and the mixture is stirred until the precipitate is white. 50 g of magnesium sulfate are added to the suspension, which is then filtered. The filtrate is concentrated, whereupon further magnesium sulfate precipitates; it is completely precipitated with MTBE and filtered off. Removal of the solvent by distillation results in 34 g of [(1R, 3S)-3-(tetrahydropyran-2-yloxy)cyclohexyl]methanol as pale yellow oil.

¹H-NMR (500 MHz, DMSO): δ = 4.67-4.72 (m, 1H); 4.36-4.42 (m, 1H); 3.73-3.81 (m, 1H); 3.44-3.52 (m, 1H); 3.37-3.44 (m, 1H); 3.16-3.27 (m, 2H); 1.84-2.04 (m, 2H); 1.66-1.75 (m, 2H); 1.54-1.64 (m, 2H); 1.32-1.51 (m, 4H); 1.08-1.30 (m, 2H); 0.67-1.02 (m, 3H).

tert-Butyl [(1R, 3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]acetate



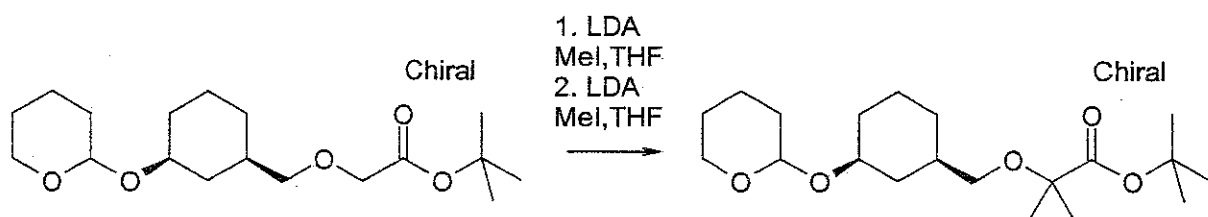
15

34 g of [(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexyl]methanol, 100 g of tert-butyl bromoacetate, 16.2 g of tetrabutylammonium bisulfate and 5.9 g of tetrabutylammonium iodide are dissolved in 250 ml of toluene and, at 10°C (ice-water bath), a solution of 63.5 g of sodium hydroxide in 80 ml of water is added, and the mixture is stirred vigorously (KPG paddle stirrer) at 10°C for 8 h. Then MTBE and water are added, and the phases are separated. The aqueous phase is extracted twice with MTBE, and the combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The residue is chromatographed on silica gel (heptane/ethyl acetate gradient). This results in 36.4 g of tert-butyl [(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]acetate and 6.8 g of [(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexyl]methanol as pale yellow oils.

25

C₁₈H₃₂O₅ (328.22); MS (Cl⁺): 329 (3) [MH⁺], 245.2 (100) [MH⁺ — C₅H₈O], 189.2 (50) [MH⁺ — C₅H₈O — C₄H₈].

5 tert-Butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]-propionate



10 100 ml of a solution of lithium diisopropylamide (2M in THF) are added to a solution of 30 g of tert-butyl [(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]acetate in 250 ml of THF at -78°C , during which the temperature should not rise above -55°C . The solution is stirred at this temperature for 10 min and then warmed to -10°C and stirred at this temperature for a further 15 min, after which the solution is again cooled to -78°C , and 17.1 ml of methyl iodide are added dropwise. The solution is warmed to -10°C and then saturated ammonium chloride solution and MTBE are added. The phases are separated, the organic phase is washed with saturated ammonium chloride solution, the combined aqueous phases are extracted once more with MTBE, and then the combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated.

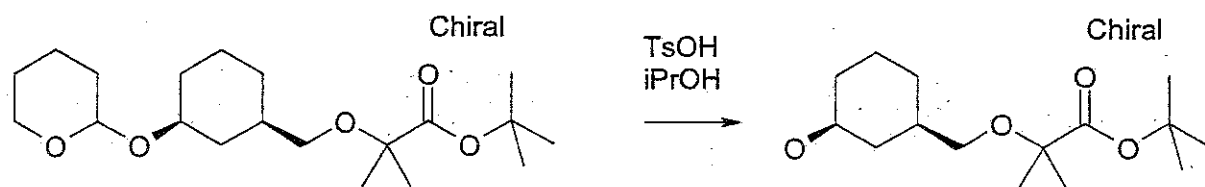
87 ml of a solution of lithium diisopropylamide (2M in THF) are added to a solution of the residue obtained in this way in 217 ml of THF at -78°C , during which the temperature should not rise above -55°C . The solution is stirred at this temperature for 10 min and then warmed to -10°C and stirred at this temperature for a further 15 min, after which the solution is again cooled to -78°C , and 14.7 ml of methyl iodide are added dropwise. The solution is warmed to -10°C and then saturated ammonium chloride solution and MTBE are added. The phases are separated, the organic phase is washed with saturated ammonium chloride solution, the combined aqueous phases

are extracted once more with MTBE, and then the combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated, resulting in 29 g of tert-butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]propionate as yellow oil.

5

¹H-NMR (500 MHz, DMSO): δ = 4.68–4.72 (m, 1H); 3.74–3.80 (m, 1H); 3.44–3.53 (m, 1H); 3.38–3.44 (m, 1H); 3.13–3.17 (m, 1H); 3.06–3.12 (m, 1H); 1.70–2.06 (m, 2H); 0.73–1.76 (m, 13H); 1.42 (s, 9H), 1.27 (s, 6H).

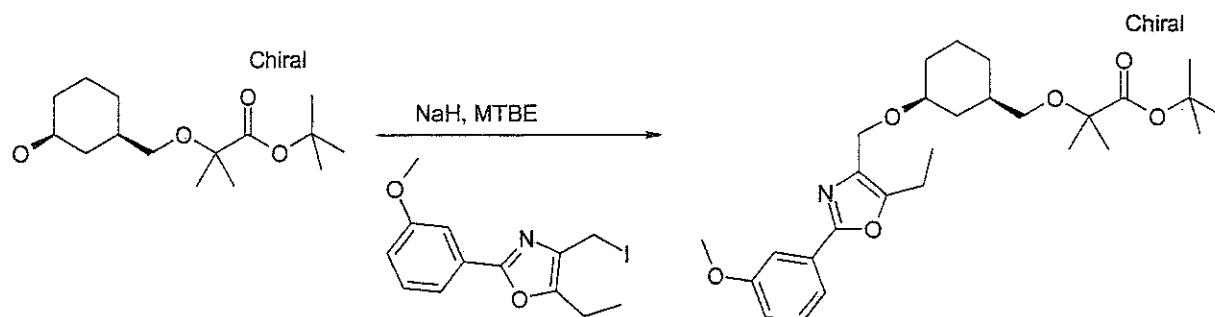
10 tert-Butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate



29 g of tert-butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]-
 15 propionate are dissolved in 150 ml of isopropanol, and 2.3 g of toluenesulfonic acid monohydrate are added. After the toluenesulfonic acid has completely dissolved, the solution is left to stand for 4 days and then mixed with saturated sodium bicarbonate solution and partly concentrated. The residue is taken up MTBE/water, the phases are separated, the aqueous phase is extracted with MTBE, and the combined organic
 20 phases are dried over magnesium sulfate and concentrated. The residue is chromatographed on silica gel with heptane/ethyl acetate 3:1, resulting in 13.8 g of tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate as yellow oil.

C₁₅H₂₈O₄ (272.20); MS (CI⁺): 273.4 (24) [MH⁺], 217.2 (100) [MH⁺ – C₄H₈], 199 (18),
 25 113 (19).

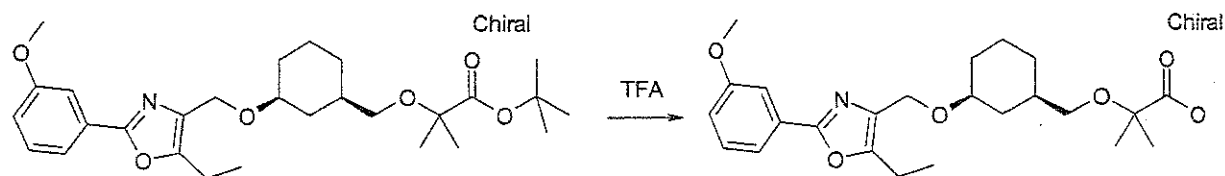
tert-Butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexylmethoxy)-2-methylpropionate



200 mg of tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate are added dropwise as solution in MTBE to a suspension of 65 mg of sodium hydride (60% by weight in mineral oil) in 10 ml of MTBE. After gas evolution ceases, 503 mg of 4-iodomethyl-5-ethyl-2-(3-methoxyphenyl)oxazole are added as solution in MTBE, and the suspension is heated under reflux overnight. Ethyl acetate (MTBE can also be used) is added to the reaction mixture, and the mixture is washed with water and saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The residue is chromatographed on silica gel (heptane/ethyl acetate gradient), resulting in 323 mg of tert-butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionate as yellow oil.

C₂₈H₄₁NO₆ (487.64): LCMS (ESI): 488.41 [MH⁺].

2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid



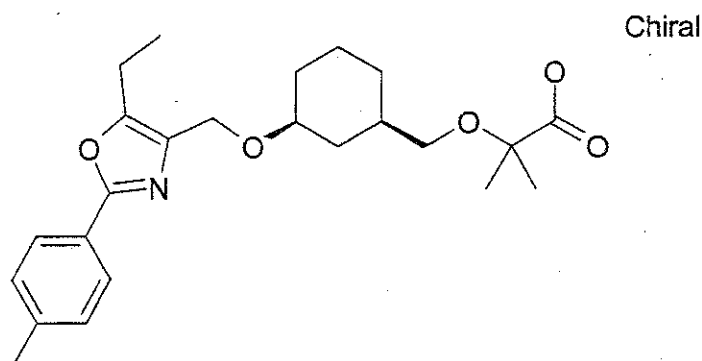
300 mg of tert-butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionate are left to stand in 1 ml of trifluoroacetic acid at RT overnight. The solution is completely evaporated, water is added to the residue, and the pH is adjusted to 3 with sodium bicarbonate solution. The solution is extracted

with ethyl acetate, and the organic phase is washed twice with water, dried over magnesium sulfate and concentrated. The residue is chromatographed on silica gel (dichloromethane/methanol gradient), resulting in 256 mg of 2-[(1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy]-2-methylpropionic acid as 5 yellow resin.

C₂₄H₃₃NO₆ (431.53): LCMS (ESI): 432.1 [MH⁺].

10 Example 2

2-[(1R,3S)-3-(5-Ethyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-2-methylpropionic acid



15

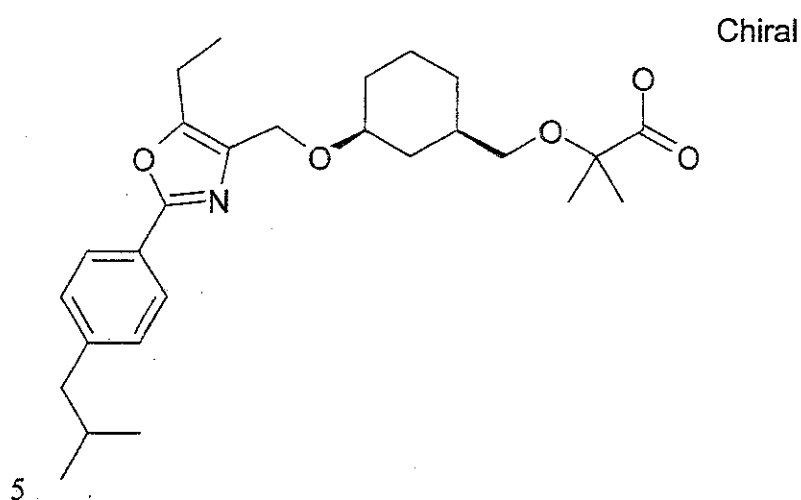
2-[(1R,3S)-3-(5-Ethyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-2-methylpropionic acid is obtained in analogy to Example 1 from tert-butyl 2-[(1R,3S)-3-hydroxycyclohexylmethoxy]-2-methylpropionate and 4-iodomethyl-5-ethyl-2-p-tolyloxazole.

20

C₂₄H₃₃NO₅ (415.24): LCMS (ESI): 416.39 [MH⁺].

Example 3

2-((1R,3S)-3-[5-Ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid

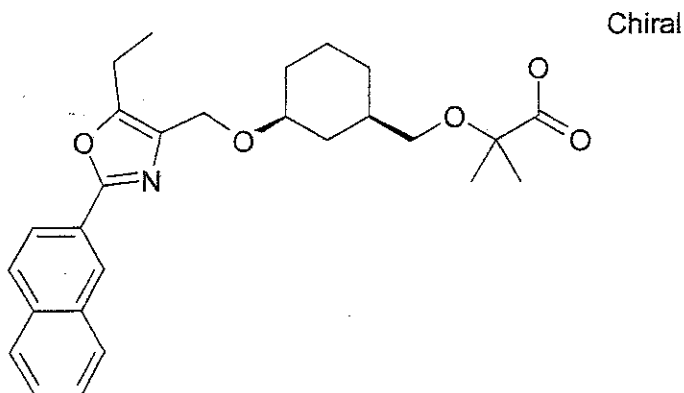


2-((1R,3S)-3-[5-Ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid is obtained in analogy to Example 1 from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate and 4-iodomethyl-5-ethyl-2-(4-isobutylphenyl)oxazole.

C₂₇H₃₉NO₅ (457.28): LCMS (ESI): 458.43 [MH⁺].

Example 4

2-((1R,3S)-3-[5-Ethyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid



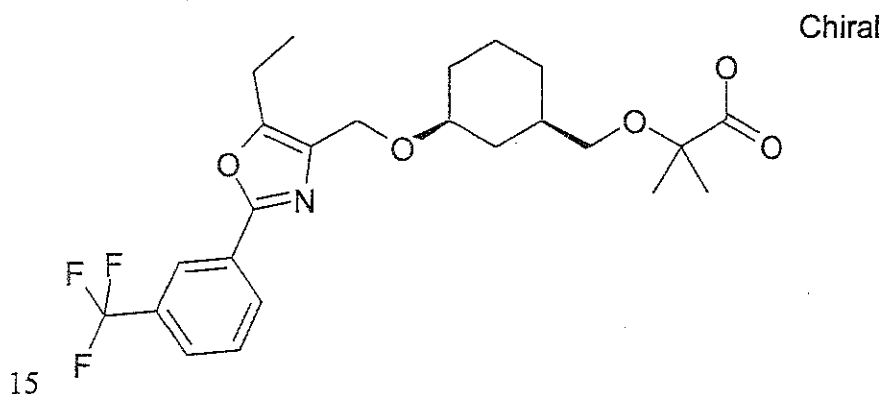
2-((1R,3S)-3-[5-Ethyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid is obtained in analogy to Example 1 from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate and 5-ethyl-4-iodomethyl-2-(naphthyl-2-yl)oxazole.

C₂₇H₃₃NO₅ (451.24): LCMS (ESI): 452.19 [MH⁺].

10

Example 5

2-((1R,3S)-3-[5-Ethyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid



2-((1R,3S)-3-[5-Ethyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid is obtained in analogy to Example 1 from tert-

butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate and 5-ethyl-4-iodomethyl-2-(3-trifluoromethylphenyl)oxazole.

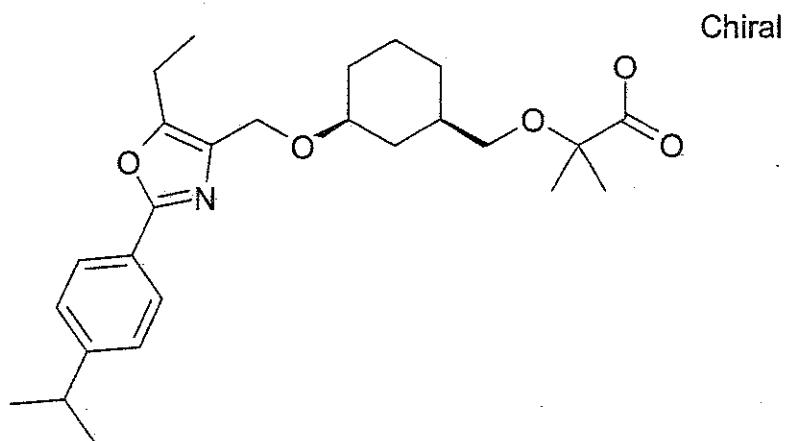
C₂₄H₃₀F₃NO₅ (469.21): LCMS (ESI): 470.20 [MH⁺].

5

Example 6

2-((1R,3S)-3-[5-Ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid

10

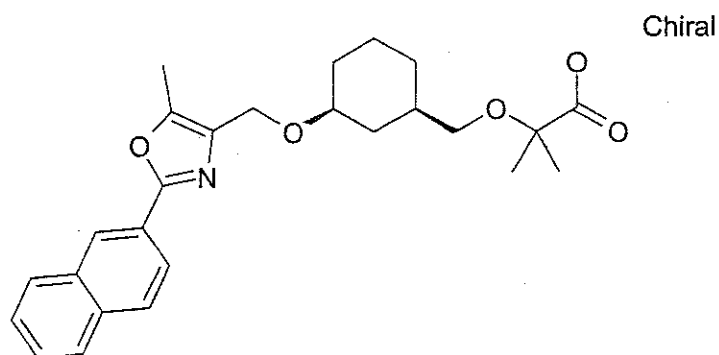


2-((1R,3S)-3-[5-Ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid is obtained in analogy to Example 1 from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate and 5-ethyl-4-iodomethyl-2-(4-isopropylphenyl)oxazole.

C₂₆H₃₇NO₅ (443.27): LCMS (ESI): 488.72 [M+HCOO].

20 Example 7

2-Methyl-2-((1R,3S)-3-[5-methyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)propionic acid



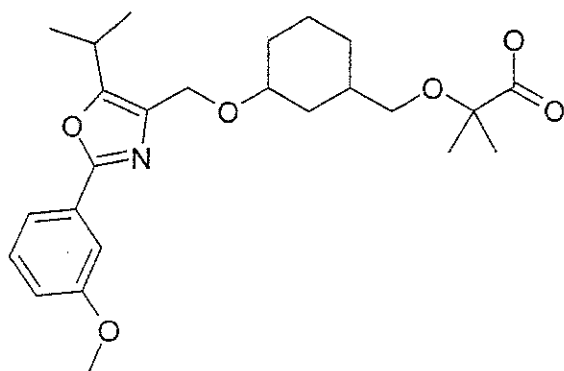
2-Methyl-2-((1R,3S)-3-[5-methyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)propionic acid is obtained in analogy to Example 1 from tert-butyl 2-5 ((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate and 5-methyl-4-iodomethyl-2-(naphth-2-yl)oxazole.

C₂₆H₃₁NO₅ (437.22): LCMS (ESI): 438.17 [MH⁺].

10

Example 8

2-{cis-3-[5-isopropyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy}-2-methylpropionic acid



15

Racemic 2-{cis-3-[5-isopropyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy}-2-methylpropionic acid is obtained in analogy to Example 1 from

racemic tert-butyl 2-(cis-3-hydroxycyclohexylmethoxy)-2-methylpropionate and 4-iodomethyl-2-(3-methoxyphenyl)-5-isopropyloxazole.

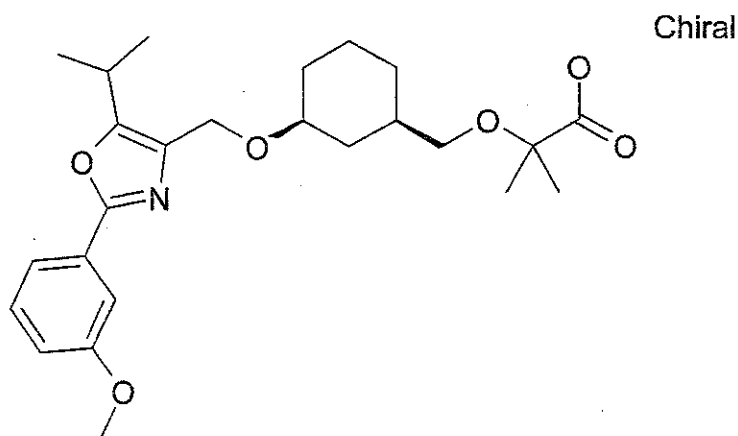
C₂₅H₃₅NO₆ (445.25): LCMS (ESI): 446.27 [MH⁺].

5

Example 9

2-((1R,3S)-3-[5-isopropyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid

10



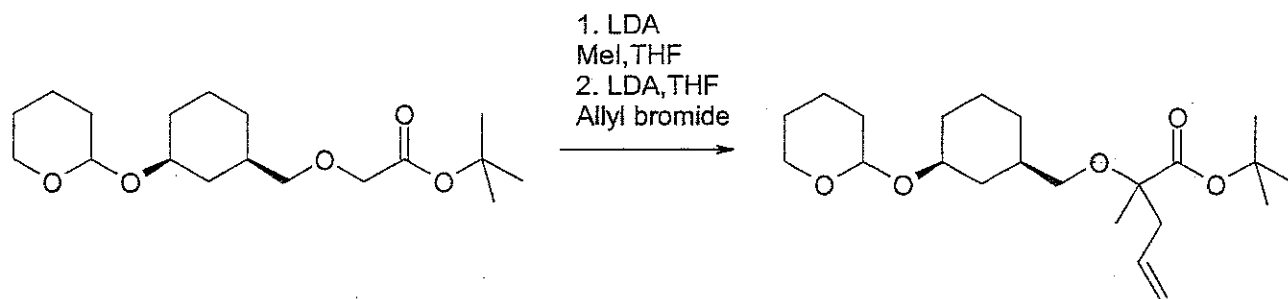
2-((1R,3S)-3-[5-isopropyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid is obtained in analogy to Example 1 from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate and 4-iodomethyl-2-(3-methoxyphenyl)-5-isopropyloxazole.

C₂₅H₃₅NO₆ (445.25): LCMS (ESI): 446.27 [MH⁺].

20

Example 10

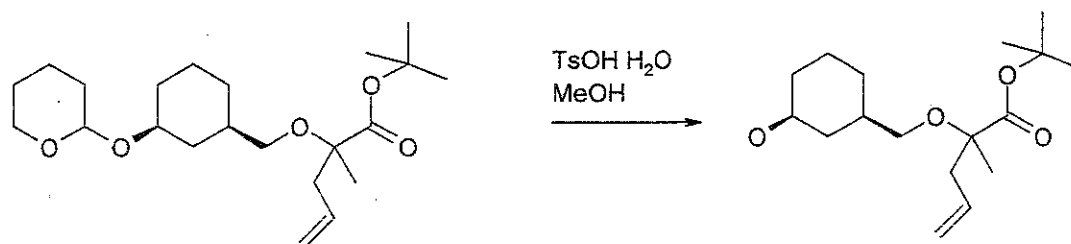
tert-Butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]pent-4-enoate



tert-Butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]pent-4-enoate is obtained as a mixture of two diastereomers from tert-butyl [(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]acetate, methyl iodide, allyl bromide and lithium diisopropylamide in analogy to the synthesis of tert-butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]propionate in Example 1.

¹H-NMR (500 MHz, DMSO): δ = 5.65-5.76 (m, 1H), 5.04-5.13 (m, 2H), 4.68-4.72 (m, 1H); 3.73-3.80 (m, 1H); 3.44-3.53 (m, 1H); 3.38-3.44 (m, 1H); 3.06-3.23 (m, 2H); 2.55-2.63 (m, 1H); 2.32-2.45 (m, 2H); 1.70-2.06 (m, 2H); 0.73-1.76 (m, 12H); 1.42 (s, 9H); 1.22 (s, 3H).

tert-Butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpent-4-enoate



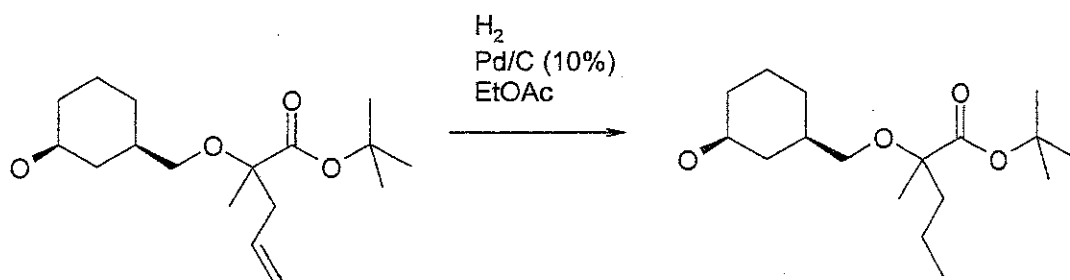
15

tert-Butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpent-4-enoate is obtained as a mixture of two diastereomers from tert-butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]pent-4-enoate and toluenesulfonic acid monohydrate in analogy to the synthesis of tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate in Example 1.

¹H-NMR (500 MHz, DMSO): δ = 5.65-5.76 (m, 1H), 5.04-5.13 (m, 2H), 4.45-4.48 (m, 1H); 3.29-3.36 (m, 1H); 3.06-3.20 (m, 2H); 2.31-2.44 (m, 2H); 1.65-1.93 (m, 2H);

1.55-1.70 (m, 2H); 1.07-1.52 (m, 2H); 0.95-1.06 (m, 1H), 0.71-0.86 (m, 2H); 1.41 (s, 9H); 1.22 (s, 3H).

tert-Butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate

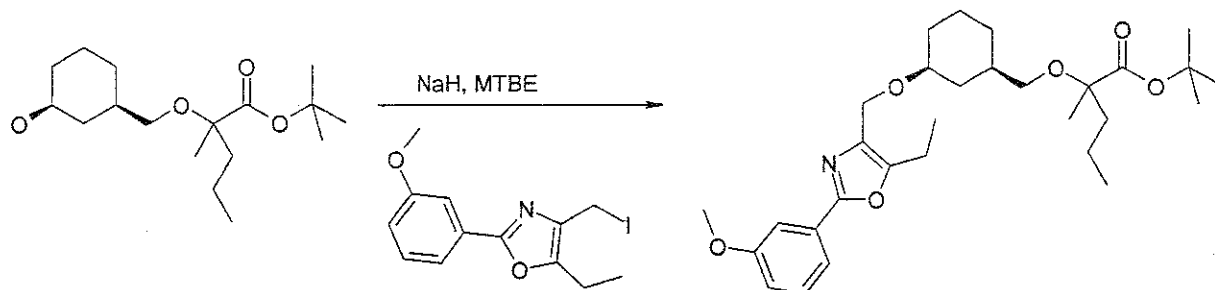


5

2.4 g of tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpent-4-enoate are dissolved in 15 ml of ethyl acetate and, under an argon atmosphere in an autoclave, a spatula tip of Pd/C (10%) is added. The autoclave is then flushed with H₂, and the solution is stirred with an H₂ pressure of 3 bar at RT overnight. The catalyst is then
10 filtered off through Celite, and the filtrate is concentrated, resulting in 2.3 g of tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate as a mixture of two diastereomers as pale yellow oil.

C₁₇H₃₂O₄ (300.44); MS (CI⁺): 301.5 (24) [MH⁺], 245.4 (100) [MH⁺ – C₄H₈], 227 (18),
15 113 (58).

tert-Butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexylmethoxy)-2-methylpentanoate



20

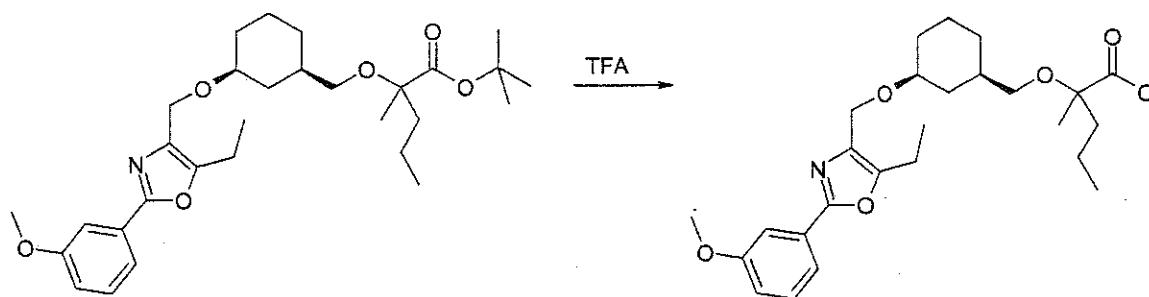
tert-Butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexylmethoxy)-2-methylpentanoate is obtained as a mixture of two diastereomers

from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate and tert-butyl 4-iodomethyl-5-ethyl-2-(3-methoxyphenyl)oxazole in analogy to the synthesis of tert-butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionate in Example 1.

5

C₃₀H₄₅NO₆ (515.32): LCMS (ESI): 516.41 [MH⁺].

2-((1R,3S)-3-[5-Ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpentanoic acid



10

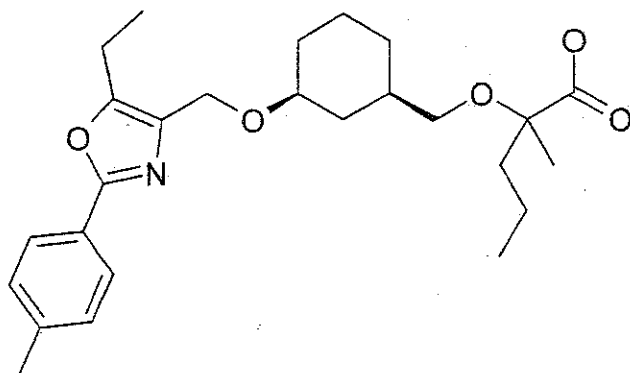
2-((1R,3S)-3-[5-Ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpentanoic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate and trifluoroacetic acid in analogy to the synthesis of 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid in Example 1.

15

C₂₆H₃₇NO₆ (459.26): LCMS (ESI): 459.58 [MH⁺].

20 Example 11

2-[(1R,3S)-3-(5-Ethyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-2-methylpentanoic acid

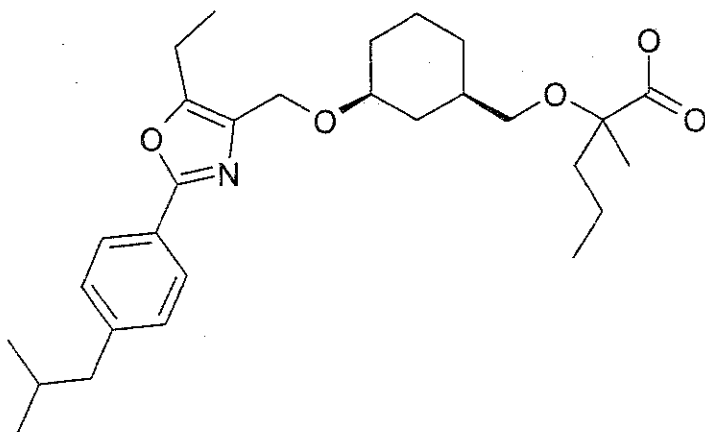


2-[(1R,3S)-3-(5-Ethyl-2-p-tolylloxazol-4-ylmethoxy)cyclohexylmethoxy]-
 2-methylpentanoic acid is obtained as a mixture of two diastereomers from tert-butyl
 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate and 4-iodomethyl-5-
 5 ethyl-2-p-tolylloxazole in analogy to Example 10.

C₂₆H₃₇NO₅ (443.27): LCMS (ESI): 488.53 [M+HCOO].

10 Example 12

2-((1R,3S)-3-[5-Ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-
 2-methylpentanoic acid

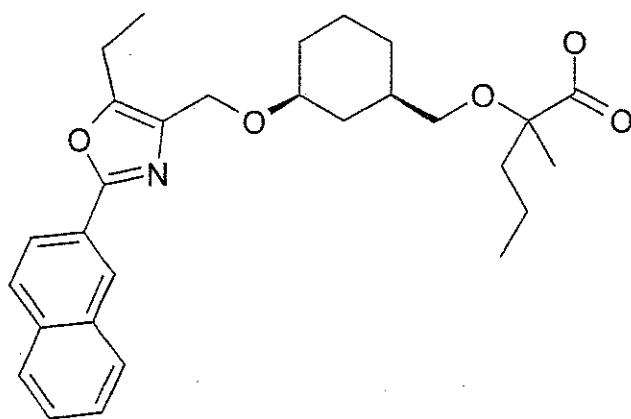


2-((1R,3S)-3-[5-Ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-
 15 2-methylpentanoic acid is obtained as a mixture of two diastereomers from tert-butyl
 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate and 4-iodomethyl-
 5-ethyl-2-(4-isobutylphenyl)oxazole in analogy to Example 10.

C₂₉H₄₃NO₅ (485.31): LCMS (ESI): 485.49 [MH⁺].

Example 13

5 2-((1R,3S)-3-[5-Ethyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpentanoic acid



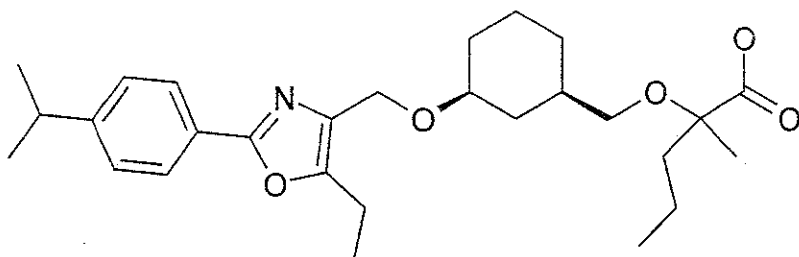
2-((1R,3S)-3-[5-Ethyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-
10 2-methylpentanoic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate and 5-ethyl-4-iodomethyl-2-(naphth-2-yl)oxazole in analogy to Example 10.

C₂₉H₃₇NO₅ (479.27): LCMS (ESI): 524.52 [M+HCOO].

15

Example 14

2-((1R,3S)-3-[5-Ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-
2-methylpentanoic acid



20

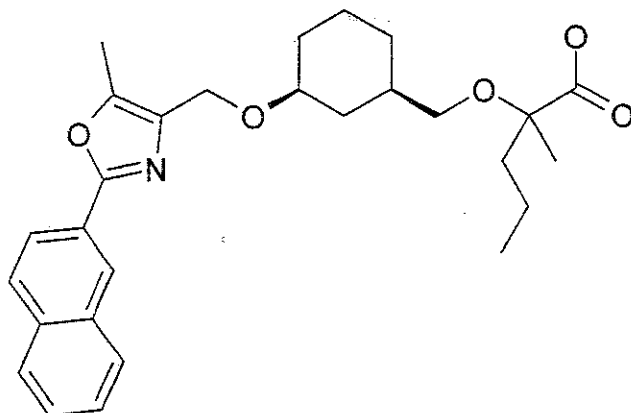
2-((1R,3S)-3-[5-Ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpentanoic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate and 5-ethyl-4-iodomethyl-2-(4-isopropylphenyl)oxazole in analogy to Example 10.

5

C₂₉H₃₇NO₅ (479.27): LCMS (ESI): 524.52 [M+HCOO].

Example 15

10 2-Methyl-2-((1R,3S)-3-[5-methyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)pentanoic acid

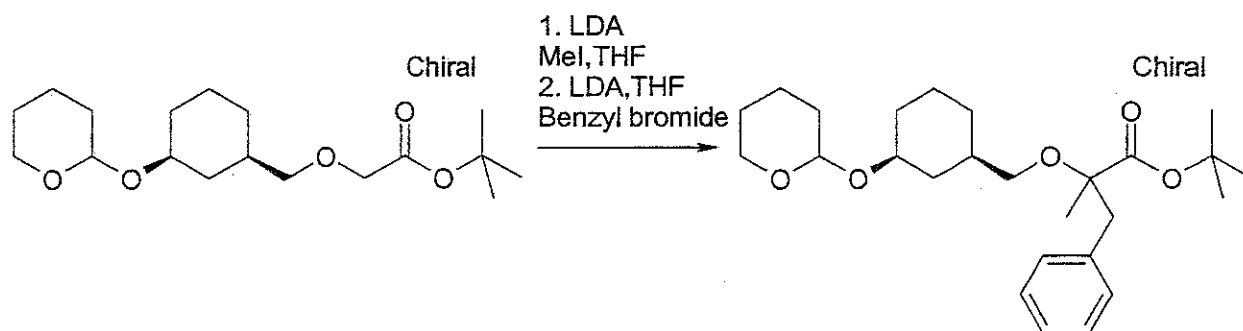


15 2-Methyl-2-((1R,3S)-3-[5-methyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)pentanoic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpentanoate and 5-methyl-4-iodomethyl-2-(naphth-2-yl)oxazole in analogy to Example 10.

20 C₂₈H₃₅NO₅ (465.25): LCMS (ESI): 510.57 [M+HCOO].

Example 16

tert-Butyl 2-methyl-3-phenyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]propionate



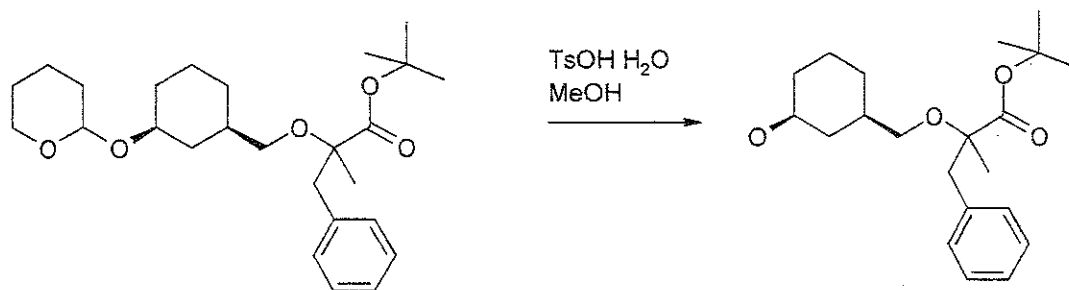
5

tert-Butyl 2-methyl-3-phenyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)-cyclohexylmethoxy]propionate is obtained as a mixture of two diastereomers from tert-butyl [(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]acetate, methyl iodide, benzyl bromide and lithium diisopropylamide in analogy to the synthesis of tert-butyl 2-methyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]propionate in Example 1.

C₂₆H₄₀O₅ (432.29): LCMS (ESI): 450.34 (13) [M⁺+H₂O]; 349.25 (22) [M-C₅H₈O]; 293.17 (100) [M-C₅H₈O-C₄H₈].

15

tert-Butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate

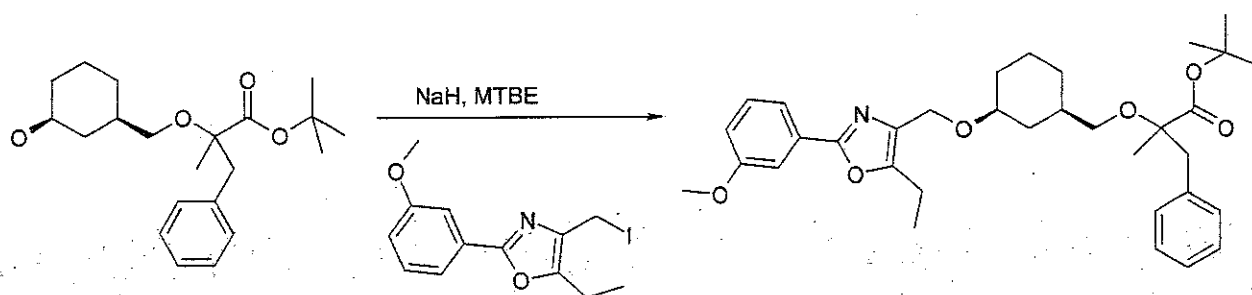


tert-Butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate is obtained as a mixture of two diastereomers from tert-butyl 2-methyl-3-phenyl-2-[(1R,3S)-3-(tetrahydropyran-2-yloxy)cyclohexylmethoxy]propionate and

toluenesulfonic acid monohydrate in analogy to the synthesis of tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methylpropionate in Example 1.

C₂₁H₃₂O₄ (348.23); MS (CI⁺): 349.6 (38) [MH⁺], 293.4 (100) [MH⁺ – C₄H₈], 247.4 (18), 113.4 (19).

tert-Butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-3-phenylpropionate



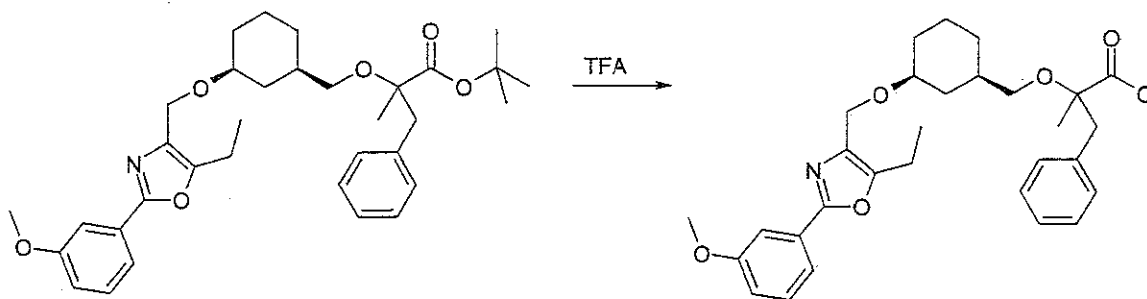
10

tert-Butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-3-phenylpropionate is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate and 4-iodomethyl-5-ethyl-2-(3-methoxyphenyl)oxazole in analogy to the synthesis of tert-butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionate in Example 1.

C₃₄H₄₅NO₆ (563.32): LCMS (ESI): 564.46 [MH⁺].

20

2-((1R,3S)-3-[5-Ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-3-phenylpropionic acid



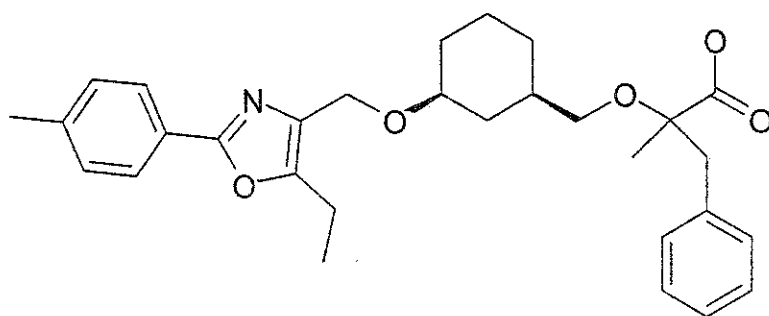
2-((1R,3S)-3-[5-Ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-3-phenylpropionic acid is obtained as a mixture of two diastereomers from

- 5 tert-butyl 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-3-phenylpropionate and trifluoroacetic acid in analogy to the synthesis of 2-((1R,3S)-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methylpropionic acid in Example 1.

10 C₃₀H₃₇NO₆ (507.26): LCMS (ESI): 508.40 [MH⁺].

Example 17

2-((1R,3S)-3-(5-Ethyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy)-2-methyl-3-phenylpropionic acid



15

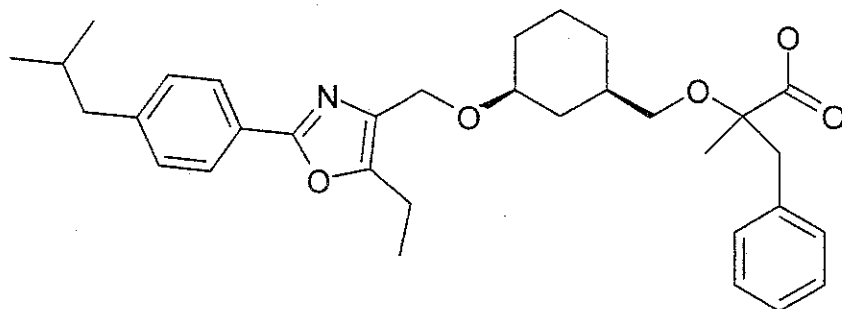
2-((1R,3S)-3-(5-Ethyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy)-2-methyl-3-phenylpropionic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate and 4-iodomethyl-5-ethyl-2-p-tolyloxazole in analogy to Example 10.

20

C₃₀H₃₇NO₅ (491.27: LCMS (ESI): 492.40 [MH⁺].

Example 18

2-((1R,3S)-3-[5-Ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-
 5 2-methyl-3-phenylpropionic acid

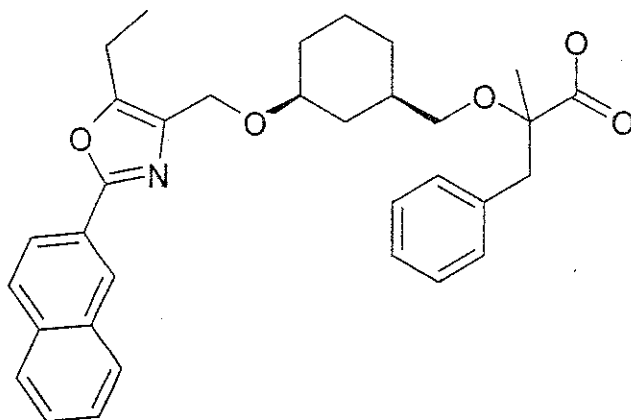


2-((1R,3S)-3-[5-Ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-
 2-methyl-3-phenylpropionic acid is obtained as a mixture of two diastereomers from
 tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate and
 10 4-iodomethyl-5-ethyl-2-(4-isobutylphenyl)oxazole in analogy to Example 10.

C₃₃H₄₃NO₅ (533.31): LCMS (ESI): 534.45 [MH⁺].

Example 19

2-((1R,3S)-3-[5-Ethyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-
 3-phenylpropionic acid



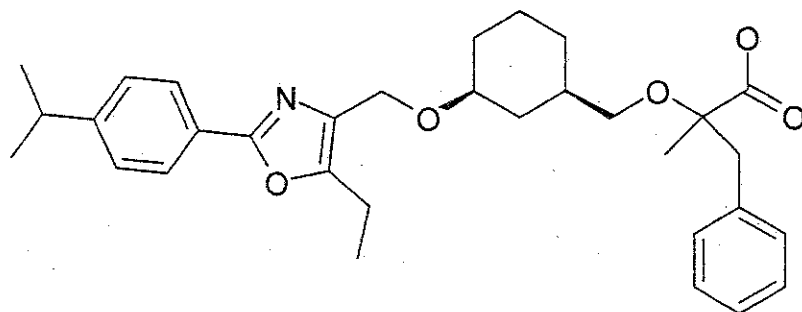
2-((1R,3S)-3-[5-Ethyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-3-phenylpropionic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate and 5-ethyl-4-iodomethyl-2-(naphth-2-yl)oxazole in analogy to Example 10.

5

C₃₃H₃₇NO₅ (527.27): LCMS (ESI): 528.40 [MH⁺].

10 Example 20

2-((1R,3S)-3-[5-Ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-2-methyl-3-phenylpropionic acid



2-((1R,3S)-3-[5-Ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-

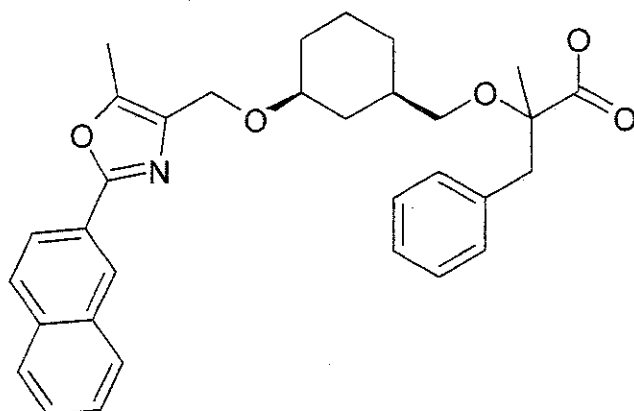
15 2-methyl-3-phenylpropionic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate and 5-ethyl-4-iodomethyl-2-(4-isopropylphenyl)oxazole in analogy to Example 10.

C₃₂H₄₁NO₅ (519.30): LCMS (ESI): 564.59 [M+HCOO].

20

Example 21

2-Methyl-2-((1R,3S)-3-[5-methyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]cyclohexylmethoxy)-3-phenylpropionic acid

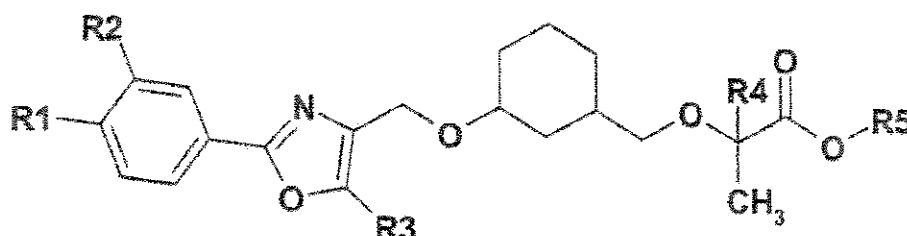


2-Methyl-2-((1R,3S)-3-[5-methyl-2-(naphth-2-yl)oxazol-4-ylmethoxy]-cyclohexylmethoxy)-3-phenylpropionic acid is obtained as a mixture of two diastereomers from tert-butyl 2-((1R,3S)-3-hydroxycyclohexylmethoxy)-2-methyl-3-phenylpropionate and 5-methyl-4-iodomethyl-2-(naphth-2-yl)oxazole in analogy to Example 10.

C₃₂H₃₅NO₅ (513.25): LCMS (ESI): 514.38 [MH⁺].

Claims:

1. A compound of the formula I



5

I

in which the meanings are:

R1 H, (C1-C6)-alkyl;

10 R2 H, O-(C1-C3)-alkyl, CF₃; or

R1 and R2 are together with the phenyl ring fused naphthyl;

R3 (C1-C6)-alkyl;

15

R4 (C1-C6)-alkyl, benzyl;

R5 H, (C1-C6)-alkyl;

wherein the following compounds are disclaimed:

20 2-[cis-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-2-methylpropionic acid,
2-[(1R, 3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-2-methylpropionic acid,

2-[(1S, 3R)-cis-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexylmethoxy]-2-methylpropionic acid,

25 2-[(1S, 3R)-3-[2-(cis-3-trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexylmethoxy]-2-methylpropionic acid, and

2-methyl-2-[(1R,3S)-cis-3-(5-methyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy)cyclohexylmethoxy]propionic acid.

and the physiologically tolerated salts and solvates thereof.

30

2. A compound of the formula I as claimed in claim 1, in which
R1 is H, methyl, propyl or butyl;

R2 is H, methoxy, CF₃; or

R1 and R2 are together with the phenyl ring fused naphthyl;

5 R3 is methyl, ethyl or propyl;

R4 is methyl, propyl or benzyl; and

R5 is H.

10

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

R1 or R2 is H.

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

R4 is methyl.

5. A medicament comprising one or more of the compounds of the formula I as
20 claimed in one or more of claims 1 to 4.

6. A medicament comprising one or more of the compounds of the formula I as
claimed in one or more of claims 1 to 4 and one or more active ingredients which have
favorable effects on metabolic disturbances or disorders associated therewith.

25

7. A medicament comprising one or more of the compounds of the formula I as
claimed in one or more of claims 1 to 4 and one or more antidiabetics.

8. A medicament comprising one or more of the compounds of the formula I as
30 claimed in one or more of claims 1 to 4 and one or more lipid modulators.

9. The use of the compounds of the formula I as claimed in one or more of claims 1 to 4 in the manufacture of a medicament for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

5 10. The use of the compounds of the formula I as claimed in one or more of claims 1 to 4 in the manufacture of a medicament for the treatment and/or prevention of disorders in which insulin resistance is involved.

11. The use of the compounds of the formula I as claimed in one or more of claims 1 to 4 in
10 the manufacture of a medicament for the treatment and/or prevention of diabetes mellitus and the sequelae associated therewith.

12. The use of the compounds of the formula I as claimed in one or more of claims 1 to 4 in the manufacture of a medicament for the treatment and/or prevention of dyslipidemias and
15 their sequelae.

13. The use of the compounds of the formula I as claimed in one or more of claims 1 to 4 in the manufacture of a medicament for the treatment and/or prevention of conditions associated with the metabolic syndrome.

20

14. The use of the compounds as claimed in one or more of claims 1 to 4 in combination with at least one further active ingredient in the manufacture of a medicament for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders.

25 15. The use of the compounds as claimed in one or more of claims 1 to 4 in combination with at least one further active ingredient in the manufacture of a medicament for the treatment and/or prevention of disorders in which insulin resistance is involved.

16. A process for producing a medicament comprising one or more of the compounds as
30 claimed in one or more of claims 1 to 4, which comprises mixing the active ingredient with a pharmaceutically suitable carrier, and bringing this mixture into a form suitable for administration.