Description

Cycloalkyl derivatives comprising bioisosteric carboxylic acid groups, method for the production thereof, and use thereof as a medicament

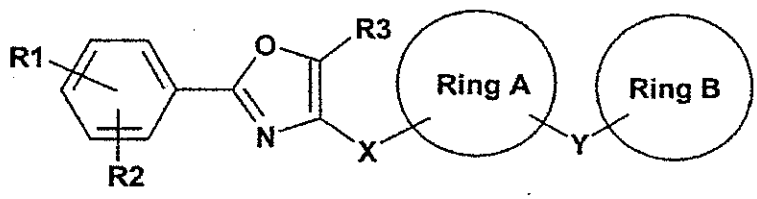
The invention relates to cycloalkyl derivatives having bioisosteric carboxylic acid groups and to their physiologically acceptable salts and physiologically functional derivatives.

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

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

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

Accordingly, the invention relates to compounds of the formula I



I

in which

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

R_1, R_2	independently of one another are H, F, Br, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, SCF_3, SF_5, OCF_2-CHF_2, O-phenyl, OH, or NO_2; or
R1 and R2	in juxtaposition together with the phenyl ring are a fused, unsaturated or completely or partially saturated bicyclic $(C_9$-$C_{12})$-aryl or $(C_9$-$C_{11})$-heteroaryl ring system;
R3	is H, CF_3, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, $(C_3$-$C_8)$-cycloalkyl or phenyl;
X	is $(C_1$-$C_6)$-alkanediyl, where one or more carbon atoms in the alkanediyl group may be replaced by oxygen atoms;
Y	is $(C_1$-$C_6)$-alkanediyl or $(C_1$-$C_6)$-alkenediyl, where one or more CH_2 groups in the alkanediyl or alkenediyl group may be replaced by O, CO, S, SO or SO_2 and alkanediyl or alkenediyl may be unsubstituted or substituted by OH;
Ring B	is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy or tetrazole; or pyrrolidin-2-one which additionally contains a nitrogen or sulfur atom in the ring and is substituted by oxo or thioxo and may be substituted on the nitrogen atom by R4;
R4	is $(C_1$-$C_6)$-alkyl, phenyl, benzyl;

and their physiologically acceptable salts.

Preference is given to compounds of the formula I in which

Ring A	is $(C_3$-$C_8)$-cycloalkanediyl or $(C_3$-$C_8)$-cycloalkenediyl, where in the cycloalkanediyl or cycloalkenediyl rings one carbon atom may be replaced by an oxygen atom;
R1, R2	independently of one another are H, F, Br, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, SCF_3, SF_5, OCF_2-CHF_2, O-phenyl, OH or NO_2; or

R1 and R2	in juxtaposition together with the phenyl ring are a fused, unsaturated or completely or partially saturated bicyclic (C_9-C_{12})-aryl or (C_9-C_{11})-heteroaryl ring system;
R3	is H, CF_3, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl or phenyl;
X	is (C_1-C_6)-alkanediyl, where one carbon atom in the alkanediyl group may be replaced by an oxygen atom;
Y	is (C_1-C_6)-alkanediyl or (C_1-C_6)-alkenediyl, where one or two CH_2 groups in the alkanediyl or alkenediyl group may be replaced by O, CO, S, SO or SO_2 and alkanediyl or alkenediyl may be unsubstituted or substituted by OH;
Ring B	is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or tetrazole; or pyrrolidin-2-one which additionally contains a nitrogen or sulfur atom in the 4-position and is substituted by oxo or thioxo in the 5-position and may be substituted on the N1-atom by R4;
R4	is (C_1-C_6)-alkyl, phenyl, benzyl;

and their physiologically acceptable salts.

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

Ring A	is (C_3-C_8)-cycloalkanediyl in which one carbon atom is replaced by an oxygen atom;
R1, R2	independently of one another are H, F, Br, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, SCF_3, SF_5, OCF_2-CHF_2, O-phenyl, OH or NO_2; or
R1 and R2	in juxtaposition together with the phenyl ring are a fused, unsaturated or completely or partially saturated bicyclic (C_9-C_{12})-aryl or (C_9-C_{11})-heteroaryl ring system;
R3	is H, CF_3, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl or phenyl;

X is (C_1-C_6)-alkanediyl, where the C1 carbon atom is replaced by an oxygen atom;

Y is (C_1-C_6)-alkanediyl or (C_1-C_6)-alkenediyl, where one or two CH_2 groups in the alkanediyl or alkenediyl group may be replaced by O, CO or SO_2 and alkanediyl or alkenediyl may be substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or tetrazole; or pyrrolidin-2-one which additionally contains a nitrogen or sulfur atom in the 4-position and is substituted by oxo or thioxo in the 5-position and may be substituted on the N1-atom by R4;

R4 is (C_1-C_6)-alkyl, phenyl, benzyl;

and their physiologically acceptable salts.

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

Ring A is cyclohexane-1,3-diyl;

R1, R2 are independently of one another H, F, Br, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, SCF_3, SF_5, OCF_2-CHF_2, O-phenyl, OH or NO_2; or

R1 and R2 in juxtaposition together with the phenyl ring are a fused, unsaturated bicyclic (C_9-C_{10})-aryl or (C_9-C_{10})-heteroaryl ring system;

R3 is H, CF_3, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl or phenyl;

X is CH_2-O;

Y is (C_1-C_4)-alkanediyl, O-(C_1-C_4)-alkenediyl, (C_1-C_4)-alkenediyl, O-(C_1-C_4)-alkenediyl, O-SO_2 or O-CO, where alkanediyl may be substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or tetrazole; or

thiazolidin-1,4-dione which may be substituted on the N3-atom by R4;

R4 is $(C_1$-$C_6)$-alkyl, phenyl or benzyl;

and their physiologically acceptable salts or

compounds of the formula I in which

Ring A is cyclohexane-1,3-diyl;

R1, R2 independently of one another are H, F, Br, CF_3, $(C_1$-$C_6)$-alkyl or O-$(C_1$-$C_6)$-alkyl; or

R1 and R2 together with the phenyl ring are naphthyl;

R3 is $(C_1$-$C_6)$-alkyl, $(C_5$-$C_6)$-cycloalkyl or phenyl;

X is CH_2-O;

Y is $(C_1$-$C_4)$-alkanediyl, O-$(C_1$-$C_4)$-alkanediyl, $(C_1$-$C_4)$-alkenediyl, O-$(C_1$-$C_4)$-alkenediyl, O-SO_2 or O-CO, where alkanediyl may be substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy or tetrazole; or

Ring B is thiazolidine-2,4-dione which may be substituted on the N3-atom by R4;

R4 is $(C_1$-$C_6)$-alkyl, phenyl or benzyl;

and their physiologically acceptable salts.

Very particular emphasis is also given to the compounds of the formula I in which one or more radicals have the following meanings:

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

R2	is hydrogen; or
R2	is hydrogen and R1 is attached in the meta- or para-position; or
X	is CH_2-O-; or
Y	is -CH_2-CH_2-; or to those compounds where
Ring B	is thiazolidine-2,4-dione.

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

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

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

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

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

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

magnesium and calcium salts) and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanol-amine, lysine or ethylenediamine.

Salts with a pharmaceutically unacceptable anion such as, for example, trifluoroacetate likewise belong within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

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

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

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

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

Use

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

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

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

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

In addition, PPAR receptors are also involved in the regulation of many further physiological processes, including those which are not directly connected with carbohydrate or lipid metabolism. The activity of the different PPAR receptors can be modulated to varying extents by various fatty acids, fatty acid derivatives and synthetic compounds.

For relevant reviews concerning functions, physiological effect and pathophysiology, see: Joel Berger et al., Annu. Rev. Med., 2002, 53, 409 – 435; Timothy Wilson et al., J. Med. Chem., 2000, Vol. 43, No. 4, 527-550; Steven Kliewer et al., Recent Prog Horm Res., 2001, 56, 239-63.

The present invention relates to compounds of the formula I which are suitable for modulating the activity of PPAR receptors, especially the activity of PPARalpha and PPARgamma. Depending on the profile of the modulation, the compounds of the formula I are suitable for the treatment, control and prophylaxis of the indications described hereinafter, and for a series of other, connected pharmaceutical applications (see, for example, Joel Berger et al., Annu. Rev. Med., 2002, 53, 409 – 435; Timothy Wilson et al., J. Med. Chem., 2000, 43(4), 527-550; Steven Kliewer et al., Recent Prog Horm Res., 2001, 56, 239-63; Jean-Charles Fruchart, Bart Staels and Patrick Duriez: PPARS, Metabolic Disease and Arteriosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52, 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease, NATURE, VOL. 405, 25 MAY 2000, 421-424; Ines Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12:2001, 245-254).

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

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

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

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

4. Various other conditions which may be associated with metabolic syndrome are such as:
   - obesity (excess weight), including central obesity
   - thromboses, stages of hypercoagulability and prothrombosis (arterial and venous)
   - high blood pressure
   - heart failure, such as, for example, (but not restricted to that) in the state after myocardial infarction, hypertensive heart disease or cardiomyopathy

5. Further disorders or conditions in which, for example, inflammatory processes or cell differentiation play a role:
   - atherosclerosis, such as, for example, (but not restricted to) coronary sclerosis including angina pectoris or myocardial infarction, stroke

- vascular restenosis or reocclusion
- chronic inflammatory bowel diseases, such as, for example, Crohn's disease and ulcerative colitis
- pancreatitis
- other inflammatory states
- retinopathy
- adipose cell tumors
- lipomatous carcinomas, such as, for example, liposarcomas
- solid tumors and neoplasms, such as, for example, (but not restricted to) carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumors, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas, etc.
- acute and chronic myeloproliferative disorders and lymphomas
- angiogenesis
- neurodegenerative diseases
- Alzheimer's disease
- multiple sclerosis
- Parkinson's disease
- erythemato-squamous dermatoses such as, for example, psoriasis
- acne vulgaris
- other skin disorders and dermatological conditions which are modulated by PPAR
- eczemas and neurodermatitis
- dermatitis, such as, for example, seborrheic dermatitis or photodermatitis
- keratitis and keratoses, such as, for example, seborrheic keratoses, senile keratoses, actinic keratosis, photo-induced keratoses or keratosis follicularis
- keloids and keloid prophylaxis
- warts, including condylomata or condylomata acuminata
- human papilloma virus (HPV) infections, such as, for example, venereal papillomata, viral warts, such as, for example, molluscum contagiosum, leukoplakia
- papular dermatoses, such as, for example, lichen planus
- skin cancer, such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas
- localized benign epidermal tumors, such as, for example, keratoderma, epidermal naevi
- chilblains
- high blood pressure

- syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic disorders, such as, for example, rheumatoid arthritis
- vasculitis
- wasting (cachexia)
- gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS) ("shock lung")

Formulation

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

produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

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

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

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles

which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

The pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

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

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

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

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

Combinations with other medicaments

The compounds of the invention can be administered alone or in combination with one or more further pharmacologically active substances which, for example, act favorably on metabolic disorders or diseases frequently associated therewith. Such medicaments are, for example,

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

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

Mention may be made by way of example of:

Antidiabetics

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

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

In one embodiment of the invention, the compounds of the formula 1 are administered in combination with insulin.

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

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

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

In one embodiment, the compounds of the formula I are in combination with a DPPIV inhibitor, as described, for example, in WO 98/19998, WO 99/61431, WO 99/67278, WO 99/67279, WO 01/72290, WO 02/38541, WO 03/040174, in particular P 93/01 (1-cyclopentyl-3-methyl-1-oxo-2-pentanammonium chloride), P-31/98, LAF237 (1-[2-[3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2-(S)-carbonitrile), TS021 ((2S, 4S)-4-fluoro-1-[[(2-hydroxy-1,1-dimethylethyl)amino]acetyl]pyrrolidine-2-carbonitrile monobenzenesulfonate).

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

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

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

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

Lipid modulators

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid absorption inhibitor (see, for example, US 6,245,744, US 6,221,897, US 6,277,831, EP 0,683,773, EP 0,683,774).

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor as described, for example, in WO 02/50027, or ezetimibe, tiqueside, pamaqueside.

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

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist such as, for example, AZ 242 (tesaglitazar, (S)-3-(4-[2-(4-methanesulfonyloxyphenyl)ethoxy]phenyl)-2-ethoxypropionic acid), BMS 298585 (N-[(4-methoxyphenoxy)carbonyl]-N-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine, or as described in WO 99/62872, WO 99/62871, WO 01/40171, WO 01/40169, WO 96/38428, WO 01/81327, WO 01/21602, WO 03/020269, WO 00/64888 or WO 00/64876.

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

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

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

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

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

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

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

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

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

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

Antiobesity agents

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

In one embodiment, the other active compound is fenfluramine or dexfenfluramine. In a further embodiment, the other active compound is sibutramine.

In a further embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated

transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.:Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists, for example N-{4-[(4-aminoquinazolin-2-ylamino)methyl]-cyclohexylmethyl}naphthalene-1-sulfonamide; hydrochloride (CGP 71683A)), MC4 agonists (for example N-[2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxamide; (WO 01/91752)), orexin antagonists (for example 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea; hydrochloride (SB-334867-A)), H3 agonists (3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (for example [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (for example urocortin), urocortin agonists, β3 agonists (for example 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol; hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (for example {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)-thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)); serotonin reuptake inhibitors (for example dexfenfluramine), mixed serotoninergic and noradrenergic compounds (for example WO 00/71549), 5HT agonists (for example 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), bombesin agonists, galanin antagonists, growth hormone (for example human growth hormone), growth-hormone-releasing compounds (tert-butyl 6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), decoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881), DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors (for example WO 00/40569), PPAR modulators (for example WO 00/78312), RXR modulators or TR-β agonists.

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

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

In one embodiment, the compounds of the formula I are administered in

combination with medicaments having effects on the coronary circulation and the vascular system, such as, for example, ACE inhibitors (e.g. ramipril), medicaments which act on the angiotensin-renin system, calcium antagonists, beta blockers, etc.

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

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

It is self-evident that any suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.

The activity of the compounds was tested as follows:

Determination of EC50 values of PPAR agonists in the PPAR alpha cell test

Principle

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

Construction of the cell line

The PPARalpha reporter cell line was prepared in 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 (in each case 5'-CGGAGTACTGTCCTCCGAG-3') were cloned in 5'-upstream of a 68 bp-long minimal MMTV promoter (Accession # V01175). The minimal MMTV promoter section contains a CCAAT box and a TATA element in order to enable efficient transcription by RNA polymerase II. The cloning and sequencing of the GAL4-MMTV construct took place in analogy to the description of Sambrook J. et. al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Then the complete Photinus pyralis luciferase gene (Accession # M15077) was cloned in 3'-downstream of the GAL4-MMTV element. After sequencing, the luciferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene was recloned into a plasmid which confers zeozin resistance in order to obtain the plasmid pdeltaM-GAL4-Luc-Zeo. This vector was transfected into HEK cells in accordance with the statements in Ausubel, F.M. et al. (Current protocols in molecular biology, Vol. 1-3, John Wiley & Sons, Inc., 1995). Then zeozin-containing medium (0.5 mg/ml) was used to select a suitable stable cell clone which showed very low basal expression of the luciferase gene.

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

Test procedure

The activity of PPARalpha agonists is determined in a 3-day test, described below:

Day 1

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

Day 2

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

Test substances are tested at 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges of from 1 µM to 10 pM or between 100 nM and 1 pM. The medium of the PPARalpha reporter cell line sown on day 1 is completely removed by aspiration, and immediately, the test substances diluted in medium are added to the cells. Dilution and addition of the substances is carried out using a robot (Beckman FX). The end volume of the test substances diluted in medium is 100 µl per well of a 96-well microtiter plate. The DMSO concentration in the test is below 0.1% v/v to prevent cytotoxic effects of the solvent.

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

Day 3

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

Evaluation

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

In this assay, the PPAR alpha EC50 values for the compounds of Examples 1 to 68 are in the range from 3 nM to >10 µM.

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

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

Table I

Example No.	EC50 PPARalpha [nM]
VIII	91
XX	1931
XXI	1251
XXIV	227
XXVI	709
XXVII	726
XXXIV	114
XXXV	187

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

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

Principle

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

Construction of the plasmids

The luciferase reporter plasmid pGL3basic-5xGAL4-TK is based on the vector pGL3basic from Promega. The reporter plasmid is prepared by cloning five binding sites of the yeast transcription factor GAL4 (each binding site with the sequence 5′-CTCGGAGGACAGTACTCCG-3′), together with a 160 bp-long thymidine kinase promoter section (Genbank Accession # AF027128) 5'-upstream into

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

The PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD was prepared by first cloning the cDNA coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386) into the plasmid pcDNA3 (from Invitrogen) 3´-downstream of the cytomegalovirus promoter. Subsequently, the cDNA of the ligand-binding domain (LBD) of the human PPARgamma receptor was cloned (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 PPARgamma expression plasmid pcDNA3-GAL4-humanPPARgammaLBD, also used for the cellular PPARgamma test are the reference plasmid pRL-CMV (from Promega) and the plasmid pBluescript SK(+) from Stratagene. All four plasmids were prepared using a plasmid preparation kit from Qiagen, which ensured a plasmid quality with a minimal endotoxin content, before transfection into HEK cells.

Test procedure

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

Day 1

Firstly, solution A, a transfection mixture which contains all four plasmids previously described in addition to DMEM, is prepared. The following amounts are used to make up 3 ml of solution A for each 96 well microtiter plate for one test: 2622 µl of antibiotic- and serum-free DMEM (# 41965-039, Invitrogen), 100 µl of reference plasmid pRL-CMV (1 ng/µl), 100 µl of luciferase reporter plasmid

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

80%-confluent HEK cells from a cell culture bottle with a capacity of 175 cm^2 are washed once with 15 ml of PBS (#14190-094, Invitrogen) and treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min. The cells are then taken up in 15 ml of DMEM (# 41965-039, Invitrogen) which is mixed with 10% FCS (# 16000-044, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). After the cell suspension has been counted in a cell counter, the suspension is diluted to 250,000 cells/ml. 15 ml of this cell suspension are mixed with 5 ml of solution C for one microtiter plate. 200 µl of the suspension are seeded in each well of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in a cell culture incubator at 37°C and 5% CO_2 for 24 h.

Day 2

PPAR agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (# 41965-039, Invitrogen) which is mixed with 2% Ultroser (#12039-012, Biosepra), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). Test substances are tested in a total of 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM.

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

Day 4

After removal of the medium by aspiration, 50 µl of Dual-Glo™ reagent (Dual-Glo™ Luciferase Assay System; Promega) are added to each well in accordance

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

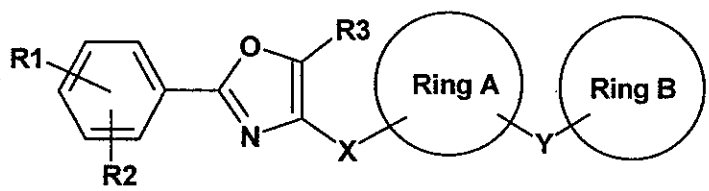
Evaluation

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

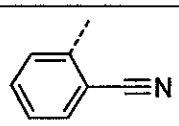
PPARgamma EC50 values in the range from 1 nM to >10 µM were measured for the PPAR agonists described in this application.

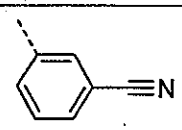
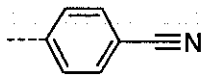
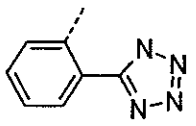
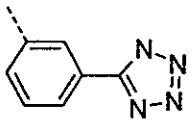
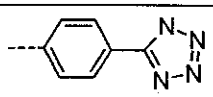
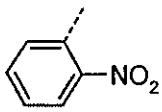
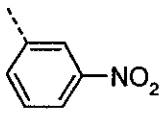
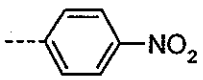
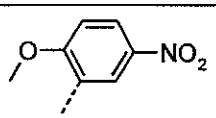
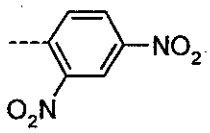
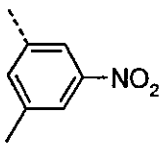
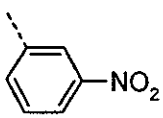
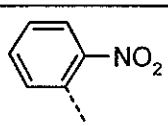
The examples given below serve to illustrate the invention, but without limiting it.

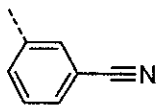
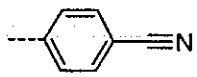
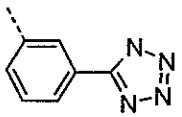
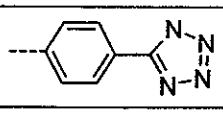
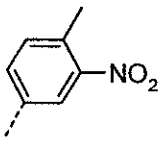
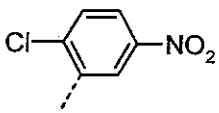
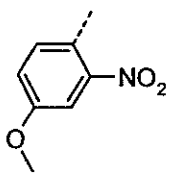
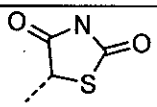
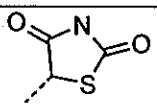
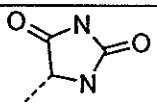
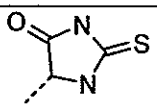
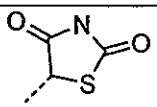
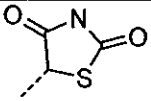
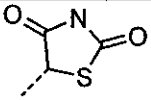
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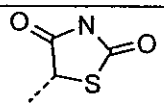
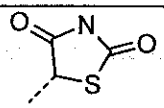
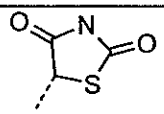
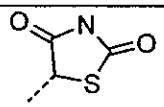
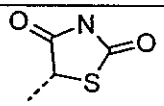
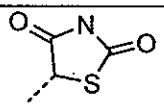
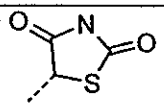
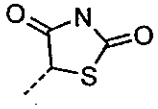
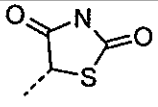
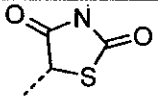
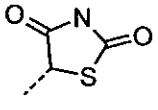
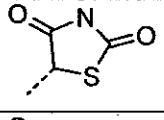
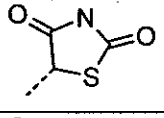
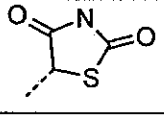
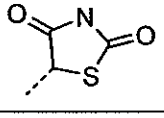


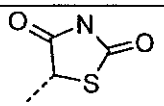
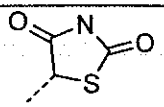
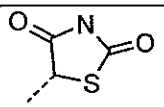
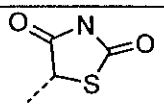
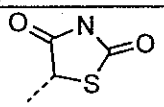
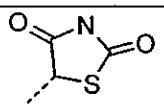
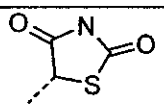
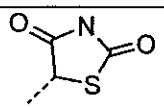
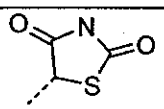
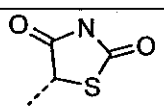
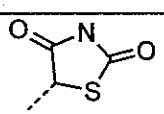
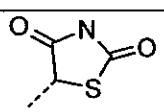
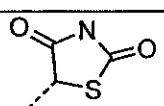
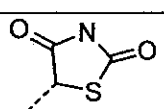
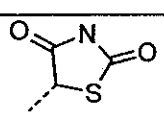
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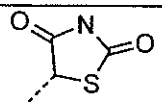
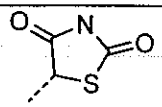
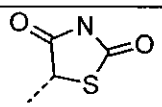
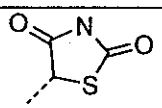
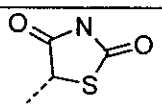
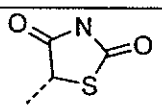
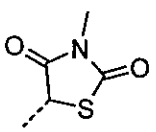
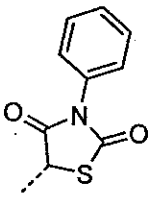
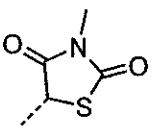
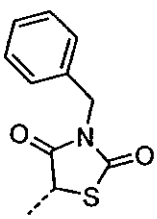
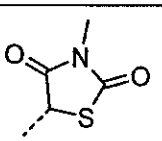
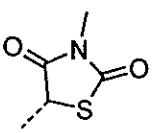
Ex.	Ring A	Ring B	R1	R2	R3	X	Y
I	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--

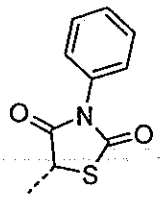
Ex.	Ring A	Ring B	R1	R2	R3	X	Y
II	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
III	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
IV	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
V	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
VI	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
VII	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
VIII	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
IX	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
X	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2--
XI	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--
XII	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--
XIII	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--
XIV	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--

Ex.	Ring A	Ring B	R1	R2	R3	X	Y
XV	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--
XVI	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--
XVII	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--
XVIII	1,3-Cy		4-F	H	Me	CH2-O	--O-C(=O)--
XIX	1,3-Cy		4-F	H	Me	CH2-O	--O-S(=O)2--
XX	1,3-Cy		4-F	H	Me	CH2-O	--O-S(=O)2--
XXI	1,3-Cy		4-F	H	Me	CH2-O	--O-S(=O)2--
XXII	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2-CH=
XXIII	1,3-Cy		3-Me	H	Me	CH2-O	--O-CH2-CH=
XXIV	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2-CH=
XXV	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2-CH=
XXVI	1,3-Cy		4-F	H	Me	CH2-O	--O-CH2-CH--
XXVII	1,3-Cy		3-Me	H	Me	CH2-O	--O-CH2-CH--
XXVIII	1,3-Cy		3-Me	H	Me	CH2-O	--CH2-CH(OH)--

Ex.	Ring A	Ring B	R1	R2	R3	X	Y
XXIX	1,3-Cy		3-OMe	H	Me	CH2-O	--CH2-CH(OH)--
XXX	1,3-Cy		4-Me	H	Me	CH2-O	--CH2-CH(OH)--
XXXI	1,3-Cy		3-Me	H	Me	CH2-O	--CH2-CH2--
XXXII	1,3-Cy		3-OMe	H	Me	CH2-O	--CH2-CH2--
XXXIII	1,3-Cy		4-Me	H	Me	CH2-O	--CH2-CH2--
XXXIV	1,3-Cy		4-Me	H	Me	CH2-O	--CH=
XXXV	1,3-Cy		4-Me	H	Me	CH2-O	--CH2--
XXXVI	1,3-Cy		3-OMe	H	Cy	CH2-O	--CH2-CH2--
XXXVII	1,3-Cy		4-Me	H	Cy	CH2-O	--CH2-CH2--
XXXVIII	1,3-Cy		3-CF_3	5-CF_3	Et	CH2-O	--CH2-CH2--
XXXIX	1,3-Cy		2-Me	6-Me	Et	CH2-O	--CH2-CH2--
XL	1,3-Cy		2-CF_3	H	Me	CH2-O	--CH2-CH2--
XLI	1,3-Cy		3-OMe	H	Et	CH2-O	--CH2-CH2--
XLII	1,3-Cy		2-CF_3	H	Et	CH2-O	--CH2-CH2--
XLIII	1,3-Cy		4-Me	H	Et	CH2-O	--CH2-CH2--

Ex.	Ring A	Ring B	R1	R2	R3	X	Y
XLIV	1,3-Cy		4-^{i}Pr	H	Et	CH2-O	--CH2-CH2--
XLV	1,3-Cy		4-Me	H	^{i}Pr	CH2-O	--CH2-CH2--
XLVI	1,3-Cy		3-CF_3	H	Me	CH2-O	--CH2-CH2--
XLVIIa [1]	1,3-Cy		3-Me	H	Me	CH2-O	--CH2-CH2--
XLVIIb [2]	1,3-Cy		3-Me	H	Me	CH2-O	--CH2-CH2--
XLVIIIa [2]	1,3-Cy		4-^{i}Pr	H	Et	CH2-O	--CH2-CH2--
XLVIIIb [1]	1,3-Cy		4-^{i}Pr	H	Et	CH2-O	--CH2-CH2--
XLIXa [2]	1,3-Cy		4-Me	H	Me	CH2-O	--CH2-CH2--
XLIXb [1]	1,3-Cy		4-Me	H	Me	CH2-O	--CH2-CH2--
L [2]	1,3-Cy		3-Me	4-Me	Et	CH2-O	--CH2-CH2--
LI [2]	1,3-Cy		4-CF_3	H	Et	CH2-O	--CH2-CH2--
LII [2]	1,3-Cy		2-Naphthyl		Et	CH2-O	--CH2-CH2--
LIII [2]	1,3-Cy		3-CF_3	H	Et	CH2-O	--CH2-CH2--
LIV [2]	1,3-Cy		4-^{t}Bu	H	Et	CH2-O	--CH2-CH2--
LV [2]	1,3-Cy		3-Me	4-Me	^{i}Pr	CH2-O	--CH2-CH2--

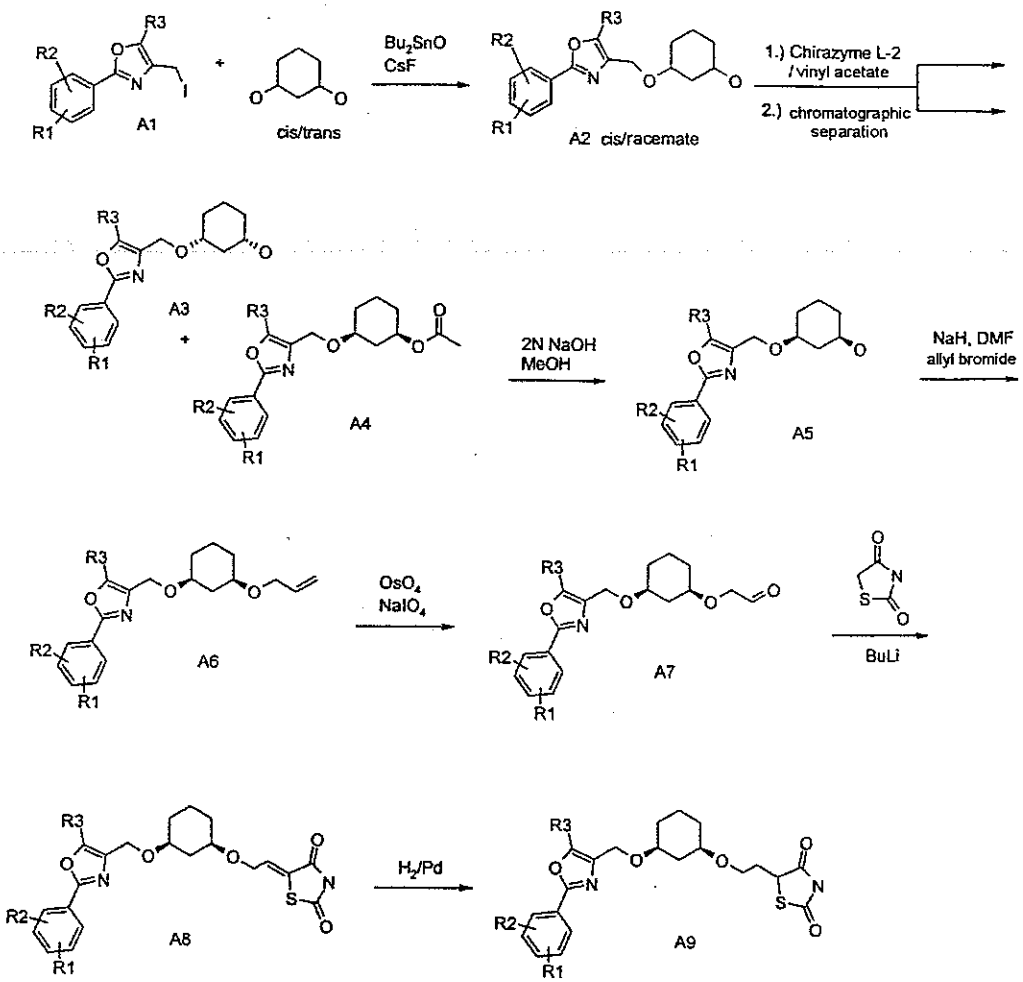
Ex.	Ring A	Ring B	R1	R2	R3	X	Y
LVI [2]	1,3-Cy		4-^{t}Bu	H	Et	CH2-O	--CH2-CH2--
LVII [2]	1,3-Cy		3-CF_3	H	^{i}Pr	CH2-O	--CH2-CH2--
LVIII [2]	1,3-Cy		4-^{t}Bu	H	^{i}Pr	CH2-O	--CH2-CH2--
LIX [2]	1,3-Cy		4-^{t}Bu	H	^{i}Pr	CH2-O	--CH2-CH2--
LX [2]	1,3-Cy		4-CF_3	H	^{i}Pr	CH2-O	--CH2-CH2--
LXI [2]	1,3-Cy		2-Naphthyl		^{i}Pr	CH2-O	--CH2-CH2--
LXII	1,3-Cy		3-OMe	H	Me	CH2-O	--CH2-CH2--
LXIII	1,3-Cy		3-OMe	H	Me	CH2-O	--CH2-CH2--
LXIV	1,3-Cy		4-Me	H	Me	CH2-O	--CH2-CH2--
LXV	1,3-Cy		4-Me	H	Me	CH2-O	--CH2-CH2--
LXVI	1,3-Cy		3-OMe	H	^{i}Pr	CH2-O	--CH2-CH2--
LXVII	1,3-Cy		3-OMe	H	Ph	CH2-O	--CH2-CH2--

Ex.	Ring A	Ring B	R1	R2	R3	X	Y
LXVIII	1,3-Cy		3-OMe	H	Ph	CH2-O	--CH2-CH2--

1,3-Cy is defined as: *cis*-1,3-cyclohexanediol having the stereochemistry according to Cahn-Ingold-Prelog as stated in the examples.
The point of attachment of ring B to Y and the points of attachment of Y to ring A and ring B are shown as a broken line (--).
[1] (1R,3R) enantiomer
[2] (1S,3S) enantiomer

Also described is a process for preparing the compounds of the formula I according to reaction schemes A to H below:

Synthesis scheme A: Preparation of enantiomerically pure or racemic compound **A9**



Initially, cyclohexanediol is heated with dibutyltin oxide in toluene on a water separator for a number of hours and then, with addition of dimethylformamide, cesium fluoride and an oxazole of the formula **A1** in which R1, R2 and R3 are as defined above, converted by stirring at room temperature for a number of hours into a compound of the formula **A2** in which R1, R2 and R3 are as defined above.

The compound of the formula **A2** is reacted using Chirazyme L2 and vinyl acetate. This results in the formation of compounds **A3** and **A4**, of which **A4**, after separation, is reacted with alkali metal hydroxides to give a compound of the structure **A5** in which R1, R2 and R3 are as defined above.

The compound of the formula **A5** or **A2** is converted into an enantiomerically pure or racemic compound of the structure **A6** in which R1, R2 and R3 are as defined above. To form the ether bond, **A5** or **A2** is deprotonated, for example in an aprotic solvent such as dimethylformamide, using strong bases, for example

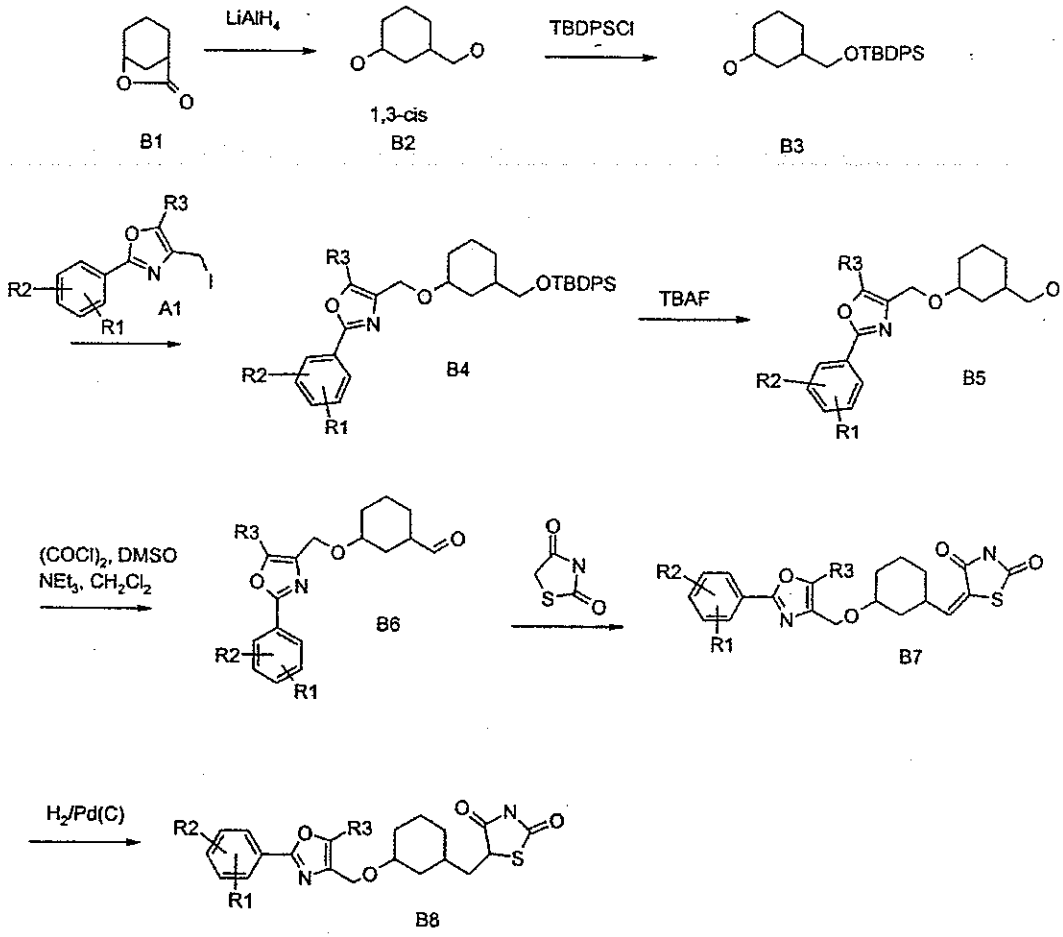
sodium hydride, and reacted with unsaturated bromides, for example allyl bromides.

The enantiomerically pure or racemic compound of the formula **A6** is, using osmium tetroxide and sodium periodate, converted into the enantiomerically pure or racemic compound of the structure **A7** in which R1, R2 and R3 are as defined above.

The enantiomerically pure or racemic compound of the formula **A7** is converted into enantiomerically pure or racemic compounds of the structure **A8** in which R1, R2 and R3 are as defined above. Here, thiazolidinedione is initially deprotonated in an inert solvent using a strong base, for example n-butyllithium, and then, at –70°C, reacted with component **A7**, giving, after acidic work-up, for example with 6N hydrochloric acid, the compound **A8.**

The enantiomerically pure or racemic compound **A8** is, by hydrogenation, using, for example, palladium-on-carbon as catalyst in solvents such as methanol or ethyl acetate, converted into an enantiomerically pure or racemic compound of the formula **A9** in which R1, R2 and R3 are as defined above.

Synthesis scheme B: Preparation of the compound **B8**



The compound of the formula **B4** in which R1, R2 and R3 are as defined above is obtained from lactone **B1** by lithium aluminum hydride reduction to diol **B2**, selective silylation at the primary alcohol function giving compound **B3**, deprotonation using strong bases, for example sodium hydride in an aprotic solvent such as dimethylformamide, and alkylation with phenyloxazoyl iodides of the formula **A1**, in which R1, R2 and R3 are as defined above.

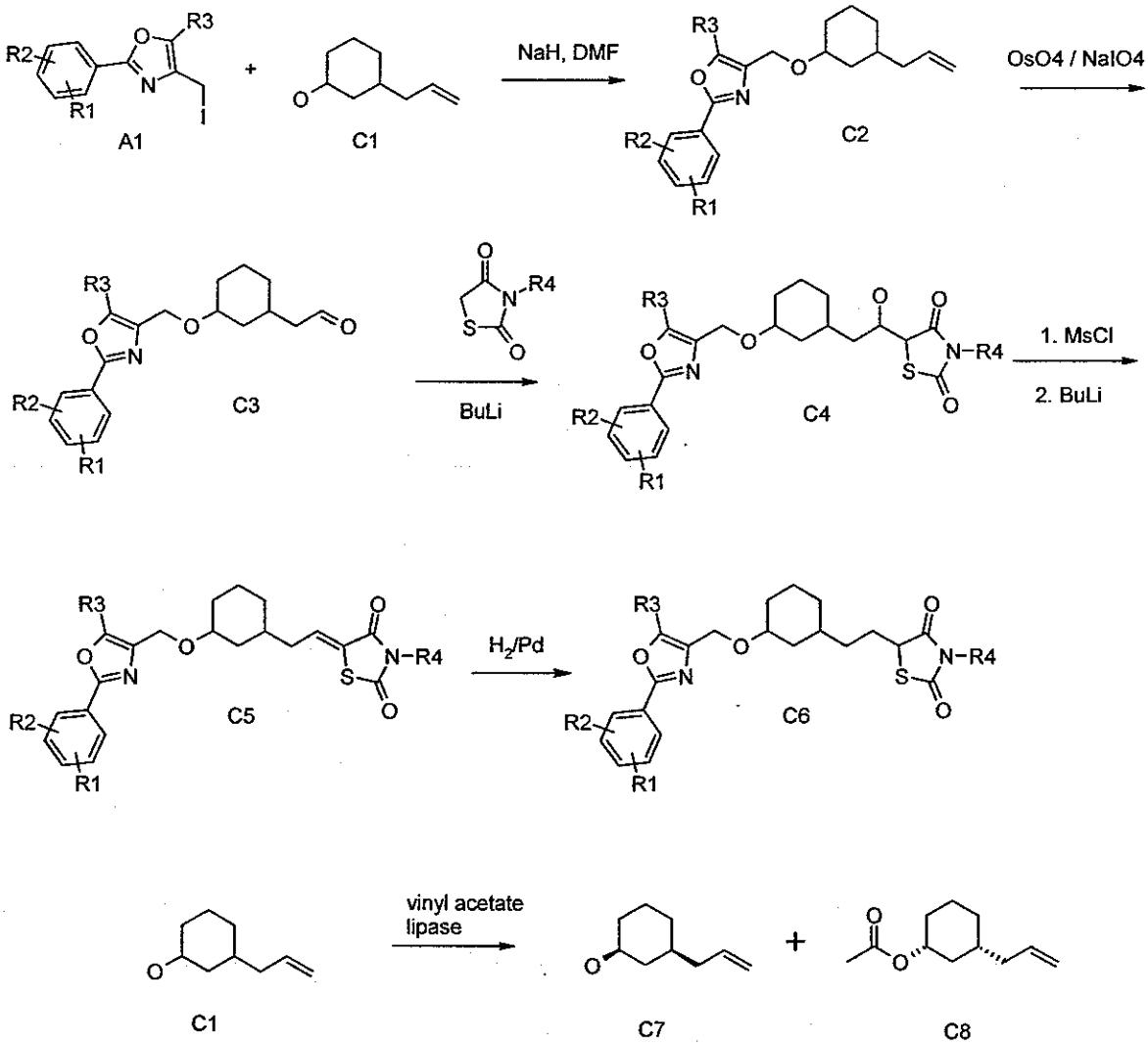
The compound of the formula **B4** in which R1, R2 and R3 are as defined above is converted into a compound of the structure **B5** in which R1, R2 and R3 are as defined above, for example by removing the silyl protective group with fluoride, for example tetrabutylammonium fluoride.

Using osmium tetroxide and sodium periodate, the compound of the formula **B5** is converted into the compound of the structure **B6** in which R1, R2 and R3 are as defined above.

The compound of the formula **B6** is converted into a compound of the structure **B7** in which R1, R2 and R3 are as defined above. Here, thiazolidinedione is initially deprotonated in an inert solvent using a strong base, such as, for example, n-butyllithium, and then, at –70°C, reacted with component **B6** giving, after acidic work-up, for example with 6N hydrochloric acid, compound **B7**.

Compound **B7** is converted by hydrogenation, for example at a hydrogen pressure of 3 bar using palladium-on-carbon as catalyst in solvents such as methanol or ethyl acetate, into a compound of the formula **B8** in which R1, R2 and R3 are as defined above.

Synthesis scheme C: Preparation of the compound **C6**



Compounds of the formula **A1** in which R1, R2 and R3 are as defined above are dissolved with cis-3-allylcyclohexanol **C1** (or optionally with (1S,3S)-3-allylcyclohexanol **C7**) in aprotic solvents, such as dimethylformamide, and reacted with strong bases, such as, for example, sodium hydride, giving compounds of the formula **C2** in which R1, R2 and R3 are as defined above.

The compound of the formula **C2** is, using osmium tetroxide and sodium periodate, converted into the compound of the structure **C3** in which R1, R2 and R3 are as defined above.

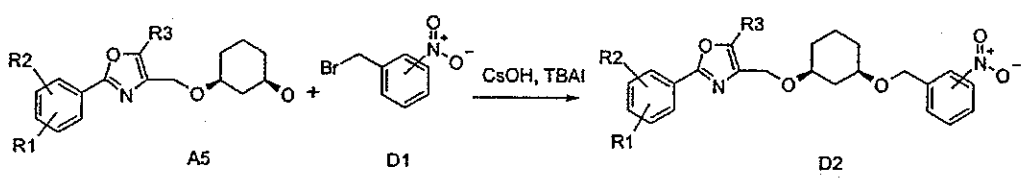
The compound of the formula **C3** is converted into a compound of the structure **C4** in which R1, R2, R3 and R4 are as defined above. Here, thiazolidinedione is initially deprotonated in an inert solvent using a strong base, such as, for example, n-butyllithium, and then, at –70°C, reacted with component **C3**, giving, after work-up, for example with 1N hydrochloric acid, a compound of the formula **C4**.

The compound **C4** is converted into a compound of the formula **C5** in which R1, R2, R3 and R4 are as defined above. Alcohol **C4** is, for example, mixed with mesyl chloride and triethylamine in polar solvents, such as dichloromethane, and the crude product is, at –70°C, converted with n-butyllithium into **C5**.

The compound of the formula **C5** is converted by hydrogenation, for example at a hydrogen pressure of 5 bar using palladium-on-carbon as catalyst in ethyl acetate, into a compound of the formula **C6** in which R1, R2, R3 and R4 are as defined above.

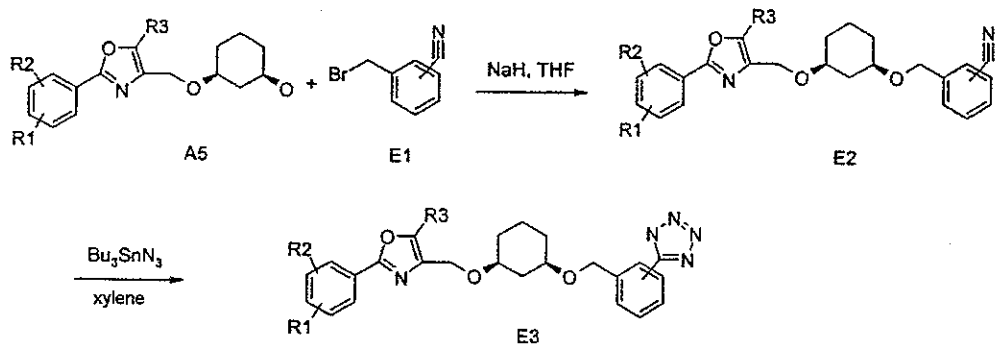
Enantiomerically pure (1S,3S)-3-allylcyclohexanol **C7** can be obtained from racemic **C1** by treatment with lipase in vinyl acetate. The coproduct (1R,3R)-3-allylcyclohexanyl acetate **C8** can be removed chromatographically.

Synthesis scheme D: Preparation of compound **D2**



The compound of the formula **A5** or **A2** is converted using bases, for example cesium hydroxide in a mixture of water and acetonitrile, using a phase-transfer catalyst, for example tetrabutylammonium iodide, with nitrobenzyl bromides of the formula **D1** into enantiomerically pure or racemic compounds of the structure **D2** in which R1, R2 and R3 are as defined above.

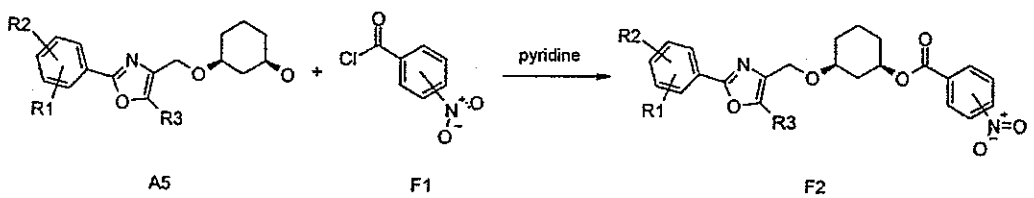
Synthesis scheme E: Preparation of enantiomerically pure or racemic compound **E3**



The compound of the formula **A5** or **A2** is, using strong bases, for example sodium hydride, deprotonated in an aprotic solvent and reacted with cyanobenzyl bromides of the formula **E1**, giving enantiomerically pure or racemic compounds of the structure **E2** in which R1, R2 and R3 are as defined above.

The compound of the formula **E2** is, using a metal azide, for example tributyltin azide, converted into enantiomerically pure or racemic compounds of the structure **E3** in which R1, R2, and R3 are as defined above.

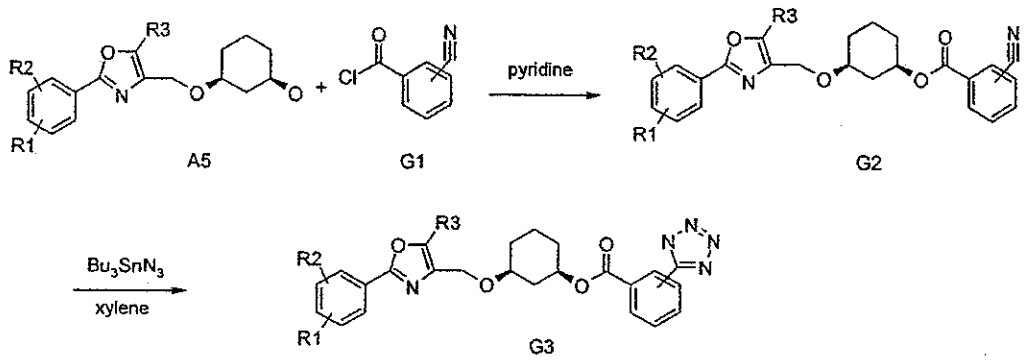
Synthesis scheme F: Preparation of enantiomerically pure or racemic compound **F2**



The compound of the formula **A5** or **A2** is, using bases, for example pyridine, reacted at about 50°C with nitrobenzoyl chlorides of the formula **F1**, giving

enantiomerically pure or racemic compounds of the formula **F2** in which R1, R2 and R3 are as defined above.

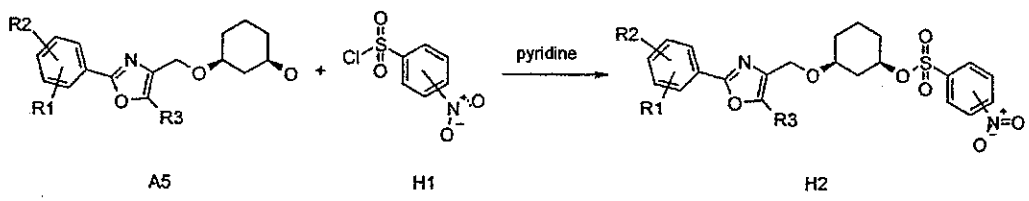
Synthesis scheme G: Preparation of enantiomerically pure or racemic compound **G3**



The compound of the formula **A5** or **A2** is, using bases, for example pyridine, reacted at about 50°C with cyanobenzoyl chlorides of the formula **G1**, giving enantiomerically pure or racemic compounds of the formula **G2** in which R1, R2 and R3 are as defined above.

The compound of the formula **G2** is, using a metal azide, for example tributyltin azide, converted at about 160°C into enantiomerically pure or racemic compounds of the structure **G3** in which R1, R2 and R3 are as defined above.

Synthesis scheme H: Preparation of enantiomerically pure or racemic compound **H2**



The compound of the formula **A5** or **A2** is, using bases, for example pyridine, reacted at room temperature with nitrobenzenesulfonyl chlorides of the formula **G1**, giving enantiomerically pure or racemic compounds of the formula **G2** in which R1, R2 and R3 are as defined above.

The abbreviations used denote:

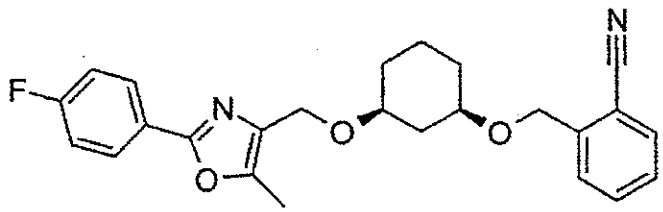
Ac	acetyl
^{i}Bu	isobutyl
^{t}Bu	tert-butyl
BuLi	*n*-butyllithium
Cy	cyclohexyl
TLC	thin-layer chromatography
DCI	direct chemical ionization (MS)
DCM	dichloromethane
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EA	ethyl acetate
EDC	N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide x HCl
EI	electron impact ionization (MS)
eq	equivalent
ESI	electron spray ionization (MS)
Et	ethyl
Sat.	saturated
h	hour
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxy-1H-benzotriazole x H_2O
HPLC	high pressure, high performance liquid chromatography
LC-MS	liquid-chromatography-coupled mass spectroscopy
Me	methyl
MS	mass spectroscopy
MsCl	methanesulfonyl chloride
NMR	nuclear magnetic resonance spectroscopy
Pd/C	palladium-on-carbon
^{i}Pr	isopropyl
^{n}Pr	n-propyl
R_f	retention time (TLC)
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide

TBDPSCl	*tert*-butyldiphenylsilyl chloride
THF	tetrahydrofuran

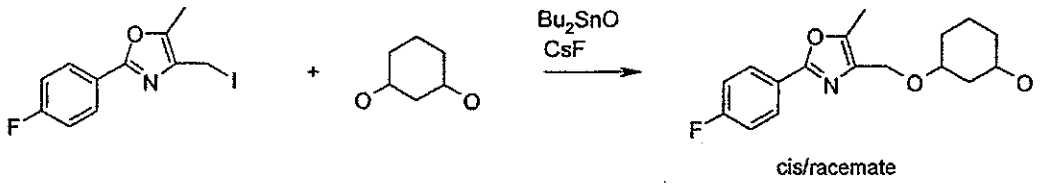
Other compounds of the formula I to be obtained by known processes are in accordance with the reaction schemes described above.

Example I

2-(4-Fluorophenyl)-5-methyl-4-[cis-3-(2-cyanobenzyloxy)cyclohexyl-oxymethyl]oxazole

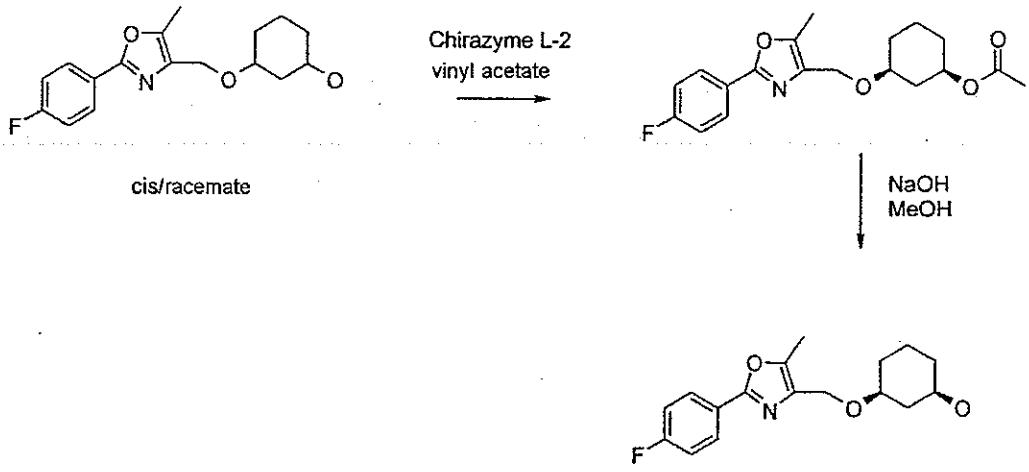


rac-3-(*cis*-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol



21.7 g of 1,3-cyclohexanediol and 30.3 g of dibutyltin oxide are dissolved in 450 ml of toluene and, under reflux on a water separator, heated to boiling. During the reaction, the reaction volume is reduced to half the original volume. After 3 hours, the reaction mixture is cooled to room temperature, and 300 ml of dimethylformamide, 29 g of 2-(4-fluorophenyl)-4-iodomethyl-5-methyloxazole **1** and 23.5 g of cesium fluoride are added. The mixture is stirred at room temperature for 18 hours. The reaction mixture is diluted by addition of ethyl acetate and washed with saturated sodium chloride solution. The organic phase is dried over magnesium sulfate, the solvent is removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 10:1 -> 1:4). This gives 58 g of *rac*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol as a yellowish solid which is recrystallized from n-heptane/ethyl acetate. $C_{17}H_{20}FNO_3$ (305.35), MS (ESI): 306 ($M + H^+$).

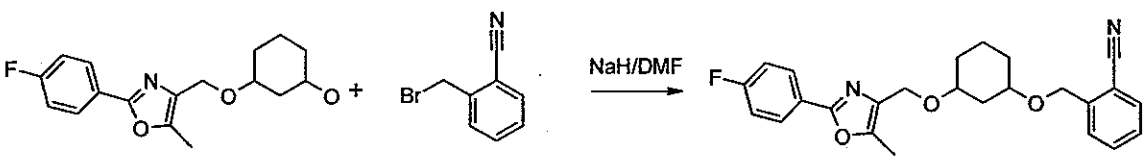
(1R,3S)-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol



cis/racemate

25 g of *rac-cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol are dissolved in 320 ml of vinyl acetate, and 1.3 g of Chirazyme L-2 Lyo (Boehringer Mannheim) are added. The mixture is stirred at room temperature for three hours (checked by LC-MS for 40-45% conversion) and the enzyme is then filtered off and washed with ethyl acetate, and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 3:1). This gives 8 g of (1R, 3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl acetate as a colorless oil. $C_{19}H_{22}FNO_4$ (347.39), MS (ESI): 348 ($M + H^+$). The acetate is taken up in 170 ml of methanol and, after addition of 27 ml of 2N aqueous sodium hydroxide solution, stirred at room temperature for one hour. Most of the solvent is removed under reduced pressure. After addition of in each case 150 ml of water and ethyl acetate, the organic phase is washed with sodium chloride solution. The organic phase is dried over magnesium sulfate and the solvent is removed under reduced pressure. This gives 6.7 g of 3-(1R,3S)-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol as a yellowish solid. $C_{17}H_{20}FNO_3$ (305.35), MS (ESI): 306 ($M + H^+$).

2-(4-Fluorophenyl)-5-methyl-4-[cis-3-(2-cyanobenzyloxy)cyclohexyl-oxymethyl]oxazole



cis/racemate

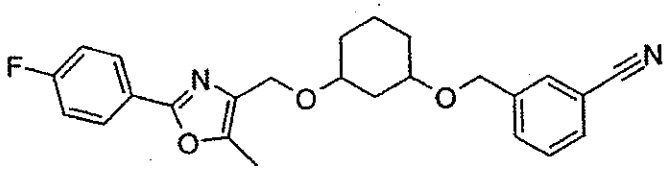
cis/racemate

In a 25 ml two-necked flask which had been dried by heating, 0.15 g of the alcohol 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol is dissolved in 5 ml of dimethylformamide (dry), and 0.05 g of sodium hydride is added. The mixture is stirred for 15 minutes, 0.19 g of 2-(bromomethyl)benzonitrile is then added, and the mixture is stirred at room temperature for 24 hours. The reaction is terminated by addition of 2 ml of 1N hydrochloric acid and the mixture is extracted with ethyl acetate (2 x 10 ml). The combined organic phases are washed with saturated sodium chloride solution and dried over magnesium sulfate and the solvent is then removed under reduced pressure. Purification by preparative HPLC gives 0.07 g of the desired product 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(2-cyanobenzyloxy)cyclohexyloxymethyl]oxazole as a colorless oil.
$C_{25}H_{25}FN_2O_3$ (420.48), MS (ESI): 421 ($M + H^+$).

Example II

2-(4-Fluorophenyl)-5-methyl-4-[cis-3-(3-cyanobenzyloxy)cyclohexyloxy-methyl]oxazole

Analogously to Example I, the alcohol 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 3-(bromomethyl)benzonitrile give the compound 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(3-cyanobenzyloxy)-cyclohexyloxymethyl]oxazole:



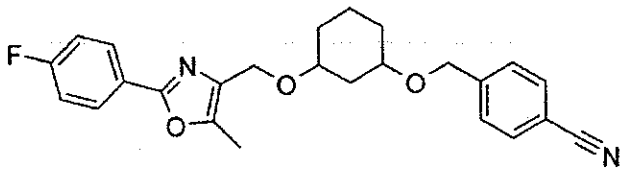
cis/racemate

$C_{25}H_{25}FN_2O_3$ (420.48), MS (ESI): 421 ($M + H^+$).

Example III

2-(4-Fluorophenyl)-5-methyl-4-[cis-3-(4-cyanobenzyloxy)cyclohexyl-oxymethyl]oxazole

Analogously to Example I, the alcohol 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 4-(bromomethyl)benzonitrile give the compound 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(4-cyanobenzyloxy)-cyclohexyloxymethyl]oxazole:



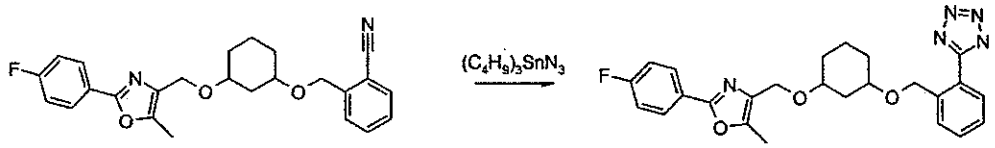
cis/racemate

$C_{25}H_{25}FN_2O_3$ (420.48), MS (ESI): 421 ($M + H^+$).

The compounds synthesized in this manner (Example I – III) can be converted into the corresponding tetrazoles:

Example IV

5-(2-{cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclo-hexyloxymethyl}phenyl)-1-H-tetrazole



cis/racemate cis/racemate

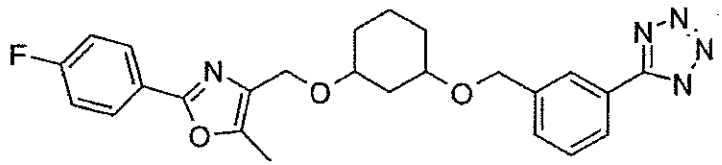
0.03 g of the nitrile 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(2-cyanobenzyloxy)cyclohexyloxymethyl]oxazole are dissolved in 5 ml of xylene, 50 µl of tributyltin azide are added and the mixture is heated under reflux at 160°C for 24 hours. The reaction is terminated by addition of 1 ml of trifluoroacetic acid (in 1 ml of methanol), 3 ml of water are added and the mixture is extracted with ethyl acetate (2 x 10 ml). The combined organic phases are washed with saturated sodium chloride solution and dried over magnesium sulfate, and the solvent is then removed under reduced pressure. Purification by preparative HPLC gives 0.02 g of the desired 5-(2-{cis-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy-methyl}phenyl)-1-H-tetrazole as an amorphous solid.

$C_{25}H_{26}FN_5O_3$ (463.51), MS (ESI): 464 ($M + H^+$).

Example V

5-(3-{cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}phenyl)-1H-tetrazole

Analogously to Example IV, 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(3-cyanobenzyloxy)cyclohexyloxymethyl]oxazole from Example II gave, by reaction with tributyltin hydride, 5-(3-{cis-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}phenyl)-1H-tetrazole:



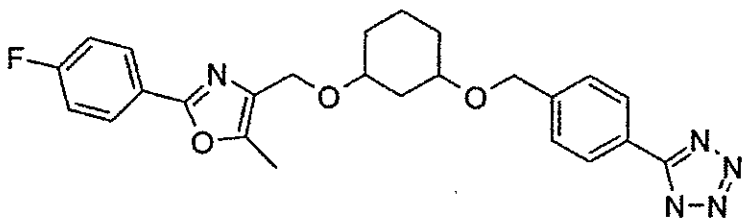
cis/racemate

$C_{25}H_{26}FN_5O_3$ (463.51), MS (ESI): 464 ($M + H^+$).

Example VI

5-(4-{cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}phenyl)-1H-tetrazole

Analogously to Example IV, 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(4-cyanobenzyloxy)cyclohexyloxymethyl]oxazole from Example III gave, by reaction with tributyltin hydride, 5-(4-{cis-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}phenyl)-1H-tetrazole:

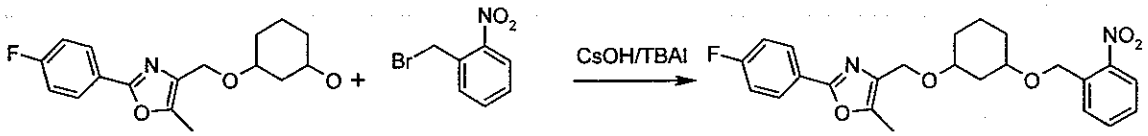


cis/racemate

$C_{25}H_{26}FN_5O_3$ (463.51), MS (ESI): 464 ($M + H^+$).

Example VII

2-(4-Fluorophenyl)-5-methyl-4-[cis-3-(2-nitrobenzyloxy)cyclohexyloxy-methyl]oxazole



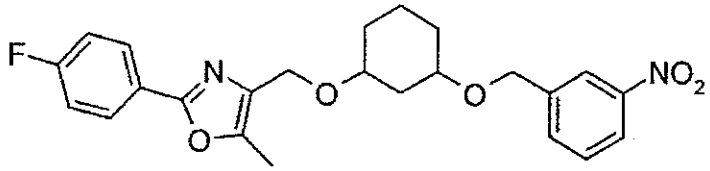
cis/racemate cis/racemate

0.1 g of 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol is dissolved in 3 ml of acetonitrile, and 0.21 g of 2-nitrobenzyl bromide and 0.36 g of tetrabutylammonium iodide are added. 0.57 ml of cesium hydroxide solution (50% strength solution in water) is added dropwise, and the two-phase mixture is stirred vigorously at room temperature, for 12 hours. The reaction is checked (LCMS), showing the formation of the desired product, in addition to unreacted alcohol 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol. By addition of a further 0.2 g of 2-nitrobenzyl bromide (2 eq) at room temperature and stirring at room temperature for a further 12 hours, the reaction is terminated by addition of 2 ml of 1N hydrochloric acid and the mixture is extracted with ethyl acetate (2 x 10 ml). The combined organic phases are washed with saturated sodium chloride solution and dried over magnesium sulfate. Purification by HPLC gives 0.05 g of the compound 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(2-nitrobenzyloxy)cyclohexyloxymethyl]oxazole as a clear colorless oil. $C_{24}H_{25}FN_2O_5$ (440.47), MS (ESI): 441 ($M + H^+$).

Example VIII

2-(4-Fluorophenyl)-5-methyl-4-[cis-3-(3-nitrobenzyloxy)cyclohexyloxy-methyl]oxazole

Analogously to Example VII, 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 3-nitrobenzyl bromide gave the compound 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(3-nitrobenzyloxy)cyclohexyloxy-methyl]oxazole below:



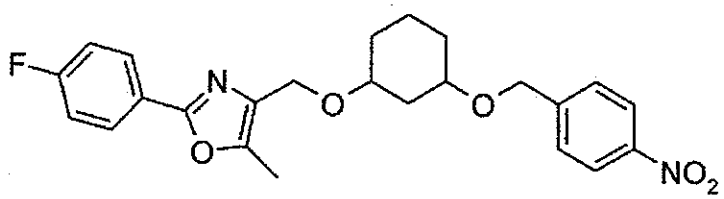
cis/racemate

$C_{24}H_{25}FN_2O_5$ (440.47), MS (ESI): 441

Example IX

2-(4-Fluorophenyl)-5-methyl-4-[cis-3-(4-nitrobenzyloxy)cyclohexyloxy-methyl]oxazole

Analogously to Example VII, 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 4-nitrobenzyl bromide gave the compound 2-(4-fluorophenyl)-5-methyl-4-[cis-3-(4-nitrobenzyloxy)cyclohexyloxy-methyl]oxazole below:



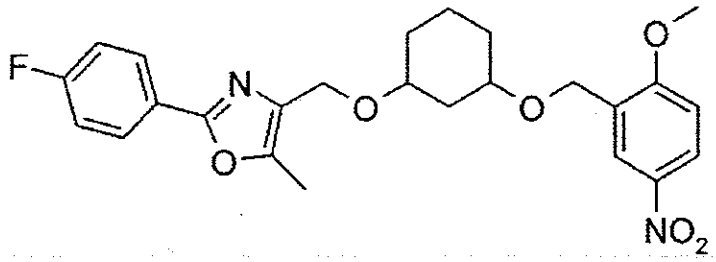
cis/racemate

$C_{24}H_{25}FN_2O_5$ (440.47), MS (ESI): 441

Example X

2-(4-Fluorophenyl)-4-[*cis*-3-(2-methoxy-5-nitrobenzyloxy)cyclohexyloxy-methyl]-5-methyloxazole

Analogously to Example VII, cis-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 2-methoxy-5-nitrobenzyl bromide gave the compound 2-(4-fluorophenyl)-4-[cis-3-(2-methoxy-5-nitrobenzyloxy)cyclo-hexyloxymethyl]-5-methyloxazole below:

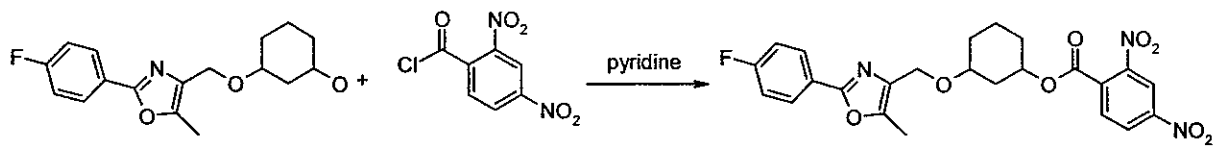


cis/racemate

$C_{25}H_{27}FN_2O_6$ (470.50), MS (ESI): 471 ($M + H^+$)

Example XI

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3,5-dinitrobenzoate



cis/racemate cis/racemate

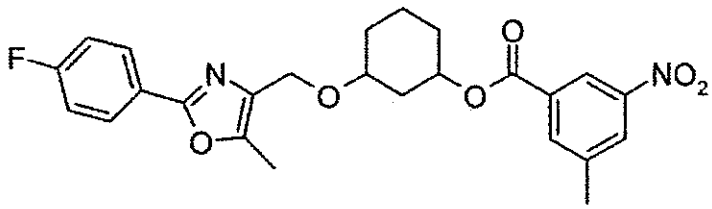
0.5 g of 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol is dissolved in 3 ml of pyridine and, at 0°C, 0.6 g of 3,5-dinitrobenzoyl chloride is added. The reaction mixture is then heated at 50°C for 10 minutes. The reaction is checked (LCMS) showing the formation of the desired product, in addition to unreacted alcohol *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol. After a further 10 minutes of stirring at room temperature, the reaction is terminated by addition of 5 ml of concentrated hydrochloric acid, and the crude product is filtered off with suction, taken up in ethyl acetate, washed with saturated sodium bicarbonate and sodium chloride solution and dried over magnesium sulfate. Purification by HPLC gives 0.15 g of the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3,5-dinitrobenzoate as yellow solid.

$C_{24}H_{22}FN_3O_8$ (499.46), MS (ESI): 500 ($M + H^+$).

Example XII

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-methyl-5-nitrobenzoate

Analogously to **Example XI**, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 3-methyl-5-nitrobenzoyl chloride gave the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-methyl-5-nitrobenzoate below:



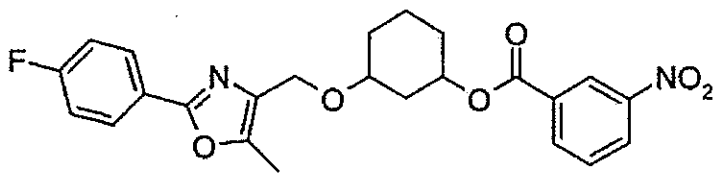
cis/racemate

$C_{25}H_{25}FN_2O_6$ (468.48), MS (ESI): 469 ($M + H^+$).

Example XIII

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-nitrobenzoate

Analogously to Example XI, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 3-nitrobenzoyl chloride gave the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-nitrobenzoate below:



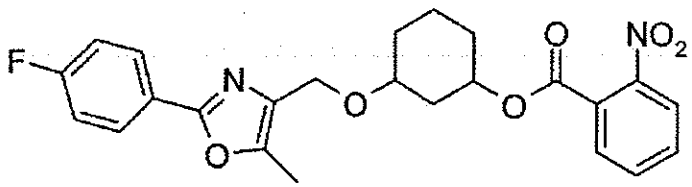
cis/racemate

$C_{24}H_{23}FN_2O_6$ (454.46), MS (ESI): 455 ($M + H^+$).

Example XIV

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 2-nitrobenzoate

Analogously to Example XI, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 2-nitrobenzoyl chloride gave the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 2-nitrobenzoate below:



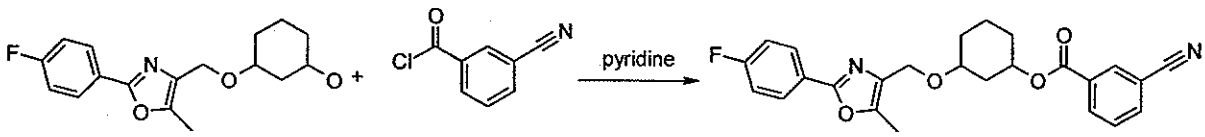
cis/racemate

$C_{24}H_{23}FN_2O_6$ (454.46), MS (ESI): 455 ($M + H^+$).

Example XV

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-cyanobenzoate

Analogously to Example XI, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 3-cyanobenzoyl chloride gave the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-cyanobenzoate below:



cis/racemate cis/racemate

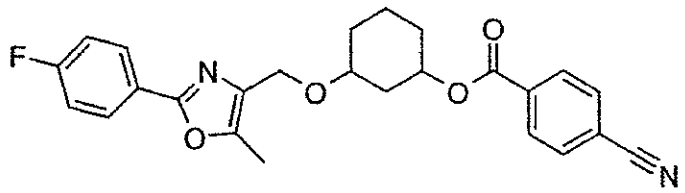
0.1 g of 3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol is dissolved in 3 ml of pyridine and, at 0°C, 0.1 g of 3-cyanobenzoyl chloride is added. The reaction mixture is then heated at 50°C for 10 minutes. The reaction is checked (LCMS), showing the formation of the desired product in addition to unreacted alcohol *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol. After addition of a further 0.9 g of 3-cyanobenzoyl chloride and 30 minutes of stirring at room temperature, the reaction is terminated by addition of 5 ml of concentrated hydrochloric acid, the mixture is extracted with ethyl acetate and the organic phase is washed with saturated sodium bicarbonate and sodium chloride solution and dried over magnesium sulfate. Purification by

HPLC gives 0.1 g of the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-cyanobenzoate as a brown solid.
$C_{25}H_{23}FN_2O_4$ (434.47), MS (ESI): 435 ($M + H^+$).

Example XVI

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-cyanobenzoate

Analogously to Example XI, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 4-cyanobenzoyl chloride gave the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-cyanobenzoate below:



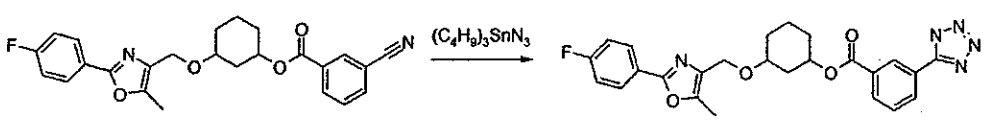
cis/racemate

$C_{25}H_{23}FN_2O_4$ (434.47), MS (ESI): 435 ($M + H^+$).

The compounds synthesized in this manner (Examples XV – XVI) can be converted into the corresponding tetrazoles by reaction with tributyltin azide.

Example XVII

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-(1H-tetrazol-5-yl)benzoate



cis/racemate cis/racemate

0.06 g of *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-cyanobenzoate is dissolved in 5 ml of xylene, 150 µm of tributyltin azide are added and the mixture is heated under reflux at 160°C for 24 hours. The reaction is terminated by addition of 1 ml of trifluoroacetic acid (in 1 ml of methanol), 3 ml of water are added and the mixture is extracted with ethyl acetate (2 x 10 ml). The

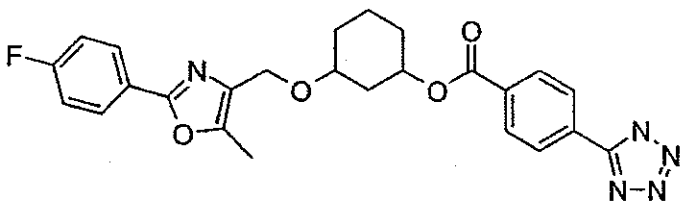
combined organic phases are washed with saturated sodium chloride solution and dried over magnesium sulfate, and the solvent is then removed under reduced pressure. Purification by preparative HPLC gives 0.04 g of the desired *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 3-(1H-tetrazol-5-yl)benzoate as an amorphous solid.

$C_{25}H_{24}FN_5O_4$ (477.49), MS (ESI): 478 ($M + H^+$).

Example XVIII

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-cyanobenzoate

Analogously to Example XVII, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-cyanobenzoate and tributyltin hydride gave *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-cyanobenzoate:

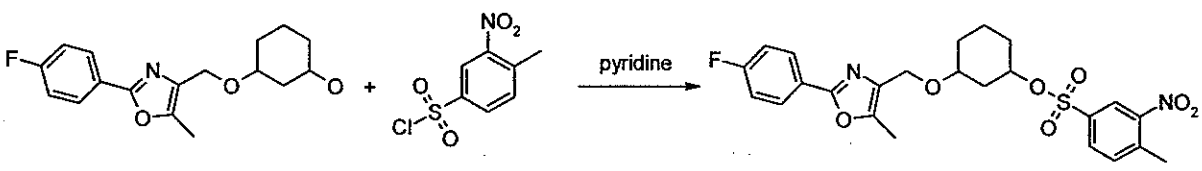


cis/racemate

$C_{25}H_{24}FN_5O_4$ (477.49), MS (ESI): 478 ($M + H^+$).

Example XIX

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-methyl-3-nitrobenzenesulfonate



cis/racemate cis/racemate

0.1 g of *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl and 0.15 of 4-methyl-3-nitrobenzenesulfonyl chloride are dissolved in 10 ml of dry chloroform and, at 0°C, 2 ml of pyridine are added. The reaction mixture is then

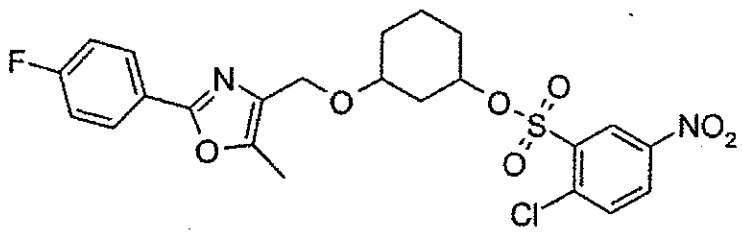
stirred at room temperature for 12 hours. The reaction is checked (LCMS), showing the formation of the desired product, in addition to unreacted alcohol *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol. After a further 10 minutes of stirring at room temperature, the reaction is terminated by addition of 2 ml of concentrated hydrochloric acid, the mixture is extracted with dichloromethane and the extract is washed with saturated sodium bicarbonate and sodium chloride solution and dried over magnesium sulfate. Purification by HPLC gives 0.14 g of the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-methyl-3-nitrobenzenesulfonate as a viscous oil

$C_{24}H_{25}FN_2O_7S$ (504.53), MS (ESI): 505 ($M + H^+$).

Example XX

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 2-chloro-5-nitrobenzoate

Analogously to Example XIX, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl and 2-chloro-5-nitrobenzenesulfonic acid gave the compound *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 2-chloro-5-nitrobenzenesulfonate:



cis/racemate

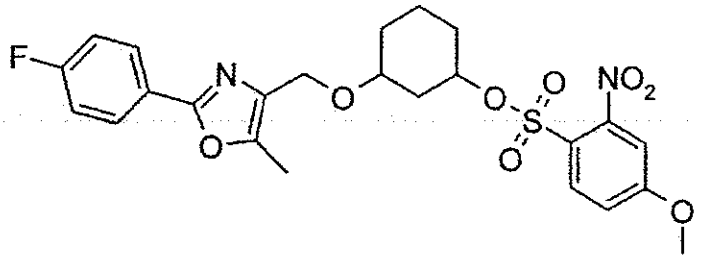
$C_{23}H_{22}FClN_2O_7S$ (524.95), MS (ESI): 525 ($M + H^+$).

Example XXI

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-methoxy-2-nitrobenzesulfonate

Analogously to Example XIX, *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol and 4-methoxy-2-nitrobenzenesulfonic acid gave *cis*-3-[2-

(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl 4-methoxy-2-nitrobenzenesulfonate;



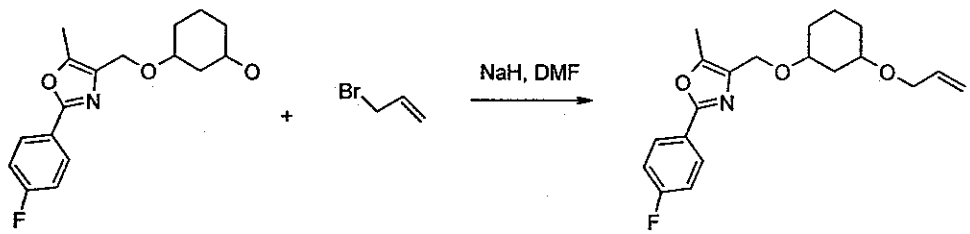
cis/racemate

$C_{24}H_{25}FN_2O_8S$ (520.53), MS (ESI): 521 ($M + H^+$)

Example XXII

5-(2-{*cis*-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}-ethylidene)thiazolidine-2,4-dione

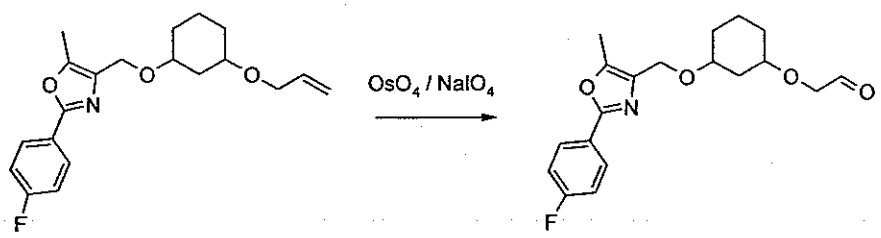
4-(*cis*-3-allyloxycyclohexyloxymethyl)-2-(4-fluorophenyl)-5-methyloxazole



cis/racemate cis/racemate

2 g of *cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol are dissolved in 15 ml of dimethylformamide, and 0.3 g of sodium hydride is added. After 30 minutes, 2.4 g of allyl bromide are added dropwise. The mixture is stirred at room temperature for 5 hours. 15 ml of 1N hydrochloric acid are then added to the reaction mixture, and the mixture is washed three times with 15 ml of ethyl acetate. The organic phase is dried over magnesium sulfate and the solvent is then removed under reduced pressure. The residue is purified by RP-HPLC. This gives 2.4 g of 4-(*cis*-3-allyloxycyclohexyloxymethyl)-2-(4-fluorophenyl)-5-methyloxazole as a yellowish oil. $C_{20}H_{24}FNO_3$ (345.42), MS (ESI): 346 ($M + H^+$)

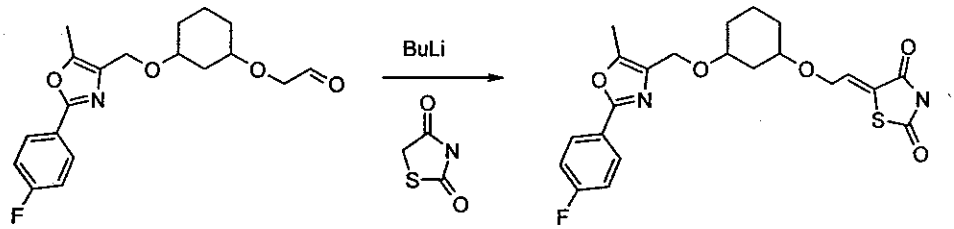
[*cis*-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde



cis/racemate cis/racemate

2.0 g of 4-(*cis*-3-allyloxycyclohexyloxymethyl)-2-(4-fluorophenyl)-5-methyl-oxazole are dissolved in 50 ml of diethyl ether, and 3.8 g of sodium periodate, dissolved in 50 ml of water, are added. At 0°C, 1 ml of an osmium tetroxide solution (2.5% by weight in tert-butanol) is added, and the mixture is stirred vigorously at room temperature. After 8 hours, 100 ml of methyl tert-butyl ether are added, and the mixture is washed with a saturated sodium thiosulfate solution. The organic phase is dried over magnesium sulfate and the solvent is removed under reduced pressure. The residue is purified on silica gel (n-heptane:ethyl acetate = 1:1 → 1:5). This gives 1.4 g of [*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde as a colorless oil. $C_{20}H_{25}NO_4$ (343.42), MS (ESI): 344 ($M + H^+$), R_f(n-heptane:ethylacetate = 1:1) = 0.25.

5-(2-{*cis*-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}-ethylidene)thiazolidine-2,4-dione



cis/racemate cis/racemate

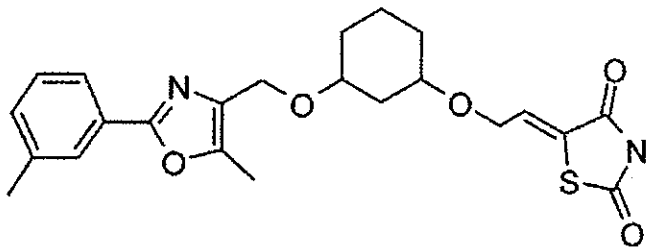
66 mg of thiazolidinedione are dissolved in 10 ml of tetrahydrofuran and, at –78°C, 0.11 ml of a 2.7 M solution of n-butyllithium in n-hexane is added. The mixture is stirred at –78°C for 30 minutes, and 150 mg of [*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde, dissolved in 5 ml of tetrahydrofuran, are then added. After 30 minutes of stirring at –78°C, the mixture is allowed to warm to room temperature. 5 ml of 1N hydrochloric acid are added, and the mixture is extracted three times with in each case 20 ml of ethyl acetate. The combined organic phases are dried over magnesium sulfate and the solvent is

then removed under reduced pressure. The residue is purified by RP-HPLC. This gives 184 mg of 5-(2-{*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl-oxy}ethylidene)thiazolidine-2,4-dione as a white solid. $C_{22}H_{23}FN_2O_5S$ (446.01), MS (ESI): 447 ($M + H^+$).

Example XXIII

5-[2-[3-(5-Methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethylidene]-thiazolidine-2,4-dione

Analogously to Example XXII, [*cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde and thiazolidinedione gave the compound 5-[2-[*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyloxy}-ethylidene]thiazolidine-2,4-dione:



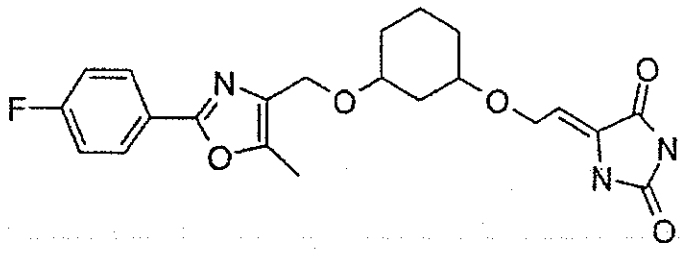
cis/racemate

$C_{23}H_{26}N_2O_5S$ (442.53), MS (ESI): 443 ($M + H^+$).

Example XXIV

5-[2-{*cis*-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}-ethylidene]imidazolidine-2,4-dione

Analogously to Example XXII, [3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde and hydantoin gave the compound 5-[2-{*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}-ethylidene]imidazolidine-2,4-dione:



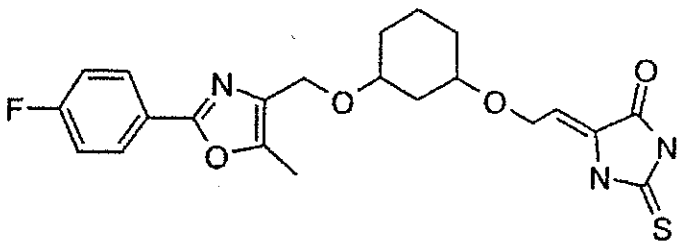
cis/racemate

$C_{22}H_{24}FN_3O_5$ (429.45), MS (ESI): 430 ($M + H^+$)

Example XXV

5-[2-{*cis*-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}-ethylidene]-2-thioxoimidazolidine-4-dione

Analogously to Example XXII, [*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl]acetaldehyde and 2-thioxoimidazolidin-4-one gave 5-[2-{*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy)cyclohexyloxy}-ethylidene)-2-thioxoimidazolidine-4-one:



cis/racemate

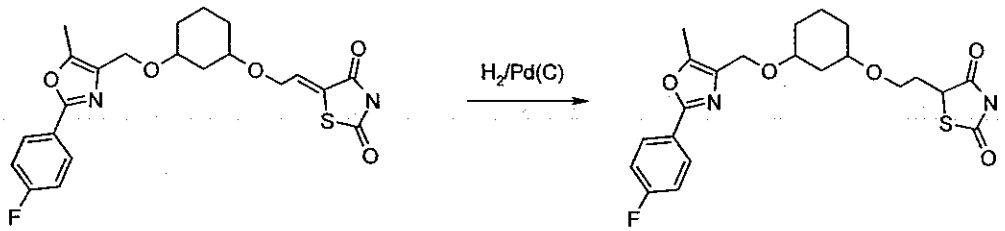
$C_{22}H_{24}FN_3O_4S$ (445.51), MS (ESI): 446 ($M + H^+$)

Example XXVI

5-(2-{*cis*-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}-ethyl)thiazolidine-2,4-dione

Hydrogenation of the compound 5-(2-{*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}ethylidene)thiazolidine-2,4-dione, mentioned in Example

Example XXII, with hydrogen gives the compound 5-(2-{*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl-oxy}ethyl)thiazolidine-2,4-dione:



cis/racemate cis/racemate

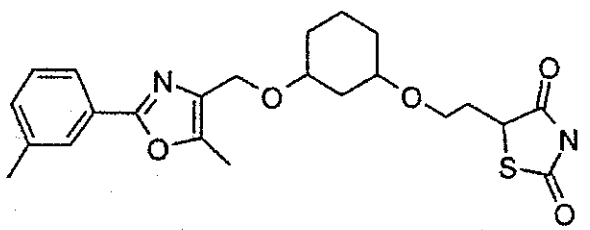
180 mg of the unsaturated 5-(2-{*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}ethylidene)thiazolidine-2,4-dione is dissolved in 10 ml of ethyl acetate, and 20 mg of palladuium-on-carbon are added. The mixture is then stirred at room temperature under a hydrogen pressure of 2 bar for 2 hours. The catalyst is filtered off, the solvent is removed under reduced pressure and the residue is purified by RP-HPLC. This gives 140 mg of the compound 5-(2-{*cis*-3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy}ethyl)thiazolidine-2,4-dione as a yellowish solid.

$C_{22}H_{25}FN_2O_5S$ (448.01), MS (ESI): 449 ($M + H^+$)

Example XXVII

5-{2-[(*cis*-3-(5-Methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}thiazol-idine-2,4-dione

As in Example XXVI, hydrogenation of the compound 5-[2-[*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethylidene]thiazolidine-2,4-dione, mentioned in Example Example XXIII, with hydrogen gives the compound 5-{2-[(*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}thiazolidine-2,4-dione:



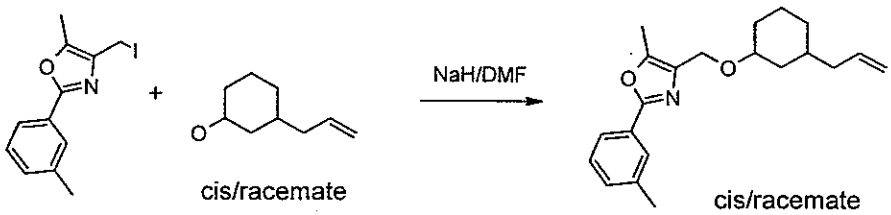
cis/racemate

$C_{23}H_{28}N_2O_5S$ (444.55), MS (ESI): 445 ($M + H^+$)

Example XXVIII

5-{2-[*cis*-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazol-idine-2,4-dione

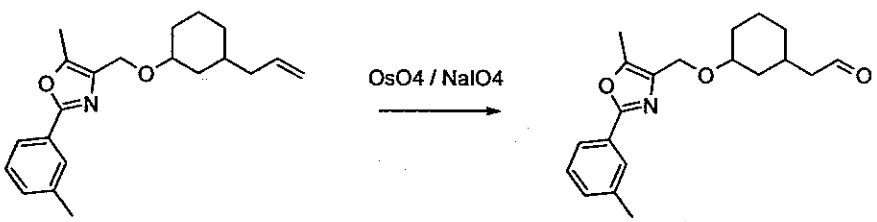
4-(*cis*-3-Allylcyclohexyloxymethyl)-2-(3-methylphenyl)-5-methyloxazole



cis/racemate cis/racemate

2 g of *cis*-3-allylcyclohexanol are dissolved in 30 ml of dimethylformamide, and 750 mg of sodium hydride (60% strength suspension in paraffin oil) are added. After 30 minutes, 6.7 g of 4-iodomethyl-5-methyl-2-(3-methylphenyl)oxazole, dissolved in 20 ml of dimethylformamide, are added dropwise. The mixture is stirred at room temperature for 1 hour. 200 ml of methy tert-buthyl ether are then added to the reaction mixture, and the mixture is washed three times with water. The organic phase is dried over magnesium sulfate and the solvent is then removed under reduced pressure. The residue is purified by RP-HPLC. This gives 1.56 g of 4-(*cis*-3-allylcyclohexyloxymethyl)-2-(3-methylphenyl)-5-methyloxazole as an oil. $C_{21}H_{27}NO_2$ (325.45), MS (ESI): 326 ($M + H^+$), R_f(n-heptane:ethylacetate = 2:1) = 0.28.

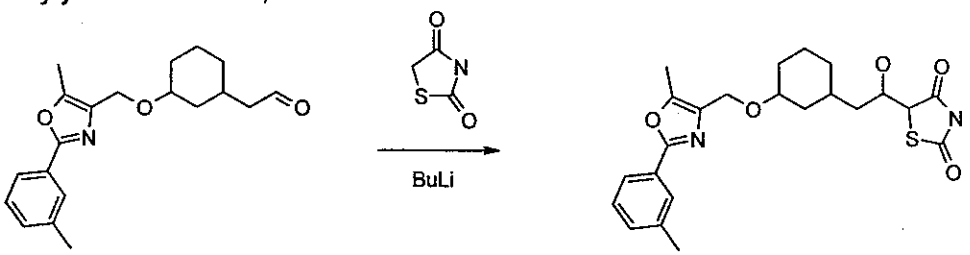
{*cis*-3-[2-(3-Methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}-acetaldehyde



cis/racemate cis/racemate

940 mg of 4-(*cis*-3-allylcyclohexyloxymethyl)-2-(3-methylphenyl)-5-methyloxazole are dissolved in 50 ml of diethyl ether, and 1.86 g of sodium periodate, dissolved in 50 ml of water, are added. At 0°C, 3 ml of an osmium tetroxide solution (2.5% by weight in tert-butanol) are added, and the mixture is stirred vigorously at room temperature. After 8 hours, 100 ml of methyl tert-butyl ether are added and the mixture is washed with a saturated sodium thiosulfate solution. The organic phase is dried over magnesium sulfate and the solvent is then removed under reduced pressure. The residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 4:1. This gives 270 mg of {*cis*-3-[2-(3-methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}acetaldehyde as a yellow-brown oil. $C_{20}H_{25}NO_3$ (327.43), MS (ESI): 328 ($M + H^+$), R_f(n-heptane:ethylacetate = 2:1) = 0.07.

5-{1-Hydroxy-2-[*cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]-ethyl}thiazolidine-2,4-dione



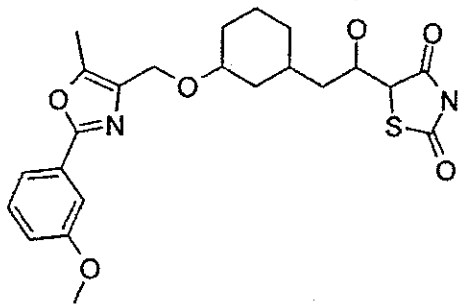
cis/racemate cis/diastereomer mixture

214 mg of thiazolidinedione are dissolved in 20 ml of tetrahydrofuran and, at –78°C, 1.4 ml of a 2.7 M solution of n-butyllithium in n-hexane are added. The mixture is stirred at –78°C for 30 minutes, and 500 mg of {*cis*-3-[2-(3-methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}acetaldehyde, dissolved in 10 ml of tetrahydrofuran, are then added. After 30 minutes of stirring at –78°C, the mixture is allowed to warm to room temperature. 20 ml of 1N hydrochloric acid are added and the mixture is extracted three times with in each case 50 ml of ethyl acetate. The combined organic phases are dried over magnesium sulfate and the solvent is then removed under reduced pressure. The residue is purified by RP-HPLC. This gives 420 mg of 5-{1-hydroxy-2-[*cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione as a white solid. $C_{23}H_{28}N_2O_5S$ (444.45), MS (ESI): 445 ($M + H^+$)

Example XXIX

5-(1-Hydroxy-2-{*cis*-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example XXVIII, {*cis*-3-[2-(3-methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}acetaldehyde and thiazolididione give the compound 5-(1-hydroxy-2-{*cis*-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



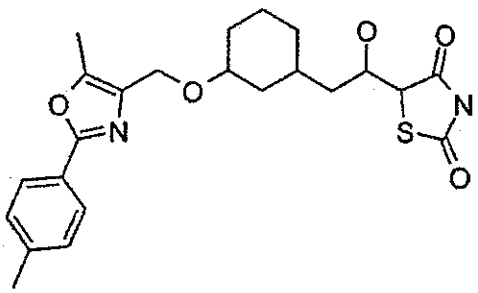
cis/diastereomer mixture

$C_{23}H_{28}N_2O_6S$ (460.55), MS (ESI): 461 ($M + H^+$).

Example XXX

5-{1-Hydroxy-2-[*cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)-cyclohexyl]-ethyl}thiazolidine-2,4-dione

Analogously to Example XXVIII, *cis*-[3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]acetaldehyde and thiazolididione gave the compound 5-{1-hydroxy-2-[*cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]-ethyl}thiazolidine-2,4-dione.

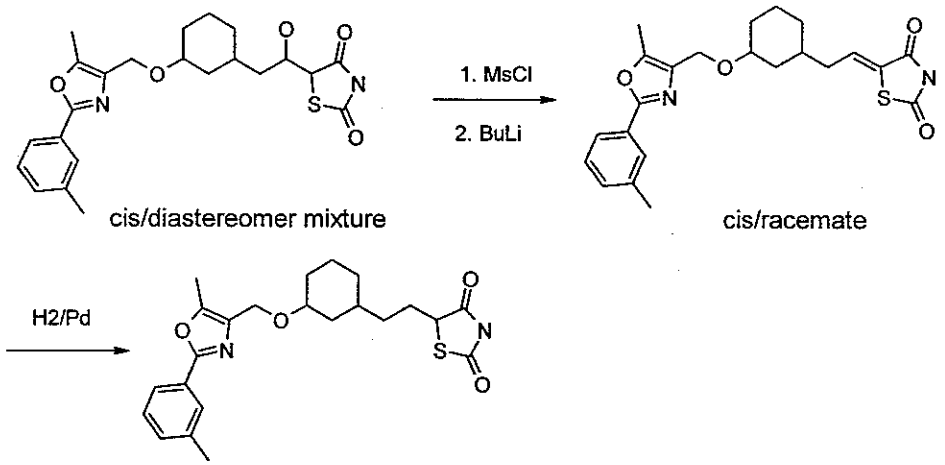


cis/diastereomer mixture

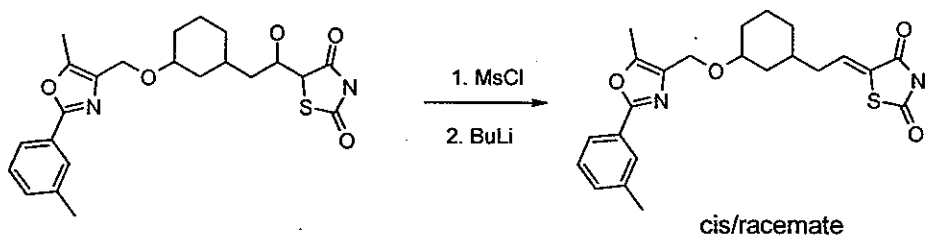
$C_{23}H_{28}N_2O_5S$ (444.55), MS (ESI): 445 ($M + H^+$).

Example XXXI

5-{2-[*cis*-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}-thiazolidine-2,4-dione



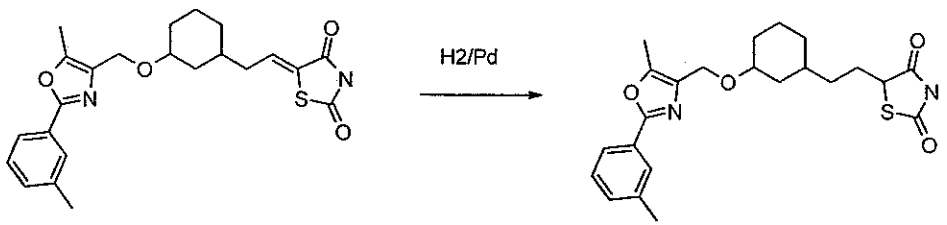
5-{2-[*cis*-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethylidene}-thiazolidine-2,4-dione.



344 mg of 5-{1-hydroxy-2-[*cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione are dissolved in 20 ml of dichloromethane, and 0.13 ml of triethylamine and and 0.12 ml of mesyl chloride are added. The mixture is stirred at room temperature for two hours, and another 0.13 ml of triethylamine and and 0.12 ml of mesyl chloride are added. The mixture is stirred at room temperature for 12 hours. 100 ml of dichloromethane are added, the mixture is washed with saturated sodium bicarbonate solution and dried over magnesium sulfate and the solvent is then removed under reduced pressure. The resulting residue is dissolved in 10 ml of tetrahydrofuran and, at –78°C, 0.22 ml of

a 2.7 M solution of n-butyllithium in n-hexane is added. The mixture is stirred at 0°C for 30 minutes, 20 ml of 1N hydrochloric acid are then added and the mixture is extracted three times with in each case 50 ml of ethyl acetate. The combined organic phases are dried over magnesium sulfate and the solvent is then removed under reduced pressure. The residue is purified by RP-HPLC. This gives 81 mg of 5-{2-[*Cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethylidene}thiazolidine-2,4-dione as a white solid. $C_{23}H_{26}N_2O_4S$ (426.54), MS (ESI): 427 ($M + H^+$).

5-{2-[*cis*-3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}-thiazolidine-2,4-dione



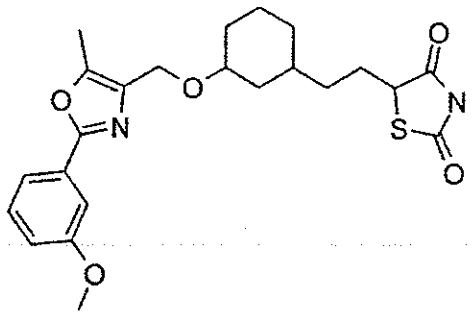
cis/racemate cis/racemate

81 mg of 5-{2-[*cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]-ethylidene}thiazolidine-2,4-dione are dissolved in 10 ml of ethyl acetate, and 10 mg of paladium (10% on activated carbon) are added. The mixture is stirred under an atmosphere of hydrogen (5 bar) for 9 hours. The catalyst is then filtered off through Celite and the filtrate is concentrated under reduced pressure. The residue is purified by RP-HPLC. This gives 60 mg of 5-{2-[*cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]-ethyl}thiazolidine-2,4-dione as a lyophilisate. $C_{23}H_{28}N_2O_4S$ (428.55), MS (ESI): 429 ($M + H^+$).

Example XXXII

5-(2-{*cis*-3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}-ethyl)thiazolidine-2,4-dione

Analogously to Example XXXI, 5-(1-hydroxy-2-{*cis*-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione gave the compound 5-(2-{*cis*-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione



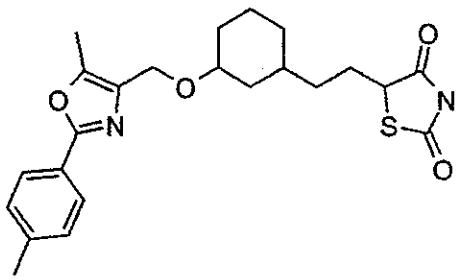
cis/racemate

$C_{23}H_{28}N_2O_5S$ (444.55), MS (ESI): 445 ($M + H^+$).

Example XXXIII

5-{2-[*cis*-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy]cyclohexyl]ethyl}-thiazolidine-2,4-dione

Analogously to Example XXXI, 5-{1-hydroxy-2-[*cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione gave the compound 5-{2-[*cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione.

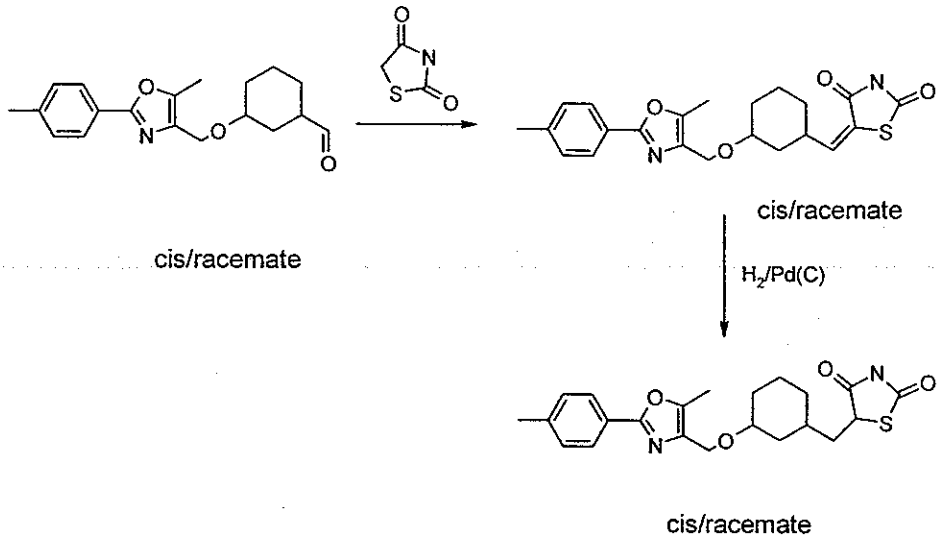


cis/racemate

$C_{23}H_{28}N_2O_4S$ (428.55), MS (ESI): 429 ($M + H^+$).

Example XXXIV

5-[1-[*cis*-3-(5-Methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyl]methylidene]-thiazolidine-2,4-dione



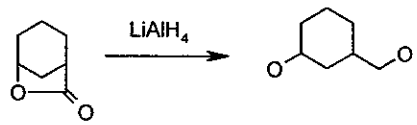
cis/racemate

cis/racemate

cis/racemate

cis/racemate

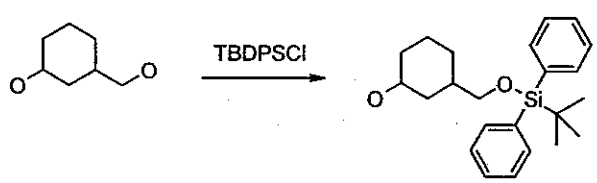
cis-3-Hydroxymethylcyclohexanol



cis/racemate cis/racemate

10 g of 6-oxabicyclo[3.2.1]octan-7-one are dissolved in 300 ml of tetrahydrofuran, and 160 ml of a 1M solution of lithium aluminum hydride in tetrahydrofuran are added with ice-cooling. After 30 minutes of stirring at room temperature, a saturated ammonium chloride solution is added and the pH is adjusted to neutral by addition of a 5% strength citric acid solution. The tetrahydrofuran is removed under reduced pressure and the residue is extracted three times with in each case 150 ml of ethyl acetate. The combined organic phases are dried over magnesium sulfate and the solvent is then removed under reduced pressure. This gives 10.5 g of *cis*-3-hydroxymethylcyclohexanol as a colorless oil. $C_7H_{14}O_2$ (130.13), Rf(ethyl acetate) = 0.14.

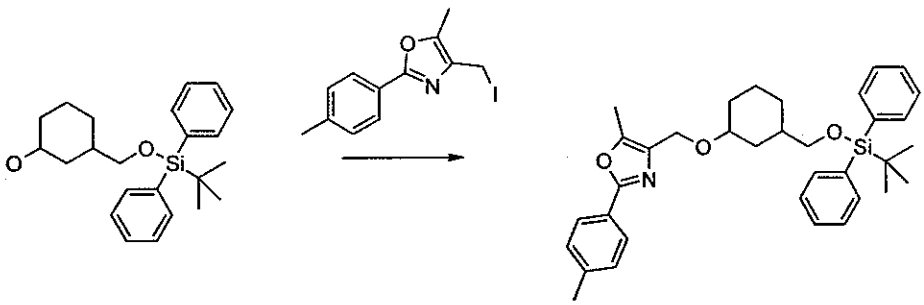
cis-3-(tert-Butyl-diphenyl-silanyloxymethyl)cyclohexanol



cis/racemate cis/racemate

10.5 g of *cis*-3-hydroxymethylcyclohexanol are dissolved in 300 ml of dimethylformamide, and 23 ml of tert-butyl-diphenyl-silanyl chloride, 8.0 g of imidazole and 200 mg of dimethylaminopyridine are added. The mixture is stirred at room temperature for 12 hours. The dimethylformamide is removed under reduced pressure and the residue is dissolved in 300 ml of ethyl acetate and washed five times with in each case 100 ml of water. The organic phase is dried over magnesium sulfate and the solvent is then removed under reduced pressure. This gives 27.0 g of cis-3-(tert-butyl-diphenyl-silanyloxymethyl)cyclohexanol as an oil. $C_{23}H_{32}O_2Si$ (368.6), Rf(n-heptane:ethyl acetate = 1:1) = 0.42.

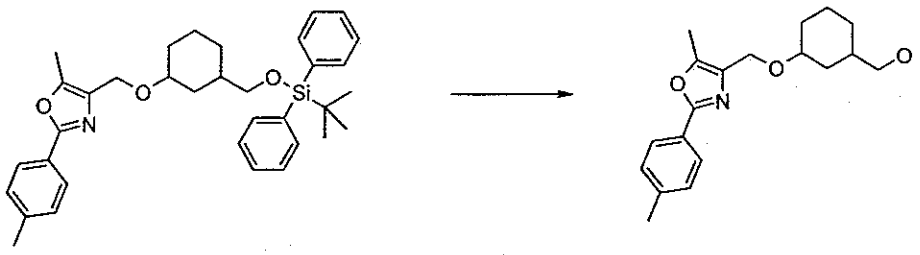
cis-3-(tert-Butyl-diphenyl-silanyloxymethyl)cyclohexyloxymethyl]-5-methyl-2-p-tolyloxazole



cis/racemate cis/racemate

6.4 g of *cis*-3-(tert-butyl-diphenyl-silanyloxymethyl)cyclohexanol and 6.5 g of 4-iodomethyl-5-methyl-2-p-tolyloxazole are dissolved in 200 ml of dimethylformamide, and 1 g of sodium hydride (60% strength suspension in mineral oil) is added. After 1 hour of stirring at room temperature, another 2 g of sodium hydride and 5 g of 4-iodomethyl-5-methyl-2-p-tolyloxazole are added. After 4 hours of stirring at room temperature, the reaction mixture is diluted by addition of 400 ml of ethyl acetate and washed five times with in each case 200 ml of water. The organic phase phase is dried over magnesium sulfate and the solvent is then removed under reduced pressure. The residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 10:1. This gives 6.8 g of 4-*cis*-3-(tert-butyl-diphenyl-silanyloxymethyl)cyclohexyloxymethyl]-5-methyl-2-p-tolyloxazole as an oil. $C_{35}H_{43}NO_3Si$ (553.28), Rf(n-heptane:ethyl acetate = 2:1) = 0.50.

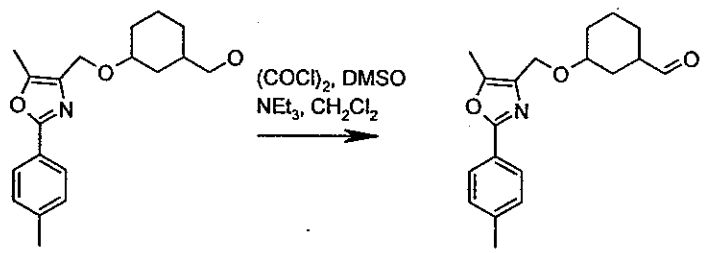
[(*cis*-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]methanol



cis/racemate cis/racemate

6.8 g of 4-*cis*-3-(tert-butyl-diphenyl-silanyloxymethyl)cyclohexyloxymethyl]-5-methyl-2-p-tolyloxazole are dissolved in 40 ml of tetrahydrofuran, and 40 ml of a 1M solution of tetrabutylammonium fluoride are added. The mixture is heated at 50°C for 1 hour and the solvent is then removed under reduced pressure and the resulting residue is purified on silica gel using the mobile phase n-heptane:ethyl acetate = 5:1=> 1:1. This gives 1.0 g of *cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]methanol as an oil. C19H25NO3 (315.42), Rf(n-heptane:ethyl acetate = 1:1) = 0.13.

cis-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbaldehyde

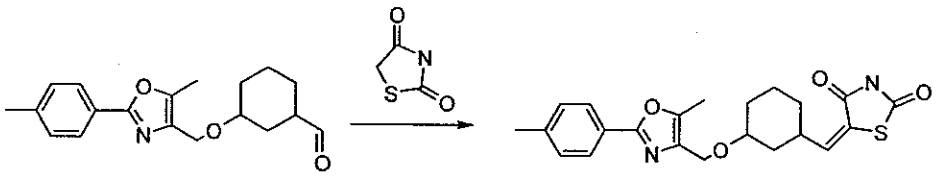


cis/racemate cis/racemate

At –78°C, 0.89 ml of DMSO in 1 ml of dichloromethane is added dropwise to 0.48 ml of oxalyl chloride in 15 ml of dichloromethane such that the temperature does not exceed –70°C. After the addition has ended, the solution is stirred at this temperature for 30 minutes. 1.5 g of *cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]methanol in 2 ml of dichloromethane are then added dropwise such that the temperature remains below -78°C. The solution is stirred at this temperature for 30 minutes. 3.2 ml of triethylamine are then added dropwise, the cooling bath is removed and the solution is warmed to 0°C. At this temperature, 10 ml of water are added and the mixture is stirred vigorously at room temperature. The aqueous phase is removed and extracted with dichloromethane. The combined organic phases are washed with saturated ammonium chloride solution, dried over magnesium sulfate and concentrated,

which gives 1.50 g of *cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbalde-hyde. $C_{19}H_{23}NO_3$ (313.40), LCMS (ESI): 314 (MH^+).

5-[1-[*cis*-3-(5-Methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyl]-methylidene]thiazolidine-2,4-dione



cis/racemate cis/racemate

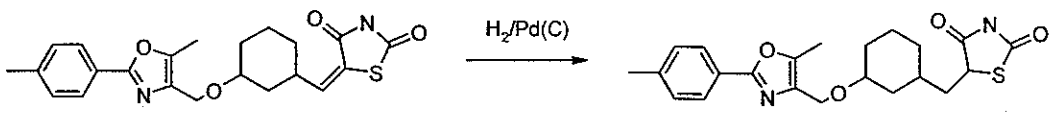
0.25 g of thiazolidinedione are initially charged in a three-necked flask, which had been dried by heating, dissolved in 15 ml of tetrahydrofuran and cooled to –78°C, and 2.4 ml of n-buthyllithium (1.6 M solution in n-hexane) are slowly added dropwise such that the internal temperature does not exceed –65°C. The solution is then warmed to room temperature, resulting in the color of the solution changing to yellow. The mixture is again cooled to -70°C, and 0.4 g of *cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexanecarbaldehyde – dissolved in 5 ml of tetrahydrofuran – is then added dropwise, and the reaction mixture is warmed to room temperature. The tertiary alcohol is formed as an adduct (reaction control (TLC and LCMS) M = 430 g/mol). Acidic work-up (5 ml 1N HCl) and extraction with 2 x 10 ml of ethyl acetate gives the desired elimination product after removal of the solvent under reduced pressure. The crude product is taken up in acetonitrile and the mother liquor is filtered off, giving 0.5 g of 5-[1-[*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyl]-methylidene]thiazolidine-2,4-dione as a white solid. $C_{22}H_{24}N_2O_4S$ (412.54), MS (ESI): 413 ($M + H^+$).

Example XXXV

5-[*cis*-3-(5-Methyl-2-tolyloxazol-4-ylmethoxy)cyclohexylmethyl]thiazolidine-2,4-dione

The compound 5-[1-[*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyl]-methylidene]thiazolidine-2,4-dione, mentioned in Example XXXIV, is obtained by

hydrogenation of the compound 5-[*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexylmethyl]thiazolidine-2,4-dione.



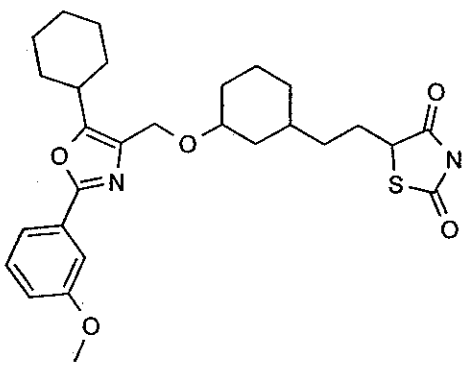
cis/racemate cis/racemate

0.35 g of 5-[1-[*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexyl]-methylidene]thiazolidine-2,4-dione is dissolved in 12 ml of a solvent mixture of ethyl acetate and methanol (3:1), and 20 mg of palladium-on-carbon are added. The mixture is then hydrogenated at room temperature under a hydrogen pressure of 3 bar for 2 hours. The catalyst is filtered off and the solvent is then removed under reduced pressure and the residue is taken up in acetonitrile. The product can be filtered off, giving 0.3 g of 5-[*cis*-3-(5-methyl-2-tolyloxazol-4-ylmethoxy)cyclohexylmethyl]thiazolidine-2,4-dione as a white solid. $C_{22}H_{26}N_2O_4S$ (414.52), MS (ESI): 415 ($M + H^+$).

Example XXXVI

5-(2-{(*cis*-3-[5-cyclohexyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-cyclohexyl-2-(3-methoxyphenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-cyclohexyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione.



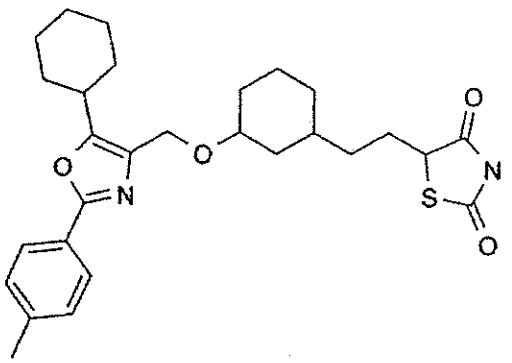
cis/racemate

C28H36N2O5S (512.67), MS(ESI): 513 ($M+H^+$)

Example XXXVII

5-(2-{(*cis*-3-[5-cyclohexyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-cyclohexyl-2-(4-methylphenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-cyclohexyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione.



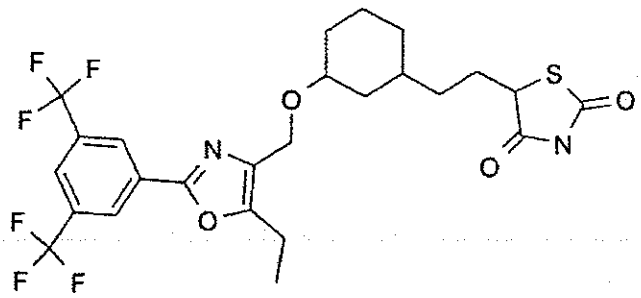
cis/racemate

C28H36N2O4S (496.67), MS(ESI): 497 ($M+H^+$).

Example XXXVIII

5-(2-{(*cis*-3-[5-ethyl-2-(3,5-bis-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(3,5-bis-trifluoromethylphenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-ethyl-2-(3,5-bis-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



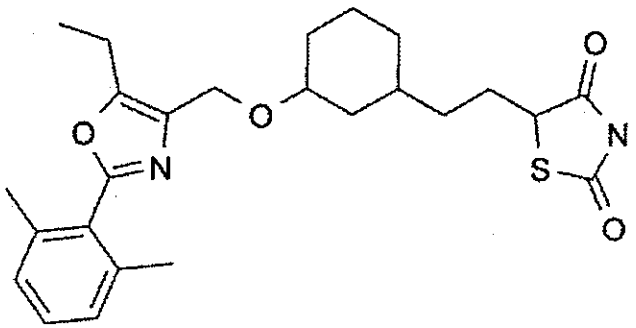
cis/racemate

C25H26F6N2O4S (564.55), MS(ESI): 565 ($M+H^+$)

Example XXXIX

5-(2-{(*cis*-3-[5-ethyl-2-(2,6-bis-dimethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(2,6-dimethylphenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-ethyl-2-(2,6-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



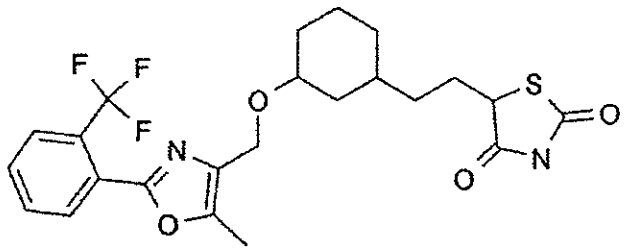
cis/racemate

C25H32N2O4S (456.64), MS(ESI): 457 ($M+H^+$).

Example XL

5-(2-{(*cis*-3-[5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-methyl-2-(2-trifluoromethylphenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-methyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



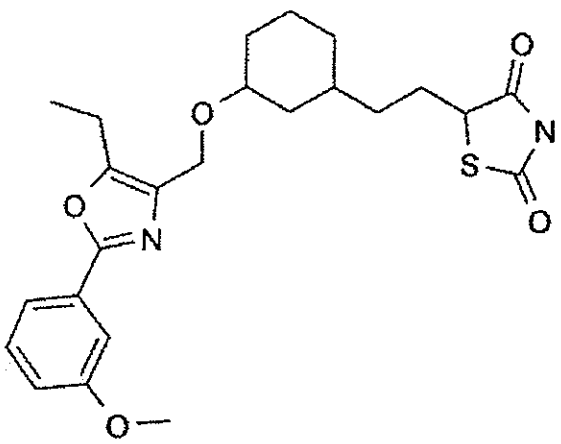
cis/racemate

C23H25F3N2O4S (482.53), MS(ESI): 483 ($M+H^+$).

Example XLI

5-(2-{(*cis*-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(3-methoxyphenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-ethyl-2-(3-methoxyphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



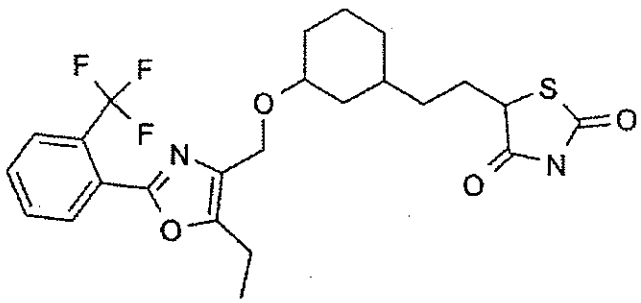
cis/racemate

C24H30N2O5S (458.58), MS(ESI): 459 ($M+H^+$).

Example XLII

5-(2-{(*cis*-3-[5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(2-trifluorophenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-ethyl-2-(2-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



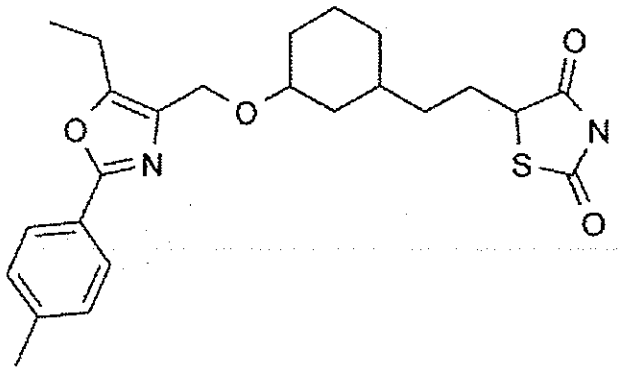
cis/racemate

C24H27F3N2O4S (496.55), MS(ESI): 497 ($M+H^+$).

Example XLIII

5-{2-[3-(5-ethyl-2-p-tolyloxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(4-methylphenyl)oxazole gave the compound 5-{2-[*cis*-3-(5-ethyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}-thiazolidine-2,4-dione.



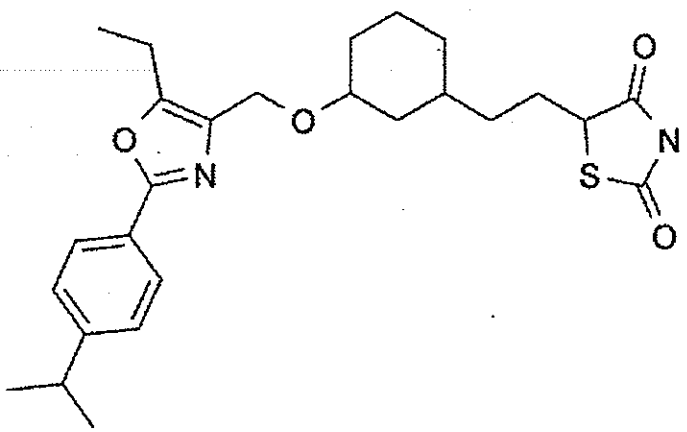
cis/racemate

C24H30N2O4S (442.58), MS(ESI): 443 ($M+H^+$).

Example XLIV

5-(2-{(*cis*-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(4-isopropylphenyl)oxazole gave the compound 5-(2-{*cis*-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



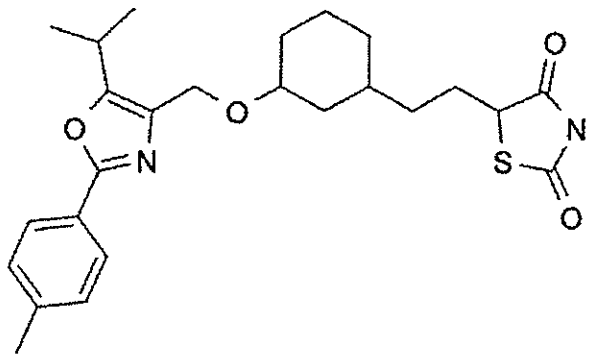
cis/racemate

C26H34N2O4S (470.64), MS(ESI): 471 ($M+H^+$).

Example XLV

5-(2-{(*cis*-3-[5-isopropyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(4-isopropylphenyl)oxazole gave the compound 5-(2-{*cis*-3-[5-isopropyl-2-(4-methylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



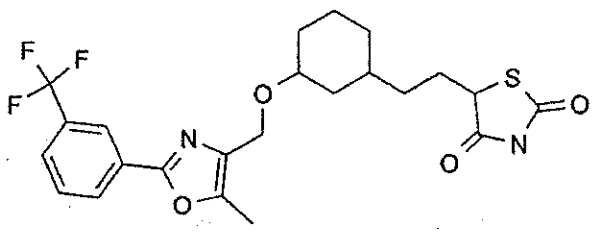
cis/racemate

C25H32N2O4S (456.61), MS(ESI): 457 ($M+H^+$).

Example XLVI

5-(2-{(*cis*-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *cis*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-methyl-2-(3-trifluoromethylphenyl)oxazole gave the compound 5-(2-{(*cis*-3-[5-methyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



cis/racemate

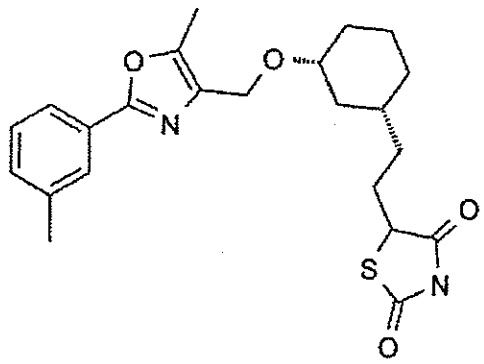
C23H25F3N2O4S (482.53), MS(ESI): 483 ($M+H^+$).

Example XLVII

The compound 5-{2-[*cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethylidene}thiazolidine-2,4-dione from Example **XXXI** was separated by chromatography on a chiral phase into the compounds 5-{2-[*(1S,3S)*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethylidene}thiazolidine-2,4-dione and 5-{2-[*(1R,3R)*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]ethylidene}thiazolidine-2,4-dione.

5-{2-[*(1R,3R)*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]-ethylidene}thiazolidine-2,4-dione:

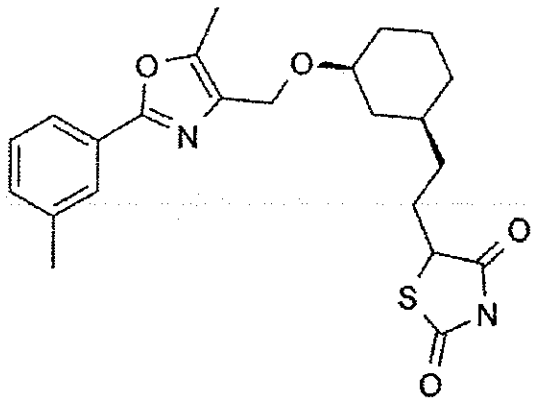
chiral



$C_{23}H_{28}N_2O_4S$ (428.55), MS(ESI): 429 ($M+H^+$).

5-{2-[*(1S,3S)*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl]-ethylidene}thiazolidine-2,4-dione:

chiral



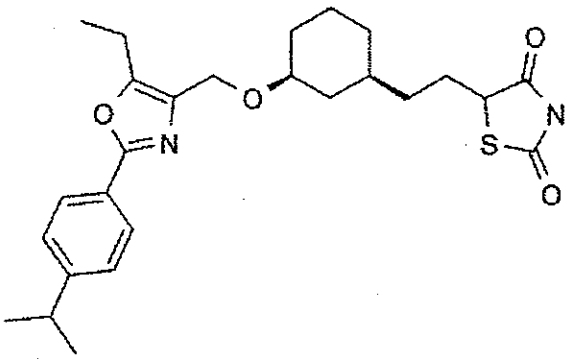
$C_{23}H_{28}N_2O_4S$ (428.55), MS(ESI): 429 ($M+H^+$).

Example XLVIII

The compound 5-(2-{*cis*-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione from Example **XLIV** was separated by chromatography on a chiral phase into the compounds 5-(2-{*(1s,3S)*-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione and 5-(2-{(1R,3R)-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.

5-(2-{*(1s,3S)*-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione:

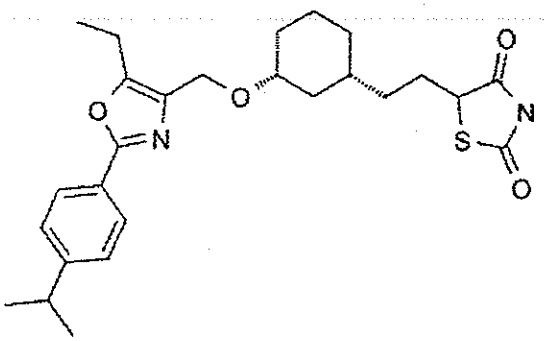
chiral



C26H34N2O4S (470.64), MS(ESI): 471 ($M+H^+$).

5-(2-{(1R,3R)-3-[5-ethyl-2-(4-isopropylphenyl)oxazol-4-ylmethoxy]cyclo-hexyl}ethyl)thiazolidine-2,4-dione:

chiral



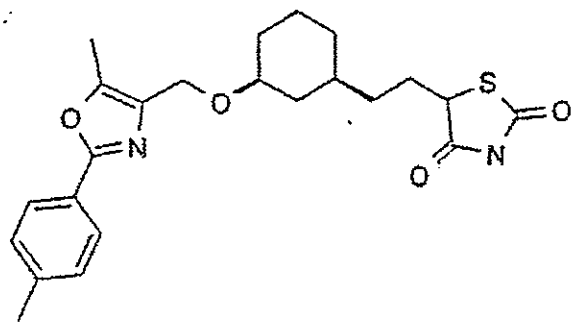
C26H34N2O4S (470.64), MS(ESI): 471 ($M+H^+$).

Example XLIX

The compound 5-{2-[*cis*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclo-hexyl]ethyl}thiazolidine-2,4-dione from Example **XXXIII** was separated by chromatography on a chiral phase into the compounds 5-{2-[*(1S,3S)*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione and 5-{2-[*(1R,3R)*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione.

5-{2-[*(1S,3S)*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}-thiazolidine-2,4-dione

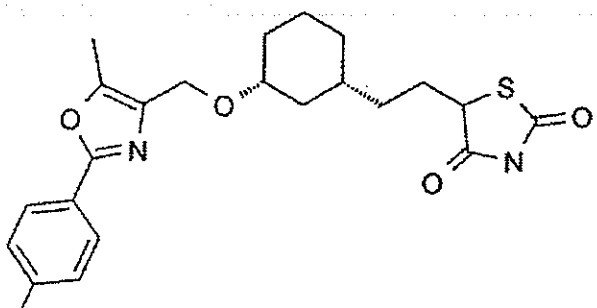
Chiral



$C_{23}H_{28}N_2O_4S$ (428.55), MS(ESI): 429 ($M+H^+$).

5-{2-[*(1R,3R)*-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]ethyl}-thiazolidine-2,4-dione

chiral

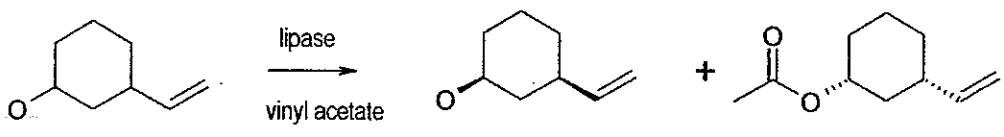


$C_{23}H_{28}N_2O_4S$ (428.55), MS(ESI): 429 ($M+H^+$).

Example L

5-(2-{(1S,3S)-3-[2-(3,4-dimethylphenyl)-5-ethyloxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione

((1S,3S)-3-allylcyclohexanol



cis/rac

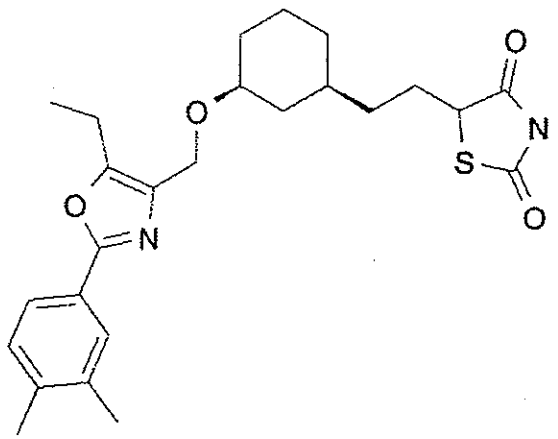
50 g of *cis*-3-allylcyclohexanol are dissolved in 200 ml vinyl acetate, and 3 g of lipase (Novozym) added. The mixture is stirred at RT until a conversion of 58% is reached (the conversion is monitored by GC). The enzyme is filtered off and the vinyl acetate is removed under reduced pressure. The resulting residue is purified chromatographically on silica gel. This gives 17 g of *(1S, 3S)*-3-allylcyclohexanol as a colorless oil.

C8H14O (126.20), Rf (n-heptane:ethyl acetate = 1:1) = 0.46.

5-(2-{(1S,3S)-3-[2-(3,4-dimethylphenyl)-5-ethyloxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(3,4-dimethylphenyl)oxazol gave the compound 5-(2-{(1S,3S)-3-[2-(3,4-dimethylphenyl)-5-ethyloxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione

chiral

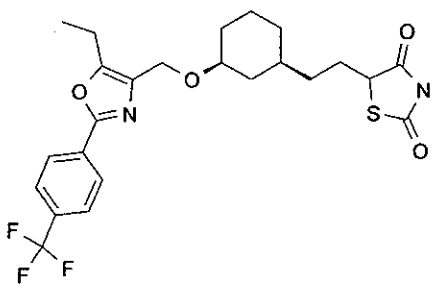


$C_{25}H_{32}N_2O_4S$ (456.61), MS(ESI): 457 ($M+H^+$).

Example LI

5-(2-{(1S,3S)-3-[5-Ethyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI**, *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(4-trifluoromethylphenyl)oxazole gave the compound 5-(2-{(1S,3S)-3-[5-ethyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



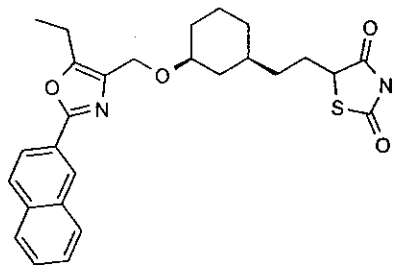
C24H27F3N2O4S (496.55), MS(ESI): 497 ($M+H^+$).

Example LII

5-{2-[(1S,3S)-3-(5-Ethyl-2-naphthalen-2-yl-oxazol-4-ylmethoxy)cyclohexyl]ethyl}-thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allyl-cyclohexanol, thiazolidinedione and 5-ethyl-4-iodomethyl-2-naphthalen-2-yloxazole gave the compound 5-{2-[(1S,3S)-3-(5-ethyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione.

chiral

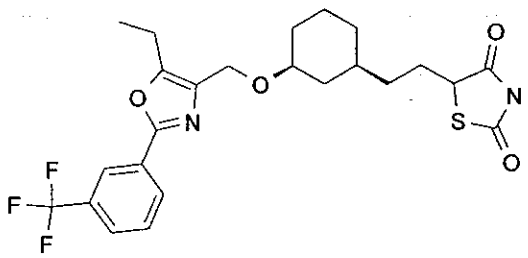


C27H30N2O4S (478.62), MS(ESI): 479 ($M+H^+$).

Example LIII

5-(2-{(1S,3S)-3-[5-Ethyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(3-trifluoromethylphenyl)oxazole gave the compound 5-(2-{(1S,3S)-3-[5-ethyl-2-(3-trifluoromethylphenyl)-oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.



C24H27F3N2O4S (496.55), MS(ESI): 497 ($M+H^+$).

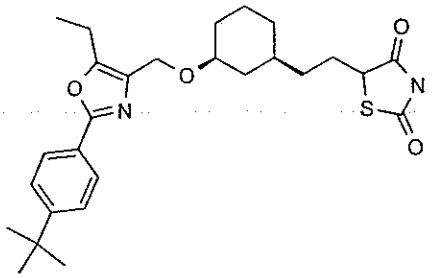
Beispiel LIV

5-(2-{(1S,3S)-3-[5-Ethyl-2-(4-tert-butylphenyl)oxazol-4-ylmethoxy]cyclohexyl}-ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(4-tert-butylphenyl)oxazole gave the

compound 5-(2-{(1S,3S)-3-[5-ethyl-2-(4-tert-butylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.

chiral



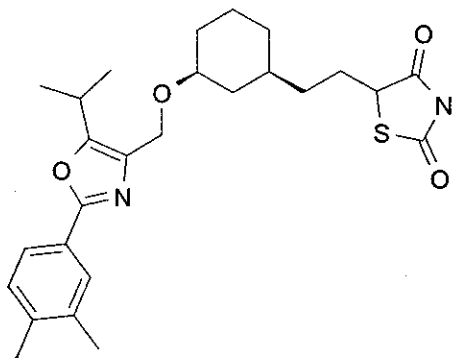
C27H36N2O4S (484.66), MS(ESI): 485 ($M+H^+$).

Example LV

5-(2-{(1S,3S)-3-[5-Isopropyl-2-(3,4-dimethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-isopropyl-2-(3,4-dimethylphenyl)oxazole gave the compound 5-(2-{(1S,3S)-3-[5-isopropyl-2-(3,4-dimethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.

chiral

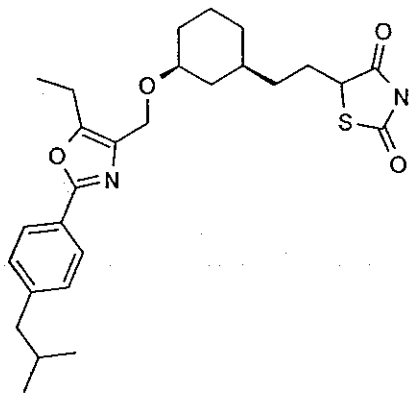


C26H34N2O4S (470.64), MS(ESI): 471 ($M+H^+$).

Example LVI

5-(2-{(1S,3S)-3-[5-Ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)-thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-ethyl-2-(4-isobutylphenyl)oxazole gave the compound 5-(2-{(1S,3S)-3-[5-ethyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidin-2,4-dione.



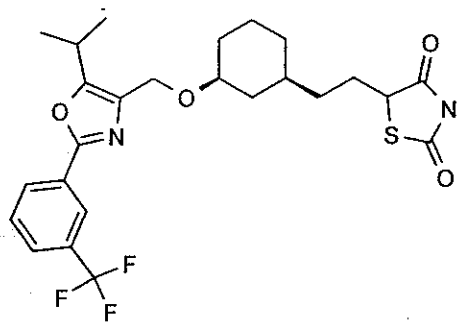
C27H36N2O4S (484.66), MS(ESI): 485 ($M+H^+$).

Example LVII

5-(2-{(1S,3S)-3-[5-Isopropyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-isopropyl-2-(3-trifluormethylphenyl)oxazole gave the compound 5-(2-{(1S,3S)-3-[5-isopropyl-2-(3-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.

chiral



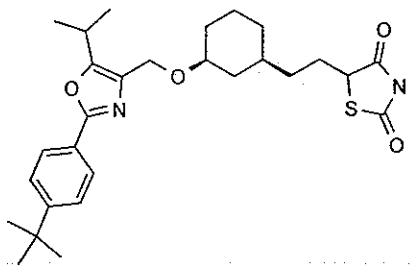
C25H29F3N2O4S (510.58), MS(ESI): 511 ($M+H^+$).

Example LVIII

5-(2-{(1S,3S)-3-[5-Isopropyl-2-(4-tert-butylphenyl)oxazol-4-ylmethoxy]cyclohexyl}-ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-isopropyl-2-(4-tert-butylphenyl)oxazol gave the following compound 5-(2-{(1S,3S)-3-[5-isopropyl-2-(4-tert-butylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.

chiral



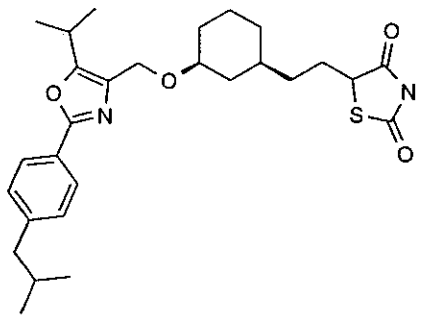
C28H38N2O4S (498.69), MS(ESI): 499 ($M+H^+$).

Example LIX

5-(2-{(1S,3S)-3-[5-Isopropyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexyl}-ethyl)thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-isopropyl-2-(4-isobutylphenyl)oxazole gave the compound 5-(2-{(1S,3S)-3-[5-isopropyl-2-(4-isobutylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.

chiral



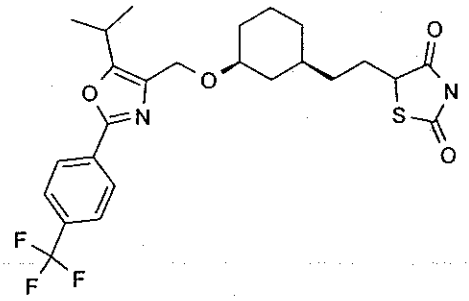
C28H38N2O4S (498.69), MS(ESI): 499 ($M+H^+$).

Example LX

5-(2-{(1S,3S)-3-[5-Isopropyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]-cyclohexyl}ethyl)thiazolidine- 2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 4-iodomethyl-5-isopropyl-2-(4-trifluoromethylphenyl)oxazole gave the compound 5-(2-{(1S,3S)-3-[5-isopropyl-2-(4-trifluoromethylphenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)thiazolidine-2,4-dione.

chiral



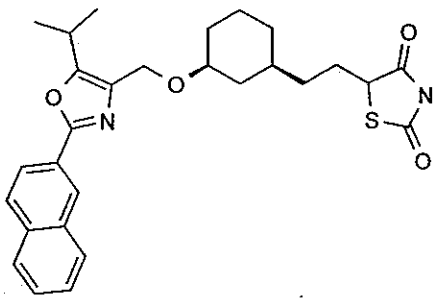
C25H29F3N2O4S (510.58), MS(ESI): 511 ($M+H^+$).

Example LXI

5-{2-[(1S,3S)-3-(5-Isopropyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclohexyl]-ethyl}thiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *(1S,3S)*-3-allylcyclohexanol, thiazolidinedione and 5-isopropyl-4-iodomethyl-2-naphthalen-2-yloxazole gave the compound 5-{2-[(1S,3S)-3-(5-isopropyl-2-naphthalen-2-yloxazol-4-ylmethoxy)cyclohexyl]ethyl}thiazolidine-2,4-dione.

chiral

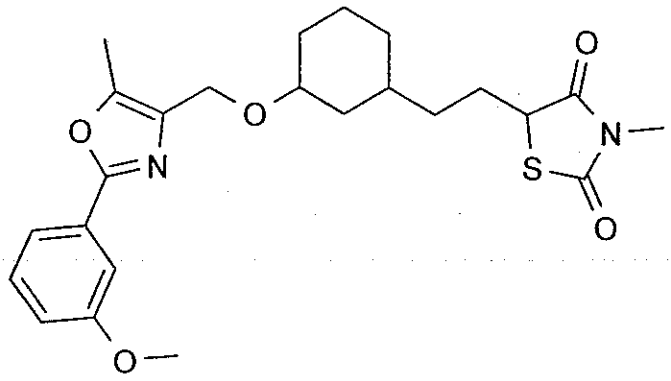


C28H32N2O4S (492.64), MS(ESI): 493 ($M+H^+$).

Example LXII

5-(2-{cis-3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *cis*-3-allylcyclohexanol, 3-methylthiazolidinedione and 4-iodomethyl-5-methyl-2-(3-methoxyphenyl)oxazole gave the compound 5-(2-{cis-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione.



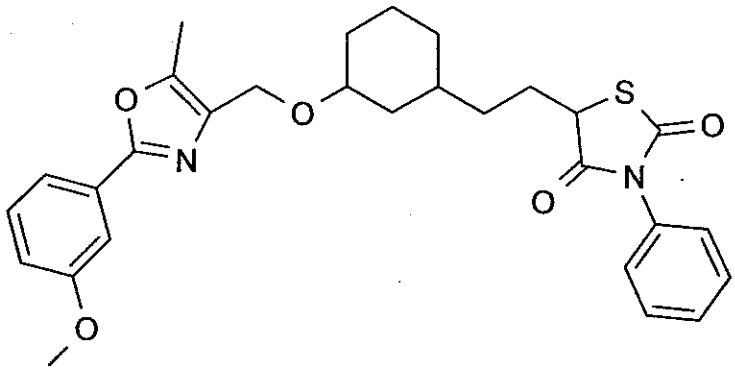
cis/racemate

C24H30N2O5S (458.58), MS(ESI): 459 ($M+H^+$).

Beispiel LXIII

5-(2-{cis-3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-phenylthiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *cis*-3-allylcyclohexanol, 3-phenylthiazolidinedione and 4-iodomethyl-5-methyl-2-(3-methoxyphenyl)oxazole gave the compound 5-(2-{cis-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-phenylthiazolidine-2,4-dione.



cis/racemate

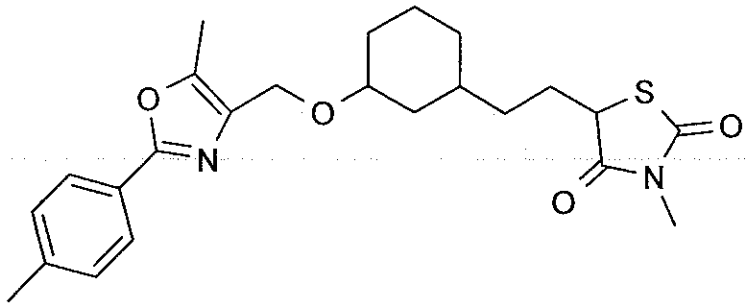
C29H32N2O5S (520.65), MS(ESI): 521 ($M+H^+$).

Example LXIV

5-(2-{cis-3-[2-(4-Methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *cis*-3-allylcyclohexanol, 3-methylthiazolidinedione and 4-iodomethyl-5-methyl-2-(4-methylphenyl)oxazole

gave the compound 5-(2-{cis-3-[2-(4-methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione.



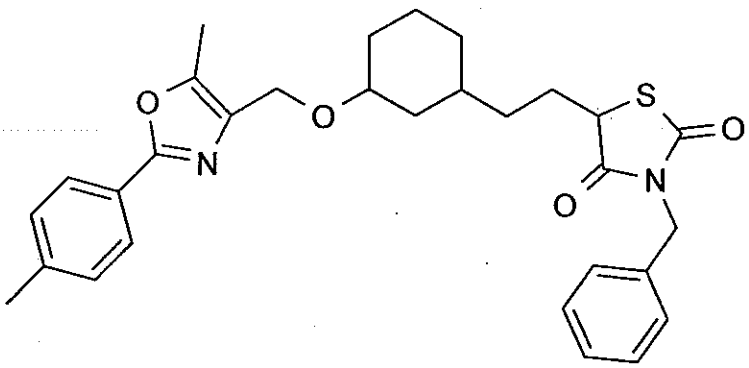
cis/racemate

C24H30N2O4S (442.58), MS(ESI): 443 ($M+H^+$).

Example LXV

5-(2-{cis-3-[2-(4-Methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-benzylthiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *cis*-3-allylcyclohexanol, 3-benzylthiazolidinedione and 4-iodomethyl-5-methyl-2-(4-methylphenyl)oxazole gave the compound 5-(2-{cis-3-[2-(4-methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-benzylthiazolidine-2,4-dione.



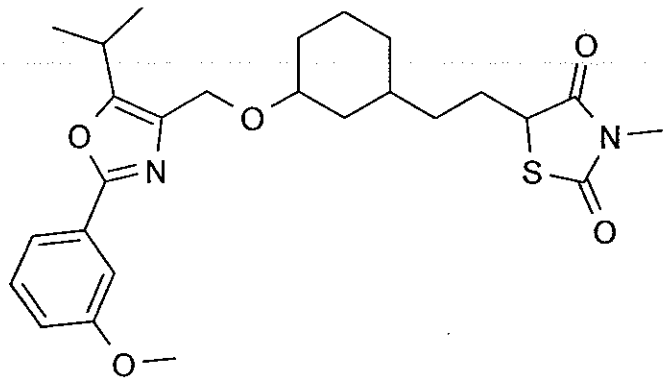
cis/racemate

C30H34N2O4S (518.58), MS(ESI): 519 ($M+H^+$).

Example LXVI

5-(2-{cis-3-[2-(3-Methoxyphenyl)-5-isopropyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *cis*-3-allylcyclohexanol, 3-methylthiazolidinedione and 4-iodomethyl-5-isopropyl-2-(3-methoxyphenyl)-oxazole gave the compound 5-(2-{cis-3-[2-(3-methoxyphenyl)-5-isopropyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione.



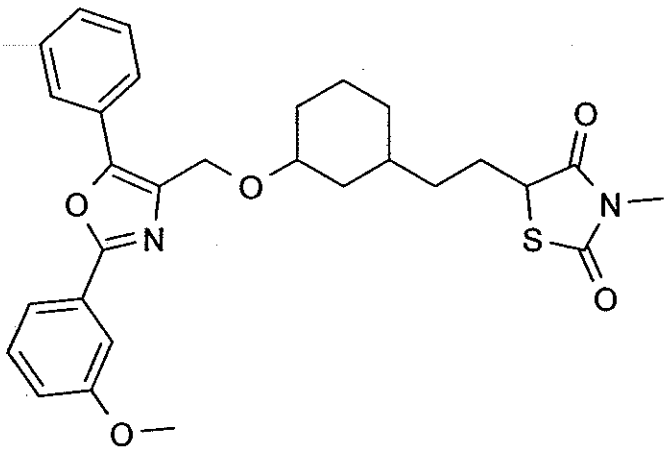
cis/racemate

$C_{26}H_{34}N_2O_5S$ (486.64), MS(ESI): 487 ($M+H^+$).

Example LXVII

5-(2-{cis-3-[2-(3-Methoxyphenyl)-5-phenyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *cis*-3-allylcyclohexanol, 3-methylthiazolidinedione and 4-iodomethyl-5-phenyl-2-(3-methoxyphenyl)oxazole gave the compound 5-(2-{cis-3-[2-(3-methoxyphenyl)-5-phenyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-methylthiazolidine-2,4-dione.



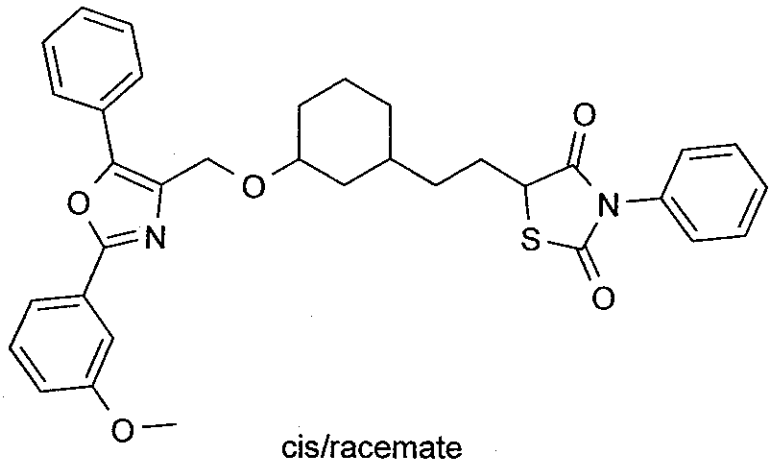
cis/racemate

$C_{29}H_{32}N_2O_5S$ (520.65), MS(ESI): 521 ($M+H^+$).

Example LXVIII

5-(2-{cis-3-[2-(3-Methoxyphenyl)-5-phenyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-phenylthiazolidine-2,4-dione

Analogously to Example **XXVIII** and Example **XXXI** *cis*-3-allylcyclohexanol, 3-phenylthiazolidinedione and 4-iodomethyl-5-phenyl-2-(3-methoxyphenyl)oxazole gave the compound 5-(2-{cis-3-[2-(3-methoxyphenyl)-5-phenyloxazol-4-ylmethoxy]cyclohexyl}ethyl)-3-phenylthiazolidine-2,4-dione.

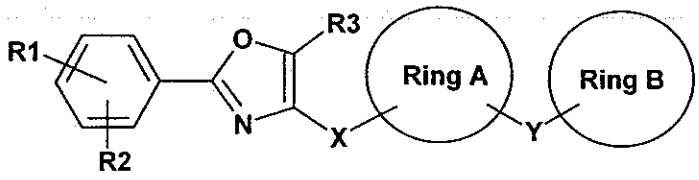


cis/racemate

$C_{34}H_{34}N_2O_5S$ (582.72), MS(ESI): 583 ($M+H^+$).

Patent Claims:

1. A compound of the formula I



I

in which

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

R1, R2 independently of one another are H, F, Br, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, SCF_3, SF_5, OCF_2-CHF_2, O-phenyl, OH, or NO_2; or

R_1 and R_2 in juxtaposition together with the phenyl ring are a fused, unsaturated or completely or partially saturated bicyclic $(C_9$-$C_{12})$-aryl or $(C_9$-$C_{11})$-heteroaryl ring system;

R3 is H, CF_3, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, $(C_3$-$C_8)$-cycloalkyl or phenyl;

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

Y is $(C_1$-$C_6)$-alkanediyl or $(C_1$-$C_6)$-alkenediyl, where one or more CH_2 groups in the alkanediyl or alkenediyl group may be replaced by O, CO, S, SO or SO_2 and alkanediyl or alkenediyl may be unsubstituted or substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy or tetrazole; or

pyrrolidin-2-one which additionally contains a nitrogen or sulfur atom in the ring and is substituted by oxo or thioxo and may be substituted on the nitrogen atom by R4;

R4 is (C_1-C_6)-alkyl, phenyl, benzyl;

and its physiologically acceptable salts.

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

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

R1, R2 independently of one another are H, F, Br, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, SCF_3, SF_5, OCF_2-CHF_2, O-phenyl, OH or NO_2; or

R1 and R2 in juxtaposition together with the phenyl ring are a fused, unsaturated or completely or partially saturated bicyclic (C_9-C_{12})-aryl or (C_9-C_{11})-heteroaryl ring system;

R3 is H, CF_3, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl or phenyl;

X is (C_1-C_6)-alkanediyl, where one carbon atom in the alkanediyl group may be replaced by an oxygen atom;

Y is (C_1-C_6)-alkanediyl or (C_1-C_6)-alkenediyl, where one or two CH_2 groups in the alkanediyl or alkenediyl group may be replaced by O, CO, S, SO or SO_2 and alkanediyl or alkenediyl may be unsubstituted or substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or tetrazole; or
pyrrolidin-2-one which additionally contains a nitrogen or sulfur atom in the 4-position and is substituted by oxo or thioxo in the 5-position and may be substituted on the N1-atom by R4;

R4 is $(C_1\text{-}C_6)$-alkyl, phenyl, benzyl;

and its physiologically acceptable salts.

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

Ring A is $(C_3\text{-}C_8)$-cycloalkanediyl in which one carbon atom is replaced by an oxygen atom;

R1, R2 independently of one another are H, F, Br, CF_3, OCF_3, $(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl, SCF_3, SF_5, $OCF_2\text{-}CHF_2$, O-phenyl, OH or NO_2; or

R1 and R2 in juxtaposition together with the phenyl ring are a fused, unsaturated or completely or partially saturated bicyclic $(C_9\text{-}C_{12})$-aryl or $(C_9\text{-}C_{11})$-heteroaryl ring system;

R3 is H, CF_3, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_8)$-cycloalkyl or phenyl;

X is $(C_1\text{-}C_6)$-alkanediyl, where the C1 carbon atom is replaced by an oxygen atom;

Y is $(C_1\text{-}C_6)$-alkanediyl or $(C_1\text{-}C_6)$-alkenediyl, where one or two CH_2 groups in the alkanediyl or alkenediyl group may be replaced by O, CO or SO_2 and alkanediyl or alkenediyl may be substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkoxy or tetrazole; or
pyrrolidin-2-one which additionally contains a nitrogen or sulfur atom in the 4-position and is substituted by oxo or thioxo in the 5-position and may be substituted on the N1-atom by R4;

R4 is $(C_1\text{-}C_6)$-alkyl, phenyl, benzyl;

and its physiologically acceptable salts.

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

Ring A is cyclohexane-1,3-diyl;

R1, R2 are independently of one another H, F, Br, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, SCF_3, SF_5, OCF_2-CHF_2, O-phenyl, OH, NO_2; or

R1 and R2 in juxtaposition together with the phenyl ring are a fused unsaturated bicyclic $(C_9$-$C_{10})$-aryl or $(C_9$-$C_{10})$-heteroaryl ring system;

R3 is H, CF_3, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, phenyl;

X is CH_2-O;

Y is $(C_1$-$C_4)$-alkanediyl, O-$(C_1$-$C_4)$-alkanediyl, $(C_1$-$C_4)$-alkenediyl, O-$(C_1$-$C_4)$-alkenediyl, O-SO_2 or O-CO, where alkanediyl may be substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy or tetrazole; or thiazolidine-1,4-dione which may be substituted on the N3-atom by R4;

R4 is $(C_1$-$C_6)$-alkyl, phenyl, benzyl;

and its physiologically acceptable salts.

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

Ring A is cyclohexane-1,3-diyl;

R1, R2 independently of one another are H, F, Br, CF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl; or

R_1 and R_2 together with the phenyl ring are naphthyl;

R3 is $(C_1$-$C_6)$-alkyl, $(C_5$-$C_6)$-cycloalkyl, phenyl;

X is CH_2-O;

Y is (C_1-C_4)-alkanediyl, O-(C_1-C_4)-alkanediyl, (C_1-C_4)-alkenediyl, O-(C_1-C_4)-alkenediyl, O-SO_2, O-CO, where alkanediyl may be substituted by OH;

Ring B is phenyl which may be mono- or disubstituted by NO_2, Cl, CN, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy or tetrazole; or

Ring B is thiazolidine-2,4-dione which may be substituted on the N3-atom by R4;

R4 is (C_1-C_6)-alkyl, phenyl, benzyl;

and its physiologically acceptable salts.

6. A compound of the formula I as claimed in any of claims 1 to 5, in which

R2 is hydrogen and
R1 is attached in the meta- or para-position.

7. A compound of the formula I as claimed in any of claims 1 to 6, in which

Y is $-CH_2-CH_2-$.

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

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

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

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

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

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

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

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

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

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

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

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