

Arylcycloalkyl-substituted alkanoic acid derivatives, processes for their preparation  
5 and their use as pharmaceuticals

### Description

The invention relates to arylcycloalkyl-substituted alkanoic acid derivatives and to  
10 their physiologically acceptable salts and physiologically functional derivatives.

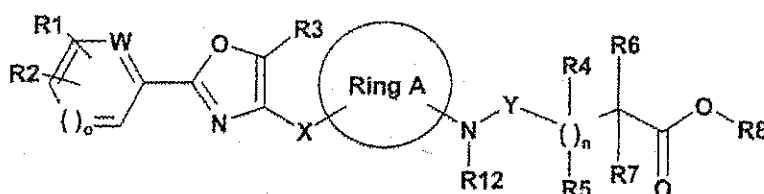
Compounds of a similar structure have already been described in the prior art for  
the treatment of hyperlipidemia and diabetes (WO 2000/64876).

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

20 Surprisingly, a number of compounds which modulate the activity of PPAR  
receptors have been found. The compounds are particularly suitable for activating  
PPARalpha and PPARgamma, where the extent of the relative activation may  
vary, depending on the compounds.

25

The invention thus relates to compounds of the formula I



in which:

- Ring A is (C3-C8)-cycloalkanediyl or (C3-C8)-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one or more carbon atoms may be replaced by oxygen atoms;
- 5 R1, R2 independently of one another are H, F, Cl, Br, CF<sub>3</sub>, OCF<sub>3</sub>, (C1-C6)-alkyl, O-(C1-C6)-alkyl, SCF<sub>3</sub>, SF<sub>5</sub>, OCF<sub>2</sub>-CHF<sub>2</sub>, (C6-C10)-aryl, (C6-C10)-aryloxy, OH, NO<sub>2</sub>; or
- 10 R1 and R2 together with the phenyl, pyridine, 1-H-pyrrole, thiophene or furan ring are fused, partially saturated or unsaturated, bicyclic (C6-C10)-aryl, (C5-C11)-heteroaryl;
- R3 is H, (C1-C6)-alkyl, (C3-C8)-cycloalkyl, (C1-C3)-alkyl-(C3-C8)-cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl, (C5-C6)-heteroaryl, (C1-C3)-alkyl-(C5-C6)-heteroaryl or (C1-C3)-alkyl which is fully or partially substituted by F;
- 15
- W is CH, N, if o = 1;
- 20 W is O, S, NR<sub>9</sub>, if o = 0;
- X is (C1-C6)-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;
- 25
- Y is CO, SO, SO<sub>2</sub>;
- n is 0 – 2;
- 30 R4 is H, F, (C1-C6)-alkyl;
- R5 is H, F, (C1-C6)-alkyl;

R6 is H, F, (C1-C6)-alkyl;

R5 and R6 together with the carbon atoms that carry them are (C3-C8)-cycloalkane-1,2-diyl;

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R7 is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, (C3-C8)-cycloalkyl, (C6-C10)-aryl, (C5-C11)-heteroaryl, O-(C3-C8)-cycloalkyl, O-phenyl, NR<sub>10</sub>R<sub>11</sub> which may be substituted by O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, O-(C3-C8)-cycloalkyl, O-phenyl, O-(C5-C11)-heteroaryl, and where (C3-C8)-cycloalkyl, phenyl, (C5-C11)-heteroaryl may additionally be substituted by (C1-C6)-alkyl, unsubstituted or fully or partially substituted by F, O-(C1-C6)-alkyl, unsubstituted or fully or partially substituted by F, Cl, Br, I, OH, NR<sub>10</sub>R<sub>11</sub>, CO-(C1-C6)-alkyl, CO-(C6-C10)-aryl, CO-(C5-C11)-heteroaryl, C(O)-O-(C1-C6)-alkyl, C(O)-O-(C6-C10)-aryl, C(O)-O-(C5-C11)-heteroaryl, SO<sub>2</sub>-(C1-C6)-alkyl, SO<sub>2</sub>-(C6-C10)-aryl, SO<sub>2</sub>-(C5-C11)-heteroaryl, it being possible for alkyl, aryl and heteroaryl to be further substituted by (C1-C6)-alkyl or phenyl;

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R6 and R7 together with the carbon atom that carries them are (C3-C8)-cycloalkane-1,1-diyl;

R8 is H, (C1-C6)-alkyl;

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R9 is H, (C1-C6)-alkyl which is unsubstituted or substituted by phenyl, phenyl;

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R10 is H, (C1-C6)-alkyl, phenyl, CO-(C1-C6)-alkyl, CO-(C6-C10)-aryl, CO-(C1-C6)-alkyl-(C6-C10)-aryl, CO-(C5-C11)-heteroaryl, C(O)-O-(C1-C6)-alkyl, C(O)-O-(C1-C6)-alkyl-(C6-C10)-aryl, C(O)-O-(C6-C10)-aryl, C(O)-O-(C5-C11)-heteroaryl, SO<sub>2</sub>-(C1-C6)-alkyl, SO<sub>2</sub>-(C1-C6)-alkyl-

(C6-C10)-aryl, SO<sub>2</sub>-(C1-C6)-alkyl-SO<sub>2</sub>-(C1-C6)-alkyl, SO<sub>2</sub>-(C6-C10)-aryl, SO<sub>2</sub>-(C5-C11)-heteroaryl, it being possible for alkyl, aryl and heteroaryl to be further substituted by (C1-C6)-alkyl or phenyl.

5 R11 is H, (C1-C6)-alkyl which is unsubstituted or substituted by phenyl, phenyl;

R12 is H, benzyl;

10 and their physiologically acceptable salts, solvates and physiologically functional derivatives.

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

15

Ring A is (C<sub>3</sub>-C<sub>8</sub>)-cycloalkanediyl or (C<sub>3</sub>-C<sub>8</sub>)-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one carbon atom may be replaced by an oxygen atom;

20 X

is (C1-C6)-alkanediyl, where in the alkanediyl group the C1 or C2 carbon atom (with respect to Ring A) may be replaced by an oxygen atom;

25 and their physiologically acceptable salts, solvates and physiologically functional derivatives.

Particular preference is given to compounds of the formula I in which one or more radicals are as defined below:

30 Ring A is cyclohexane-1,3-diyl; or

R1 is (C1-C6)-alkyl, O-(C1-C6)-alkyl; or

those in which the substituent

R1 is located in the meta-position; or

R2 is H; or

R3 is (C1-C6)-alkyl; or

W is CH, if o = 1; or

X is CH<sub>2</sub>-O-CH<sub>2</sub>; or

n is 1; or

R4 is H, F; or

R5 is H, F; or

R6 is H, F; or

R5 and R6 together with the carbon atom that carries them are (C3-C8)-cycloalkane-1,2-diyl; or

R7 is H, F, (C1-C6)-alkyl, phenyl, NHCbz; or

R8 is H; or

R12 is H, benzyl.

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

in which

R1 is 3-(C1-C4)-alkyl, 3-O-(C1-C4)-alkyl;

R2 is H;

R3 is (C1-C4)-alkyl;

5

W is CH, if o = 1;

X is CH<sub>2</sub>-O-CH<sub>2</sub>;

10

n is 1;

R4 is H, F;

R5 is H, F;

15

R6 is H, F;

R5 and R6 together with the carbon atom that carries them are (C3-C8)-  
cycloalkane-1,2-diyl; or

20

R7 is H, F, (C1-C6)-alkyl, phenyl, NH-C(O)-O-CH<sub>2</sub>Ph;

R8 is H; and

25

R12 is H, benzyl.

The alkyl, alkenyl, alkynyl radicals in the substituents R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 may be either straight-chain or branched.

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Aryl means an aromatic carbocyclic mono- or bicyclic ring system which comprises 6 to 10 atoms in the ring or rings.

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

- 5 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 exist in the form of their racemates, racemic mixtures, pure enantiomers, diastereomers and mixtures of diastereomers. The present invention encompasses all these isomeric forms of the compounds of the formula I. These  
10 isomeric forms can be obtained by known methods even if not specifically 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  
15 applications. 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,  
20 ethanesulfonic, fumaric, gluconic, glycolic, 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), and salts of trometamol (2-amino-2-hydroxymethyl-  
25 1,3-propanediol), diethanolamine, lysine or ethylenediamine.

- Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful  
30 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.

- 5 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.
- 10 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.
- 15 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

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

- 25 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).

- 30 Two variants of PPARgamma exist, PPARgamma<sub>1</sub> and gamma<sub>2</sub>, which are the result of alternative use of promoters and differential mRNA splicing (Vidal-Puig et al. J. Clin. Invest., 97:2553-2561, 1996). Different PPARs have different tissue distribution and modulate different physiological functions. The PPARs 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, PPARs 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 PPARs can be modulated by various fatty acids, fatty acid derivatives and synthetic  
10 compounds to varying extents. For relevant reviews about functions, physiological effect and pathophysiology, see: Joel Berger et al., Annu. Rev. Med. 2002, 53, 409 – 435; Timothy Wilson et al. J. Med. Chem., 2000, Vol. 43, No. 4, 527-550; Steven Kliewer et al., Recent Prog Horm Res. 2001; 56: 239-63.

The present invention relates to compounds of the formula I suitable for  
15 modulating the activity of PPARs, 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 –  
20 435; Timothy Wilson et al. J. Med. Chem., 2000, Vol. 43, No. 4, 527-550; Steven Kliewer et al., Recent Prog Horm Res. 2001; 56: 239-63; Jean-Charles Fruchart, Bart Staels and Patrick Duriez: PPARs, Metabolic Disease and Arteriosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52; 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease,  
25 NATURE, VOL 405, 25 MAY 2000; 421-4; Ines Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

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

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 sequelae associated therewith.

Particular aspects in this connection are

- hyperglycemia,
  - 5 - improvement in insulin resistance,
  - improvement in glucose tolerance,
  - protection of the pancreatic  $\beta$  cells
  - prevention of macro- and microvascular disorders
- 10 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:
- high plasma triglyceride concentrations, high postprandial plasma
  - 15 triglyceride concentrations,
  - low HDL cholesterol concentrations
  - low ApoA lipoprotein concentrations
  - high LDL cholesterol concentrations
  - small dense LDL cholesterol particles
  - 20 - high ApoB lipoprotein concentrations
4. Various other conditions which may be associated with the metabolic syndrome, such as:
- obesity (excess weight), including central obesity
  - 25 - thromboses, hypercoagulable and prothrombotic states (arterial and venous)
  - high blood pressure
  - heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy
- 30 5. Other disorders or conditions in which inflammatory reactions or cell differentiation may for example be involved are:
- atherosclerosis such as, for example (but not restricted thereto), coronary

- sclerosis including angina pectoris or myocardial infarction, stroke
- vascular restenosis or reocclusion
- chronic inflammatory bowel diseases such as, for example, Crohn's disease and ulcerative colitis
- 5     - pancreatitis
- other inflammatory states
- retinopathy
- adipose cell tumors
- lipomatous carcinomas such as, for example, liposarcomas
- 10    - 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
- 15    - angiogenesis
- neurodegenerative disorders
- Alzheimer's disease
- multiple sclerosis
- Parkinson's disease
- 20    - erythematous-squamous dermatoses such as, for example, psoriasis
- acne vulgaris
- other skin disorders and dermatological conditions which are modulated by PPAR
- eczemas and neurodermitis
- 25    - 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
- 30    - human papilloma viral (HPV) infections such as, for example, venereal papillomata, viral warts such as, for example, molluscum contagiosum, leukoplakia
- papular dermatoses such as, for example, Lichen planus

- skin cancer such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas
- localized benign epidermal tumors such as, for example, keratoderma, epidermal naevi
- 5      - chilblains
- high blood pressure
- syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- 10      - osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis
- vasculitis
- wasting (cachexia)
- 15      - gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS)

### Formulations

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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

25      100 mg (typically from 0.01 mg to 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

30      ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampules 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  
5 in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other  
10 compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

15 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  
20 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  
25 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  
30 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  
5 molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced  
10 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  
15 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  
20 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  
25 resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

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

Pharmaceutical compositions suitable for topical use on the skin are preferably in the form of ointment, 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%.

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 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).

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.

### **Combinations with other medicaments**

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances which have, for example, favorable effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

1. medicaments which lower blood glucose, antidiabetics,
2. active ingredients for the treatment of dyslipidemias,
3. antiatherosclerotic medicaments,
4. antiobesity agents,
5. antiinflammatory active ingredients
6. active ingredients for the treatment of malignant tumors

7. antithrombotic active ingredients
  8. active ingredients for the treatment of high blood pressure
  9. active ingredients for the treatment of heart failure and
  10. active ingredients for the treatment and/or prevention of complications
- 5       caused by diabetes or associated with diabetes.

They can be combined with the compounds of the invention of the formula I in particular for a synergistic improvement in the effect. Administration of the active ingredient combination can take place either by separate administration of the

10       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:

#### 15    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 2001. Antidiabetics include all insulins and insulin

20       derivatives such as, for example, Lantus® (see [www.lantus.com](http://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,

25       sulfonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, 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

30       of glucose uptake, compounds which alter lipid metabolism and lead to a change in the blood lipid composition, compounds which reduce food intake, 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 administered 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)

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

15 In one embodiment, the compounds of the formula I are administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

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

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

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

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

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

5 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.

10 In one embodiment, the compounds of the formula I are administered in combination with an  $\alpha$ -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  
15 combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

#### Lipid modulators

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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.

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

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

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

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

10 In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax<sup>®</sup> (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 &  
15 Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main)). Combination with Caromax<sup>®</sup> is possible in one preparation or by separate administration of compounds of the formula I and Caromax<sup>®</sup>. Caromax<sup>®</sup> can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

20

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  
25 example, AZ 242 (Tesaglitazar, (S)-3-(4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl)-2-ethoxypropionic acid), BMS 298585 (N-[(4-methoxyphenoxy)carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine) or as described in WO 99/62872, WO 99/62871, WO 01/40171, WO 01/40169, WO96/38428, WO 01/81327, WO  
30 01/21602, WO 03/020269, WO 00/64888 or WO 00/64876.

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

gemfibrozil, clofibrate, bezafibrate.

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

5

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).

10

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

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

15

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

20

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

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

25

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.

30

#### Antiobesity agents

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

administered in combination with a lipase inhibitor such as, for example, orlistat.

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

5

In another embodiment, the further active ingredient is sibutramine.

In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.: Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists, e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}amide hydrochloride (CGP 71683A)), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-amide; (WO 01/91752)), orexin antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A)), H3 agonists (3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (e.g. 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 tertiary butyl ester (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), uncoupling protein 2 or 3 modulators,

leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. *Drugs of the Future* (2001), 26(9), 873-881), DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR modulators or TR- $\beta$  agonists.

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

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

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

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

20

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

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

30 The activity of the compounds was tested as follows:

Determination of EC<sub>50</sub> values of PPAR agonists in the cellular PPAR $\alpha$  assay

Principle

The potency of substances which bind to human PPAR $\alpha$  and activate 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 (p $\delta$ M-GAL4-Luc-Zeo) and a PPARalpha fusion protein (GR-GAL4-humanPPAR $\alpha$ -LBD) which mediates expression of the luciferase reporter element depending on a PPARalpha ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARalpha-LBD binds in the cell nucleus of the PPARalpha reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is integrated in the genome of the cell line. There is only little expression of the luciferase reporter gene without addition of a PPARalpha ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the assay. PPAR $\alpha$  ligands bind and activate the PPAR $\alpha$  fusion protein and thereby bring about expression of the luciferase reporter gene. The luciferase which is formed can be detected by means of chemiluminescence via an appropriate substrate.

#### Construction of the cell line

The PPARalpha reporter cell line was prepared in 2 stages. 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 (each 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* gene (Genbank Accession # M15077) was cloned in 3'-downstream of the GAL4-MMTV element. After sequencing, the luciferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene was recloned into a plasmid which confers zeocin resistance in

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

In a second step, the PPARα fusion protein (GR-GAL4-humanPPARα-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 PPARα 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-humanPPARα-LBD) was recloned into the plasmid pcDNA3 (from Invitrogen) in order to enable constitutive expression therein by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase reporter element. The finished PPARα reporter cell line which contains a luciferase reporter element and constitutively expresses the PPARα fusion protein (GR-GAL4-human PPARα-LBD) was isolated by selection with zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

#### Assay procedure

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

##### Day 1

The PPARα reporter cell line is cultivated to 80% confluence in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% cs-FCS (fetal calf serum; #SH-30068.03, Hyclone), 0.5 mg/ml zeocin (#R250-01, Invitrogen), 0.5 mg/ml G418 (#10131-027, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). The cultivation takes place in standard cell culture bottles (# 353112, Becton

Dickinson) in a cell culture incubator at 37°C in the presence of 5% CO<sub>2</sub>. 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 described and counted in a cell counter. After  
5 dilution to 500.000 cells/ml, 35,000 cells are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in the cell culture incubator at 37°C and 5% CO<sub>2</sub> for 24 h.

#### Day 2

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

15 Test substances are tested in 11 different concentrations in the range from 10  $\mu$ M to 100 pM. More potent compounds are tested in concentration ranges from 1  $\mu$ M to 10 pM or between 100 nM and 1 pM.

The medium of the PPAR $\alpha$  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  $\mu$ l per well of a 96 well microtiter plate. The DMSO concentration in the assay is less than 0.1 % v/v in order to avoid cytotoxic effects of the solvent.

Each plate was charged with a standard PPAR $\alpha$  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% CO<sub>2</sub> for 24 h.

#### Day 3

30 The PPAR $\alpha$  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  $\mu$ l of Bright Glo reagent (from Promega) into each well of a 96 well microtiter plate. After incubation at room temperature in the dark for 10 minutes, the microtiter plates are measured in the luminometer (Trilux from Wallac). The measuring time for each

well of a microtiter plate is 1 sec.

## Evaluation

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

- 10 The PPARAlpha EC50 values for the compounds of Examples 1 to 18 in this assay are in the range from 0.6nM to >10  $\mu$ M.

- 15 The compounds of the invention of the formula I activate the PPARAlpha receptor and thus bring about for example in analogy to fibrates in clinical use a lowering of triglycerides in the body (see, for example, J.-Ch. Fruchard et al.: PPARS, Metabolic Disease and Atherosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52, 2001; S. Kersten et al.: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000, 421-4; I. Pineda et al.: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

20

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

- 25 Principle

- 30 A transient transfection system is employed to determine the cellular PPARgamma activity of PPAR agonists. It is based on the use of a luciferase reporter plasmid (pGL3basic-5xGAL4-TK) and of a PPARgamma expression plasmid (pcDNA3-GAL4-humanPPARgammaLBD). Both plasmids are transiently transfected into human embryonic kidney cells (HEK cells). There is then expression in these cells of the fusion protein GAL4-humanPPARgammaLBD which binds to the GAL4 binding sites of the reporter plasmid. In the presence of a PPARgamma-active

ligand, the activated fusion protein GAL4-humanPPARgammaLBD induces expression of the luciferase reporter gene, which can be detected in the form of a chemiluminescence signal after addition of a luciferase substrate. As a difference from the stably transfected PPARalpha reporter cell line, in the cellular PPAR $\gamma$  assay the two components (luciferase reporter plasmid and PPARgamma expression plasmid) are transiently transfected into HEK cells because stable and permanent expression of the PPARgamma fusion protein is cytotoxic.

#### Construction of the plasmids

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

The PPARgamma expression plasmid pcDNA3-GAL4-humanPPAR $\gamma$ LBD 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 PPAR $\gamma$  receptor (amino acids I152-Y475; Accession # g1480099) 3'-downstream of the GAL4 DNA binding domain. Cloning and sequencing of the PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD again took place in analogy to the description in Sambrook J. *et. al.* (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Besides the luciferase reporter plasmid pGL3basic-5xGAL4-TK and the PPAR $\gamma$  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.

5

## Assay procedure

The activity of PPARgamma agonists is determined in a 4-day assay which is described below. Before the transfection, HEK cells are cultivated in DMEM  
10 (# 41965-039, Invitrogen) which is mixed with the following additions: 10% FCS (#16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen).

## Day 1

15 Firstly, solution A, a transfection mixture which contains all four plasmids previously described in addition to DMEM, is prepared. The following amounts are used to make up 3 ml of solution A for each 96 well microtiter plate for an assay: 2622 µl of antibiotic- and serum-free DMEM (# 41965-039, Invitrogen), 100 µl of reference plasmid pRL-CMV (1 ng/µl), 100 µl of luciferase reporter plasmid  
20 pGL3basic-5xGAL4-TK (10 ng/µl), 100 µl of PPAR $\gamma$  expression plasmid pcDNA3-GAL4-humanPPAR $\gamma$ LBD (100 ng/µl) and 78 µl of plasmid pBluescript SK(+) (500 ng/µl). Then 2 ml of solution B are prepared by mixing 1.9 ml of DMEM (# 41965-039, Invitrogen) with 100 µl of PolyFect transfection reagent (from Qiagen) for each 96 well microtiter plate. Subsequently, 3 ml of solution A are mixed with 2 ml  
25 of solution B to give 5 ml of solution C, which is thoroughly mixed by multiple pipetting and incubated at room temperature for 10 min.

80%-confluent HEK cells from a cell culture bottle with a capacity of 175 cm<sup>2</sup> 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  
30 taken up in 15 ml of DMEM (# 41965-039, Invitrogen) which is mixed with 10% FCS (# 16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). After the cell suspension has been counted in a cell counter, the suspension is diluted to

250,000 cells/ml. 15 ml of this cell suspension are mixed with 5 ml of solution C for one microtiter plate. 200  $\mu$ 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% CO<sub>2</sub> for 24 h.

5

#### Day 2

PPAR agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (# 41965-039, Invitrogen) which is mixed with 2% Ultroser (#12039-012, Biosepra), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). Test substances are tested in a total of 11 different concentrations in the range from 10  $\mu$ M to 100 pM. More potent compounds are tested in concentration ranges from 1  $\mu$ 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  $\mu$ l per well of a 96 well microtiter plate. Each plate is charged with a standard PPAR $\gamma$  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% CO<sub>2</sub>.

#### Day 4

After removal of the medium by aspiration, 50  $\mu$ l 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 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  $\mu$ l of the Dual-Glo™ Stop & Glo reagent (Dual-Glo™ Luciferase Assay System; Promega) is added to each well in order to stop the activity of the firefly luciferase and provide the substrate for the Renilla luciferase expressed by the reference plasmid pRL-CMV. After incubation at room temperature in the dark for a further 10 minutes, a chemiluminescence

mediated by the Renilla luciferase is again measured for 1 sec/well in the measuring instrument.

#### Evaluation

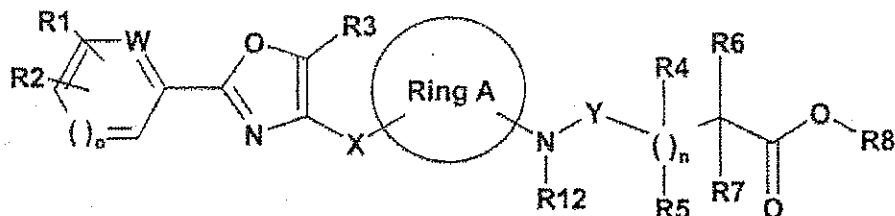
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The crude data from the luminometer are transferred into a Microsoft Excel file. The firefly/Renilla luciferase activity ratio is determined for each measurement derived from one well of the microtiter plate. The dose-effect plots and EC50 values of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

10

PPARgamma EC50 values in the range from 1nM to >10  $\mu$ M were measured for the PPAR agonists described in this application.

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



hereinbelow:

Ring A = cis-cyclohexane-1,3-diyl; W = CH; o=1; R2 = H; R3 = Methyl; X = CH<sub>2</sub>-O-

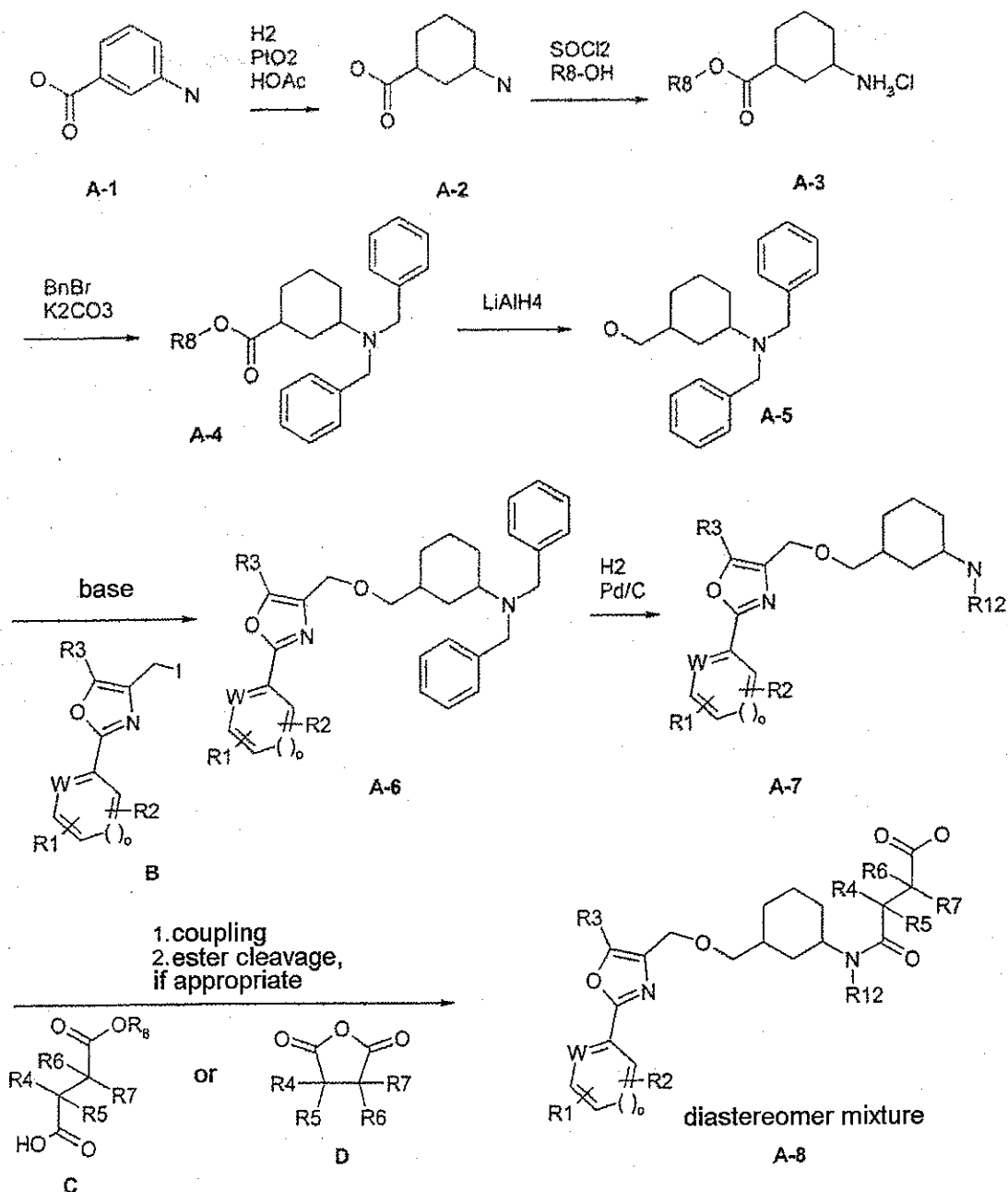
5 Ch<sub>2</sub>; Y=CO; n=1; R8 = H.

Cbz = benzyloxycarbonyl

| Ex. | R1                 | R12                 | R4 | R5                    | R6              | R7              |
|-----|--------------------|---------------------|----|-----------------------|-----------------|-----------------|
| 1   | 3-CH <sub>3</sub>  | H                   | H  | cyclobutane-1,2-diyl  |                 | H               |
| 2   | 3-CH <sub>3</sub>  | H                   | H  | H                     | CH <sub>3</sub> | CH <sub>3</sub> |
| 3   | 3-CH <sub>3</sub>  | H                   | H  | H                     | H               | Ph              |
| 4   | 3-CH <sub>3</sub>  | H                   | H  | cyclohexane-1,2-diyl  |                 | H               |
| 5   | 3-CH <sub>3</sub>  | H                   | F  | F                     | F               | F               |
| 6   | 3-CH <sub>3</sub>  | H                   | H  | H                     | H               | NHCbz           |
| 7   | 3-CH <sub>3</sub>  | H                   | H  | cyclopropane-1,2-diyl |                 | H               |
| 8   | 3-CH <sub>3</sub>  | H                   | H  | cyclopentane-1,2-diyl |                 | H               |
| 9   | 3-CH <sub>3</sub>  | CH <sub>2</sub> -Ph | H  | cyclobutane-1,2-diyl  |                 | H               |
| 10  | 3-OCH <sub>3</sub> | H                   | H  | H                     | CH <sub>3</sub> | CH <sub>3</sub> |
| 11  | 3-OCH <sub>3</sub> | H                   | H  | H                     | H               | Ph              |
| 12  | 3-OCH <sub>3</sub> | H                   | H  | cyclohexane-1,2-diyl  |                 | H               |
| 13  | 3-OCH <sub>3</sub> | H                   | F  | F                     | F               | F               |
| 14  | 3-OCH <sub>3</sub> | H                   | H  | H                     | H               | NHCbz           |
| 15  | 3-OCH <sub>3</sub> | H                   | H  | cyclopropane-1,2-diyl |                 | H               |
| 16  | 3-OCH <sub>3</sub> | H                   | H  | cyclopentane-1,2-diyl |                 | H               |
| 17  | 3-OCH <sub>3</sub> | H                   | H  | cyclobutane-1,2-diyl  |                 | H               |
| 18  | 3-OCH <sub>3</sub> | H                   | H  | H                     | H               | H               |
|     |                    |                     |    |                       |                 |                 |

The compounds of the formula I according to the invention can be obtained according to the reaction schemes below:

### 5 Process A:



In an inert solvent (for example acetic acid), the compound A-1 (3-aminobenzoic acid) is, at elevated pressure and at temperatures between 10°C and 150°C, hydrogenated using hydrogen over a heterogeneous catalyst (for example

platinum dioxide), which gives the compound A-2. Using thionyl chloride in an alcohol R8-OH, where R8 is as defined above (except for R8 = H), this compound is converted into an ester, giving the compound A-3. Compound A-3 is then reacted with a benzyl halide (for example benzyl bromide) and a base (for example potassium carbonate or cesium carbonate) in an inert solvent (for example DMF, THF) to give the dibenzylamine A-4. Reduction of A-4 with a reducing agent (for example LiAlH<sub>4</sub>) in an ethereal solvent (for example diethyl ether or THF) gives the alcohol A-5.

In the presence of a base (for example sodium hydride or potassium tert-butoxide) and in an inert solvent (for example THF, MTBE or DMF), the compound A-5 is reacted with a compound B, prepared using literature procedures, to give the compound A-6 where R1, R2, W and R3 are as defined above. Using hydrogen over a heterogeneous catalyst (for example palladium hydroxide on carbon), the compound A-6 is hydrogenated to give the compound A-7 in which R1, R2, W, R3 and R12 are as defined above.

Compound A-7 is coupled with carboxylic acid derivatives C in which R4, R5, R6, R7 and R8 are as defined above. If dicarboxylic acid monoalkylesters C are used, the coupling is followed by an ester hydrolysis (using, for example, LiOH in THF/methanol/water for R8 = methyl or ethyl). This gives compound A-8 in which R1, R2, W, R3, R4, R5, R6 and R7 are as defined above. If dicarboxylic anhydrides D are used, compound A-8 in which R1, R2, W, R3, R4, R5, R6 and R7 are as defined above is obtained directly.

According to this process, it is possible to synthesize examples 1 to 18.

The abbreviations used denote:

|      |                        |
|------|------------------------|
| Ac   | acetyl                 |
| Bn   | benzyl                 |
| Bu   | butyl                  |
| iBu  | isobutyl               |
| tBu  | tert-butyl             |
| BuLi | <i>n</i> -butyllithium |
| Bz   | benzoyl                |

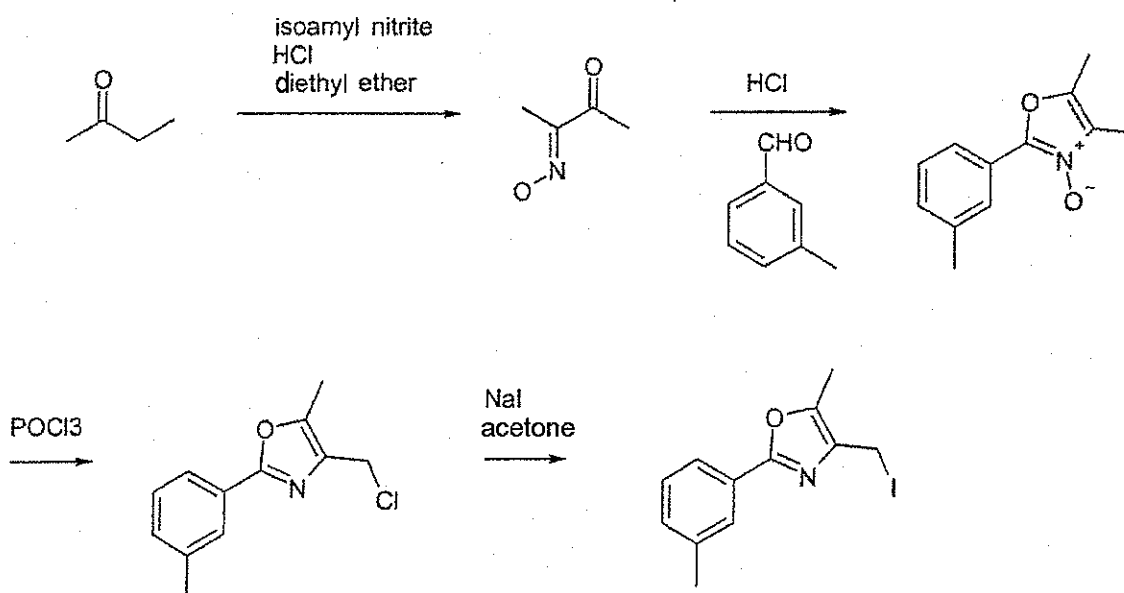
|                |                                                                                |
|----------------|--------------------------------------------------------------------------------|
| Cbz            | carboxybenzyl                                                                  |
| Cy             | cyclohexyl                                                                     |
| TLC            | thin-layer chromatography                                                      |
| 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                                                                          |
| sat.           | saturated                                                                      |
| h              | hour                                                                           |
| HATU           | O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium<br>hexafluorophosphate |
| HOBt           | 1-hydroxy-1H-benzotriazole x H <sub>2</sub> O                                  |
| HPLC           | high pressure, high performance liquid chromatography                          |
| LC-MS          | liquid chromatography-coupled 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 <sub>f</sub> | retention ratio (in TLC)                                                       |
| RT             | room temperature                                                               |

|      |                             |
|------|-----------------------------|
| Rt   | retention time (in HPLC)    |
| TBAF | tetrabutylammonium fluoride |
| TBAI | tetrabutylammonium iodide   |
| e.g. | for example                 |

It is possible to prepare other compounds by the processes mentioned above.

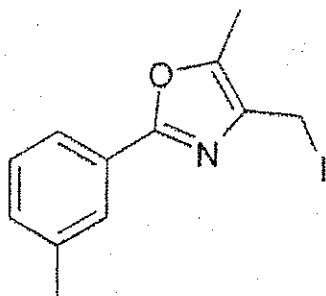
Building block synthesis of the compounds of the formula D:

5



Ethyl methyl ketone is reacted with isoamyl nitrite and HCl in diethyl ether, which gives diacetylmonoxime (G. Buechi, J. Galindo, J. Org. Chem. (1991) 56(8), 2605-2606). This is reacted with m-methylbenzaldehyde and HCl in acetic acid to give 4,5-dimethyl-2-m-tolylloxazole 3-oxide (P.M. Weintraub, J. Med. Chem. (1972) 15(4), 419-420). This compound is boiled with phosphoryl chloride in chloroform, which gives 4-chloromethyl-5-methyl-2-m-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 under reflux with sodium iodide in acetone, which gives 4-iodomethyl-5-methyl-2-m-tolylloxazole (A. Zlatkov, P. Peikov,

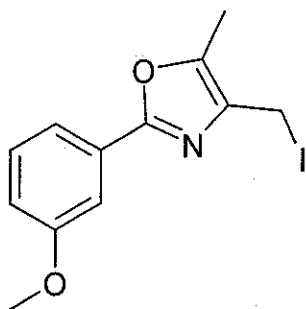
J. Rodriguez-Alvarez, N. Danchev, I. Nikolova, J. Mitkov, Eur. J. Med. Chem. Chim. Ther. (2000) 35(10), 941-948):



5

C<sub>12</sub>H<sub>12</sub>INO (313.14), MS(ESI): 314 (M+H<sup>+</sup>).

10 Analogously to the building block synthesis of 4-iodomethyl-5-phenyl-2-m-tolyl-oxazole, diacetylmonoxime and m-anisaldehyde gave 4-iodomethyl-2-(3-methoxyphenyl)-5-methyloxazole.

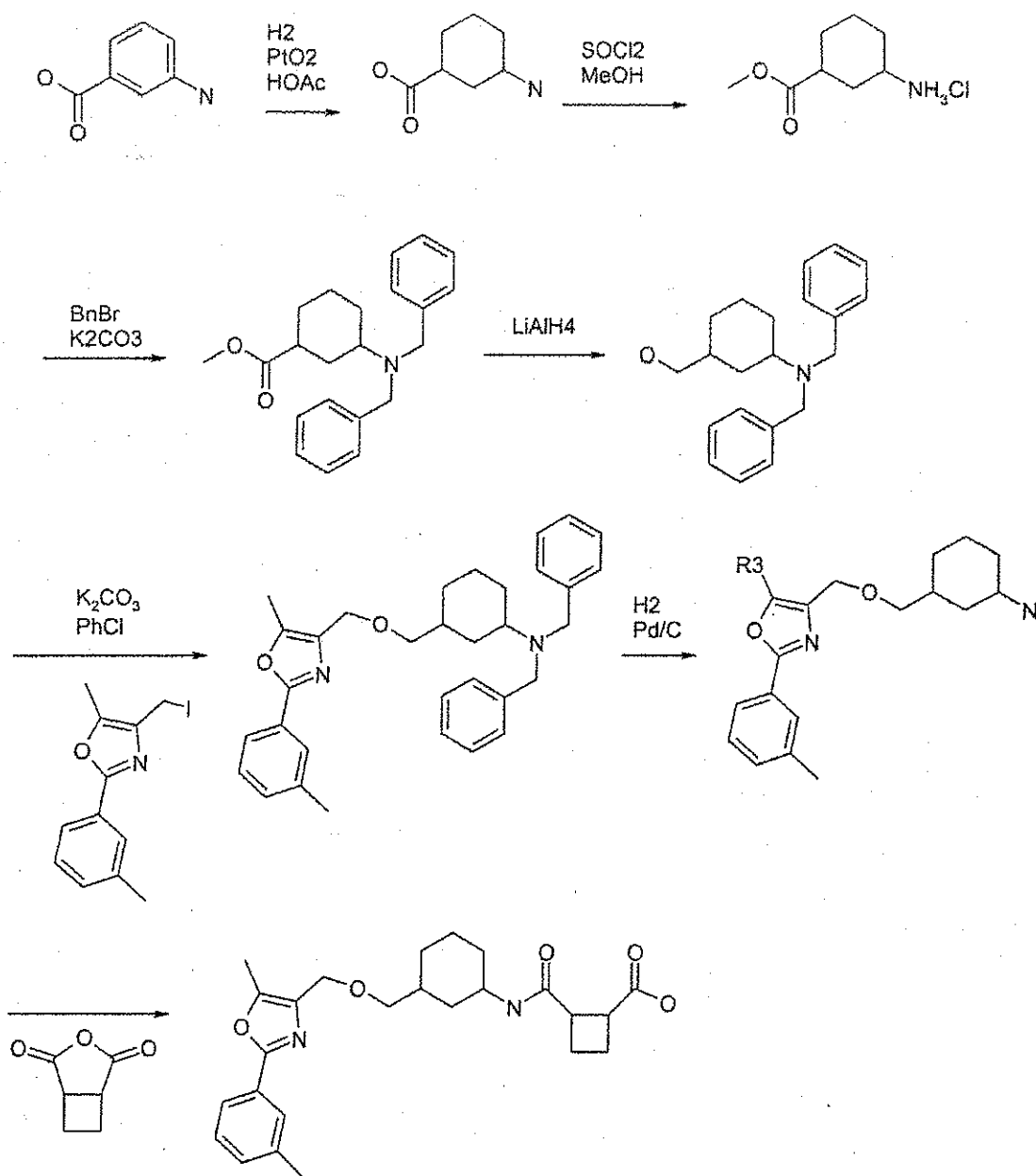


C<sub>12</sub>H<sub>12</sub>INO<sub>2</sub> (329.14), MS(ESI): 330 (M+H<sup>+</sup>).

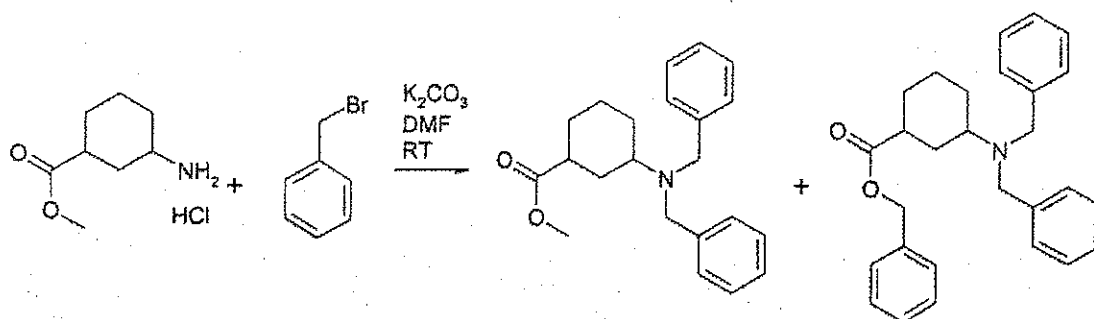
15

### Example 1

2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]cyclobutanecarboxylic acid



Methyl 3-dibenzylaminocyclohexanoate and benzyl 3-dibenzylaminocyclohexanoate



At room temperature, 28.7 g of benzyl bromide and then 37 g of potassium carbonate were added to a suspension of 9.37 g of methyl 3-aminocyclohexanecarboxylate hydrochloride in 78 ml of DMF. The mixture was stirred overnight.

LCMS control showed that the starting material had reacted completely, giving a 1:3.5 mixture of methyl 3-dibenzylaminocyclohexanoate and benzyl 3-dibenzylaminocyclohexanoate. About 150 ml each of water and MTBE were added to the reaction solution, the organic phase was separated off, the aqueous phase was extracted again with MTBE and the organic phases were combined. This organic phase was washed with about 100 ml of water and then with about 50 ml of

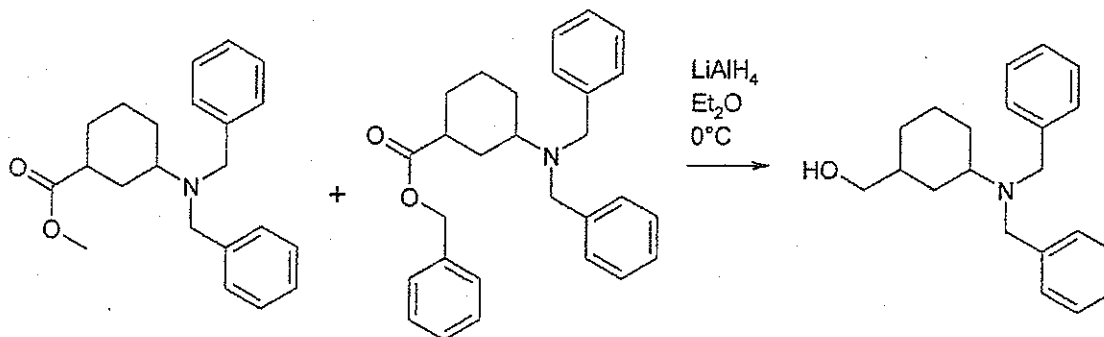
saturated NaCl solution, dried over  $\text{MgSO}_4$  and concentrated. The residue was dried under reduced pressure, giving 23 g of the mixture as an oil. LCMS:

Methyl 3-dibenzylaminocyclohexanoate:  $R_t = 1.243$  min;  $\text{C}_{22}\text{H}_{27}\text{NO}_2$  (337.47), LCMS (ESI): 338 ( $\text{MH}^+$ ).

Benzyl 3-dibenzylaminocyclohexanoate:  $R_t = 1.512$  min;  $\text{C}_{28}\text{H}_{31}\text{NO}_2$  (413.56),

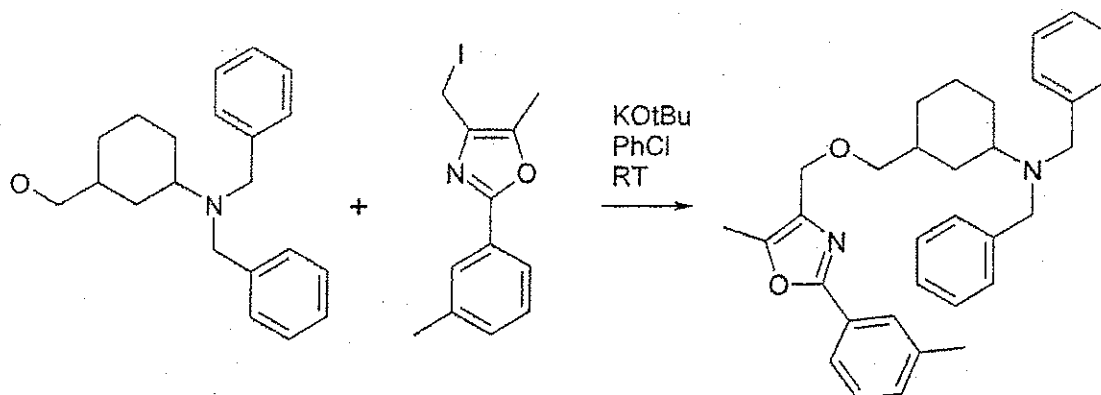
LCMS (ESI): 414 ( $\text{MH}^+$ ).

### 3-Dibenzylaminocyclohexylmethanol



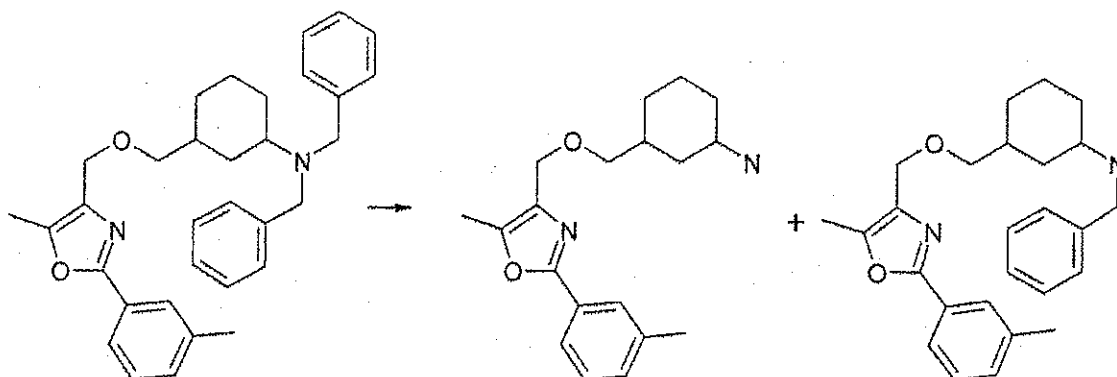
At  $0^\circ\text{C}$ , 23 g of a 1:3.5 mixture of methyl 3-dibenzylaminocyclohexanoate and benzyl 3-dibenzylaminocyclohexanoate were added dropwise to a suspension of 4.4 g of  $\text{LiAlH}_4$  in 250 ml of diethyl ether. The suspension was stirred at  $0^\circ\text{C}$  for 2 h and then quenched using 2 ml of EtOAc, and 10 ml of 10N KOH were added. 50 g of  $\text{MgSO}_4$  were then added and the suspension was filtered. The residue was digested with EtOAc for 2 h and filtered again. The filtrate was concentrated, giving the product as an oil.  $\text{C}_{21}\text{H}_{27}\text{NO}$  (309.46), LCMS (ESI): 310.2 ( $\text{MH}^+$ ).

Dibenzyl-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexyl]amine



5.0 g of 3-dibenzylaminocyclohexylmethanol and 1.72 g of KOtBu were initially charged in PhCl, and 7.59 g of 4-iodomethyl-5-methyl-2-p-tolylloxazole were added a little at a time. At room temperature and under an atmosphere of argon, the mixture was stirred for 2 days. Another 1.0 g of KOtBu was added, and stirring of the mixture was continued. The reaction was then complete. For work-up, water and MTBE were added, the phases were separated and the organic phase was washed with water and sat. NaCl solution, dried over MgSO<sub>4</sub> and concentrated. Chromatography of the residue on silica gel (heptane/ethyl acetate 10:1 → 3:1) gave 7.0 g of dibenzyl-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)-cyclohexyl]amine as a brown oil. C<sub>33</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub> (494.68), LCMS (ESI): 495.3 (MH<sup>+</sup>).

3-(5-Methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexylamine and benzyl-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexyl]amine



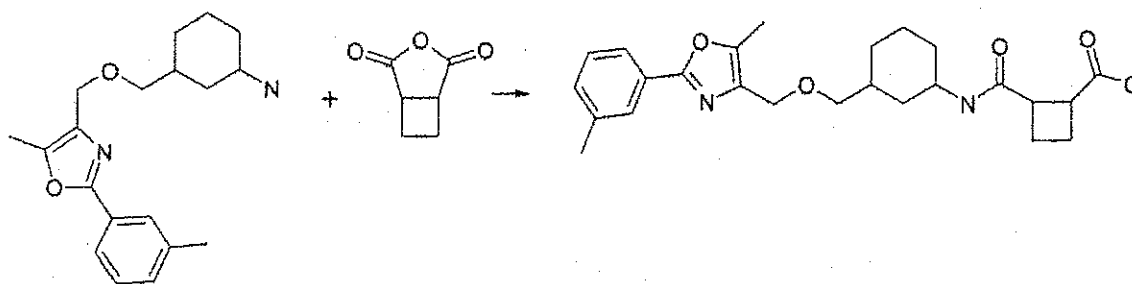
7.0 g of dibenzyl-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]amine were dissolved in 100 ml of MeOH, and palladium/carbon (10%) was added. The mixture was stirred at a hydrogen pressure of 5 bar and at room temperature overnight. For work-up, the catalyst was filtered off and the filtrate was

concentrated. This gave 5.8 g of a light-brown oil. This was separated by preparative HPLC, giving 2.0 g of 3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)-cyclohexylamine and 0.5 g of benzyl-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]amine as brown oils.

3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylamine: C<sub>19</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> (314.43), LCMS (ESI): 315 (MH<sup>+</sup>).

Benzyl-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]amine: C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> (404.56): LCMS (ESI): 405 (MH<sup>+</sup>).

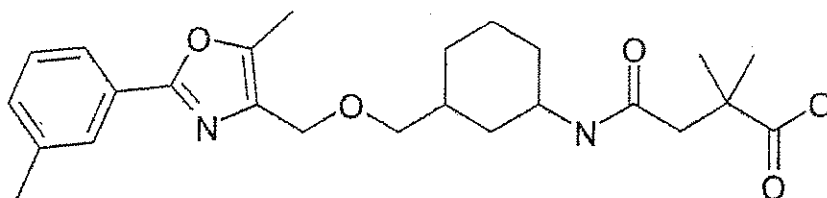
2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]cyclobutanecarboxylic acid



50 mg of 3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylamine were dissolved in 0.97 ml of DMF, and 32 mg of triethylamine were added. 22 mg of cis-cyclobutane-1,2-dicarboxylic anhydride were then added, and the solution was stirred at RT overnight. The solution was purified directly by HPLC, which gave 36 mg of 2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]-cyclobutanecarboxylic acid. C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub> (440.54), MS (ESI): 441 (MH<sup>+</sup>).

## Example 2:

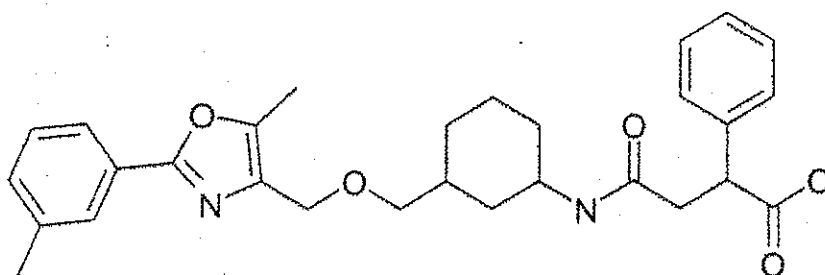
2,2-Dimethyl-N-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]succinamide



Analogously to the reaction conditions of example 1, 3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexylamine and 2,2-dimethylsuccinic anhydride give 2,2-dimethyl-N-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexyl]succinamide. C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub> (442.56), MS (ESI): 443 (MH<sup>+</sup>).

### Example 3:

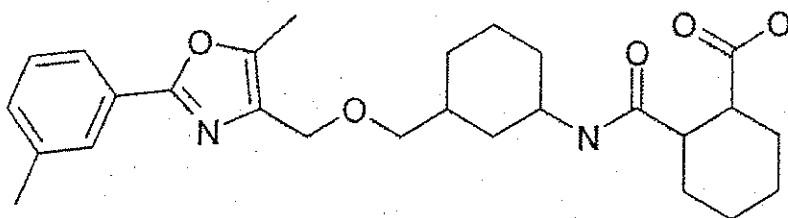
2-Phenyl-N-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexyl]succinamide



Analogously to the reaction conditions of example 1, 3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexylamine and 2-phenylsuccinic anhydride give 2-phenyl-N-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexyl]succinamide. C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub> (490.60), MS (ESI): 491 (MH<sup>+</sup>).

### Example 4:

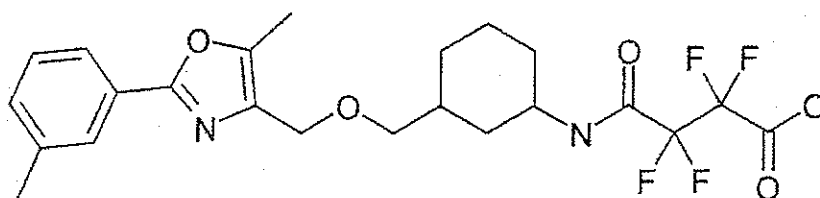
2-[3-(5-Methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]cyclohexanecarboxylic acid



Analogously to the reaction conditions of example 1, 3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylamine and cis-cyclohexane-1,2-dicarboxylic anhydride give 2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl-carbamoyl]cyclohexanecarboxylic acid. C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub> (468.60), MS (ESI): 469 (MH<sup>+</sup>).

#### Example 5:

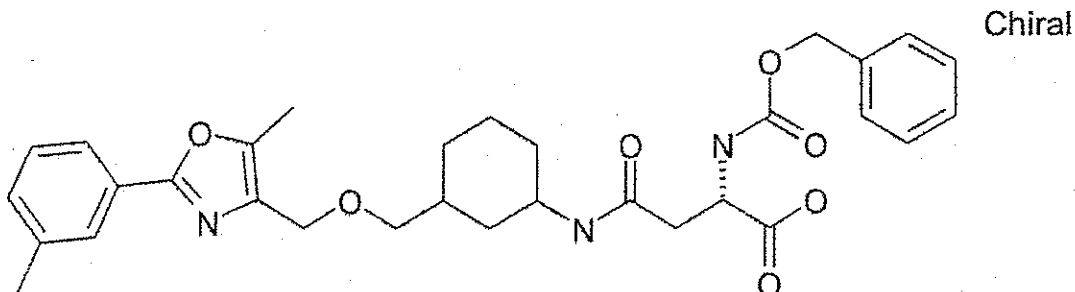
2,2,3,3-Tetrafluoro-N-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl-succinamide



Analogously to the reaction conditions of example 1, 3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylamine and 2,2,3,3-tetrafluorosuccinic anhydride give 2,2,3,3-tetrafluoro-N-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]-succinamide. C<sub>23</sub>H<sub>26</sub>F<sub>4</sub>N<sub>2</sub>O<sub>5</sub> (486.47), MS (ESI): 487 (MH<sup>+</sup>).

#### Example 6:

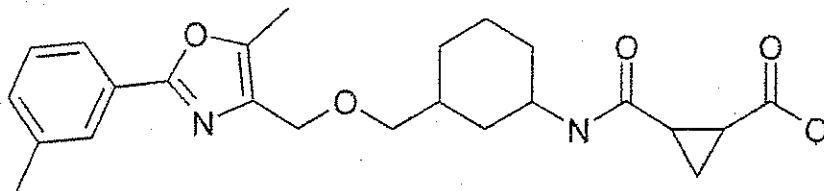
(S)-2-Benzyloxycarbonylamino-N-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]succinamide



Analogously to the reaction conditions of example 1, 3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylamine and (S)-2-benzyloxycarbonylaminosuccinic anhydride give (S)-2-benzyloxycarbonylamino-N-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]succinamide. C<sub>31</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub> (563.66), MS (ESI): 564 (MH<sup>+</sup>).

**Example 7:**

2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]cyclopropanecarboxylic acid

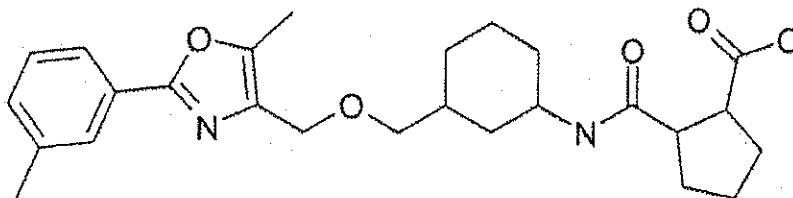


- 5 Analogously to the reaction conditions of example 1, 3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylamine and cis-cyclopropane-1,2-dicarboxylic anhydride give 2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]cyclopropanecarboxylic acid. C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub> (426.52), MS (ESI): 427 (MH<sup>+</sup>).

10

**Example 8:**

2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]cyclopentanecarboxylic acid

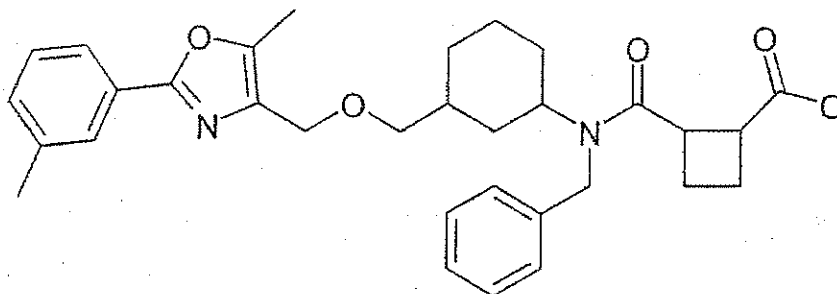


- 15 Analogously to the reaction conditions of example 1, 3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylamine and cis-cyclopentane-1,2-dicarboxylic anhydride give 2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexylcarbamoyl]cyclopentanecarboxylic acid. C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub> (454.57), MS (ESI): 455 (MH<sup>+</sup>).

20

**Example 9:**

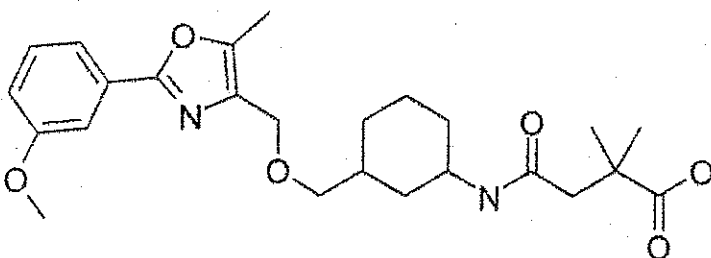
2-[Benzyl-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxymethyl)cyclohexyl]carbamoyl]cyclobutanecarboxylic acid



Analogously to the reaction conditions of example 1, benzyl-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexyl]amine and cis-cyclobutane-1,2-dicarboxylic anhydride give 2-{benzyl-[3-(5-methyl-2-m-tolylloxazol-4-ylmethoxymethyl)cyclohexyl]carbamoyl}cyclobutanecarboxylic acid. C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub> (530.67), MS (ESI): 531 (MH<sup>+</sup>).

**Example 10:**

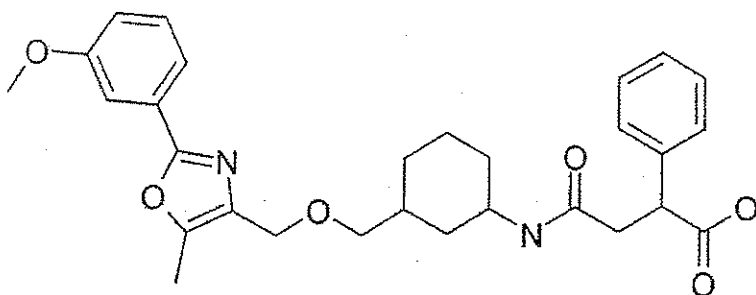
N-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}-2,2-dimethylsuccinamide



Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and 2,2-dimethylsuccinic anhydride give N-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}-2,2-dimethylsuccinamide. C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub> (458.56), MS (ESI): 459 (MH<sup>+</sup>).

**Example 11:**

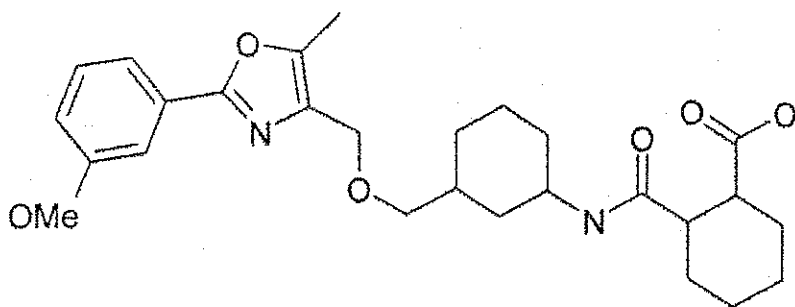
N-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}-2-phenylsuccinamide



Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and 2-phenylsuccinic anhydride give N-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}-2-phenylsuccinamide. C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub> (506.60), MS (ESI): 507 (MH<sup>+</sup>).

#### Example 12:

2-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylcarbamoyl}cyclohexanecarboxylic acid



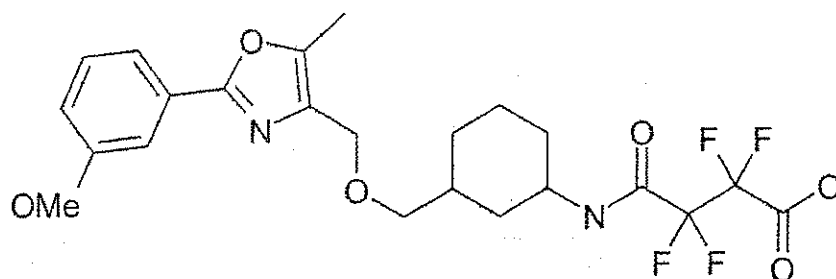
10

Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and cis-cyclohexan-1,2-dicarboxylic anhydride give 2-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylcarbamoyl}cyclohexanecarboxylic acid. C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub> (484.60), MS (ESI): 485 (MH<sup>+</sup>).

15

#### Example 13:

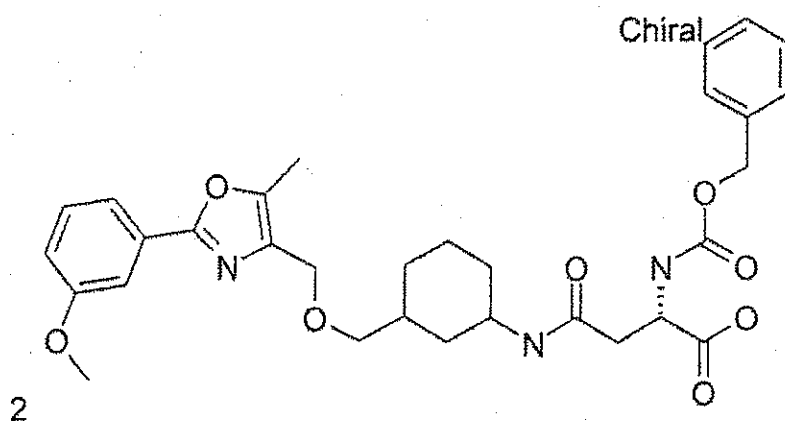
2,2,3,3-Tetrafluoro-N-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}succinamide



Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and cis-2,2,3,3-tetrafluorosuccinic anhydride give 2,2,3,3-tetrafluoro-N-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}succinamide. C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub> (484.60), MS (ESI): 485 (MH<sup>+</sup>).

#### Example 14:

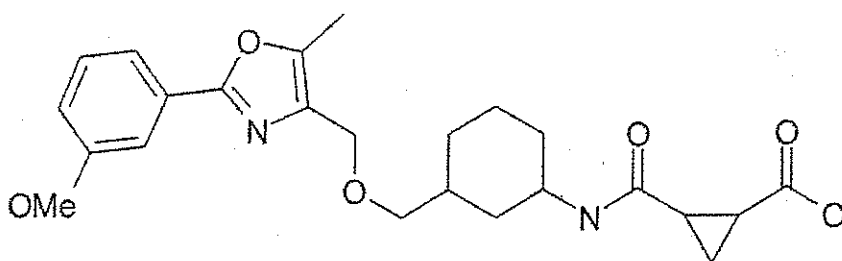
(S)-2-Benzyloxycarbonylamino-N-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}succinamide



Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and (S)-2-benzyloxycarbonylamino-succinic anhydride give (S)-2-benzyloxycarbonylamino-N-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}succinamide. C<sub>31</sub>H<sub>37</sub>N<sub>3</sub>O<sub>8</sub> (579.65), MS (ESI): 580 (MH<sup>+</sup>).

#### Example 15:

2-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl-carbamoyl}cyclopropanecarboxylic acid

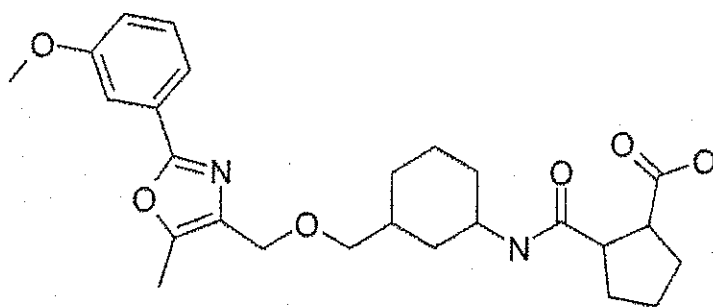


Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and cis-cyclopropane-1,2-

5 dicarboxylic anhydride give 2-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylcarbamoyl}cyclopropanecarboxylic acid. C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub> (442.52), MS (ESI): 443 (MH<sup>+</sup>).

#### Example 16:

2-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl-  
10 carbamoyl}cyclopentanecarboxylic acid

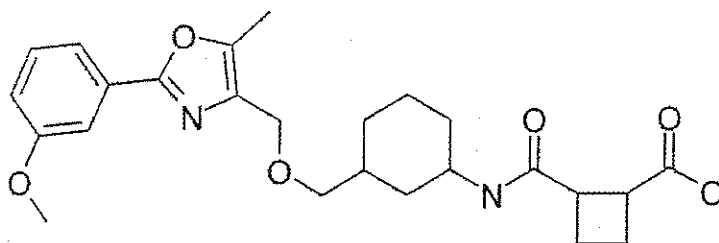


Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and cis-cyclopentane-1,2-

15 dicarboxylic anhydride give 2-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylcarbamoyl}cyclopentanecarboxylic acid. C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub> (470.57), MS (ESI): 471 (MH<sup>+</sup>).

#### Example 17:

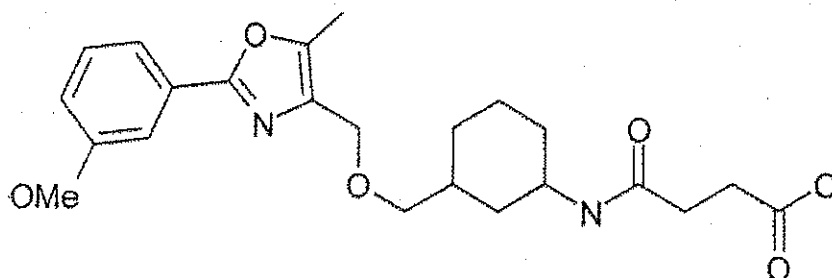
2-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl-  
20 carbamoyl}cyclobutanecarboxylic acid



Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and cis-cyclobutane-1,2-dicarboxylic anhydride give 2-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}cyclobutanecarboxylic acid. C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub> (456.54), MS (ESI): 457 (MH<sup>+</sup>).

#### Example 18:

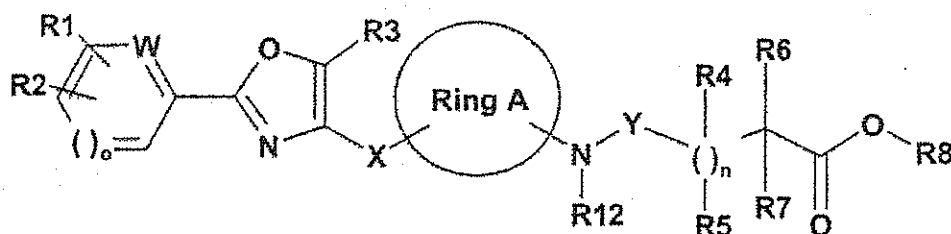
N-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}-succinamide



Analogously to the reaction conditions of example 1, 3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexylamine and succinic anhydride give N-{3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxymethyl]cyclohexyl}-succinamide. C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub> (430.51), MS (ESI): 431 (MH<sup>+</sup>).

We claim:

1. A compound of the formula I



I

in which:

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

R1, R2 independently of one another are H, F, Cl, Br, CF<sub>3</sub>, OCF<sub>3</sub>, (C1-C6)-alkyl, O-(C1-C6)-alkyl, SCF<sub>3</sub>, SF<sub>5</sub>, OCF<sub>2</sub>-CHF<sub>2</sub>, (C6-C10)-aryl, (C6-C10)-aryloxy, OH, NO<sub>2</sub>; or

R1 and R2 together with the phenyl, pyridine, 1-H-pyrrole, thiophene or furan ring are fused, partially saturated or unsaturated, bicyclic (C6-C10)-aryl, (C5-C11)-heteroaryl;

R3 is H, (C1-C6)-alkyl, (C3-C8)-cycloalkyl, (C1-C3)-alkyl-(C3-C8)-cycloalkyl, phenyl, (C1-C3)-alkyl-phenyl, (C5-C6)-heteroaryl, (C1-C3)-alkyl-(C5-C6)-heteroaryl or (C1-C3)-alkyl which is fully or partially substituted by F;

W is CH, N, if o = 1;

W is O, S, NR<sub>9</sub>, if o = 0;

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

Y is CO, SO, SO<sub>2</sub>;

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n is 0 – 2;

R4 is H, F, (C1-C6)-alkyl;

10 R5 is H, F, (C1-C6)-alkyl;

R6 is H, F, (C1-C6)-alkyl;

R5 and R6 together with the carbon atoms that carry them are (C3-C8)-  
cycloalkane-1,2-diyl;

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R7 is H, (C1-C6)-alkyl, (C2-C6)-alkenyl, (C2-C6)-alkynyl, O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, (C3-C8)-cycloalkyl, (C6-C10)-aryl, (C5-C11)-heteroaryl, O-(C3-C8)-cycloalkyl, O-phenyl, NR<sub>10</sub>R<sub>11</sub> which may be substituted by O-(C1-C6)-alkyl, O-(C2-C6)-alkenyl, O-(C2-C6)-alkynyl, O-(C3-C8)-cycloalkyl, O-phenyl, O-(C5-C11)-heteroaryl, and where (C3-C8)-cycloalkyl, phenyl, (C5-C11)-heteroaryl may additionally be substituted by (C1-C6)-alkyl, unsubstituted or fully or partially substituted by F, O-(C1-C6)-alkyl, unsubstituted or fully or partially substituted by F, Cl, Br, I, OH, NR<sub>10</sub>R<sub>11</sub>, CO-(C1-C6)-alkyl, CO-(C6-C10)-aryl, CO-(C5-C11)-heteroaryl, C(O)-O-(C1-C6)-alkyl, C(O)-O-(C6-C10)-aryl, C(O)-O-(C5-C11)-heteroaryl, SO<sub>2</sub>-(C1-C6)-alkyl, SO<sub>2</sub>-(C6-C10)-aryl, SO<sub>2</sub>-(C5-C11)-heteroaryl, it being possible for alkyl, aryl and heteroaryl to be further substituted by (C1-C6)-alkyl or phenyl;

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R6 and R7 together with the carbon atom that carries them are (C<sub>3</sub>-C<sub>8</sub>)-cycloalkane-1,1-diyl;

R8 is H, (C<sub>1</sub>-C<sub>6</sub>)-alkyl;

R9 is H, (C<sub>1</sub>-C<sub>6</sub>)-alkyl which is unsubstituted or substituted by phenyl, phenyl;

R10 is H, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, CO-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, CO-(C<sub>6</sub>-C<sub>10</sub>)-aryl, CO-(C<sub>1</sub>-C<sub>6</sub>)-alkyl-(C<sub>6</sub>-C<sub>10</sub>)-aryl, CO-(C<sub>5</sub>-C<sub>11</sub>)-heteroaryl, C(O)-O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, C(O)-O-(C<sub>1</sub>-C<sub>6</sub>)-alkyl-(C<sub>6</sub>-C<sub>10</sub>)-aryl, C(O)-O-(C<sub>6</sub>-C<sub>10</sub>)-aryl, C(O)-O-(C<sub>5</sub>-C<sub>11</sub>)-heteroaryl, SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>)-alkyl-(C<sub>6</sub>-C<sub>10</sub>)-aryl, SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>)-alkyl-SO<sub>2</sub>-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, SO<sub>2</sub>-(C<sub>6</sub>-C<sub>10</sub>)-aryl, SO<sub>2</sub>-(C<sub>5</sub>-C<sub>11</sub>)-heteroaryl, it being possible for alkyl, aryl and heteroaryl to be further substituted by (C<sub>1</sub>-C<sub>6</sub>)-alkyl or phenyl.

R11 is H, (C<sub>1</sub>-C<sub>6</sub>)-alkyl which is unsubstituted or substituted by phenyl, phenyl;

R12 is H, benzyl;

or a physiologically acceptable salt, solvate or physiologically functional derivative thereof.

2. A compound of the formula I as claimed in claim 1 where:

Ring A is (C<sub>3</sub>-C<sub>8</sub>)-cycloalkanediyl or (C<sub>3</sub>-C<sub>8</sub>)-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one carbon atom may be replaced by an oxygen atom;

X is (C1-C6)-alkanediyl, where in the alkanediyl group the C1 or C2 carbon atom (with respect to Ring A) may be replaced by an oxygen atom;

5 or a physiologically acceptable salt, solvate or physiologically functional derivative thereof.

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

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R1 is 3-(C1-C4)-alkyl, 3-O-(C1-C4)-alkyl;

R2 is H;

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R3 is (C1-C4)-alkyl;

W is CH, if o = 1;

X is CH<sub>2</sub>-O-CH<sub>2</sub>;

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n is 1;

R4 is H, F;

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R5 is H, F;

R6 is H, F;

R5 and R6 together with the carbon atom that carries them are (C3-C8)-  
30 cycloalkane-1,2-diyl; or

R7 is H, F, (C1-C6)-alkyl, phenyl, NH-C(O)-O-CH<sub>2</sub>Ph;

R8 is H; and

R12 is H, benzyl.

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4. A pharmaceutical, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 3.

5. A pharmaceutical, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 3 and one or more active compounds having favorable effects on metabolic disorders or diseases associated therewith.

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6. A pharmaceutical, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 3 and one or more antidiabetics.

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7. A pharmaceutical, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 3 and one or more lipid modulators.

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8. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of disorders of the fatty acid metabolism and glucose utilization disorders.

9. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of disorders where insulin resistance is involved.

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10. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of diabetes mellitus and its sequelae.

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11. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of dyslipidemias and their

sequelae.

12. The use of the compounds of the formula I as claimed in one or more of claims 1 to 3 for the treatment and/or prevention of states associated with metabolic syndrome.

13. The use of the compounds as claimed in one or more of claims 1 to 3 in combination with at least one further active compound for the treatment and/or prevention of disorders of the fatty acid metabolism and glucose utilization disorders.

14. The use of the compounds as claimed in one or more of claims 1 to 3 in combination with at least one further active compound for the treatment and/or prevention of disorders in which insulin resistance is involved.

15. A process for preparing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 3, which comprises mixing the active compound with a pharmaceutically acceptable carrier and bringing this mixture into a form suitable for administration.