Description

1,3-Substituted cycloalkyl derivatives containing acidic, mainly heterocyclic groups, corresponding production method and use of said derivatives as medicaments

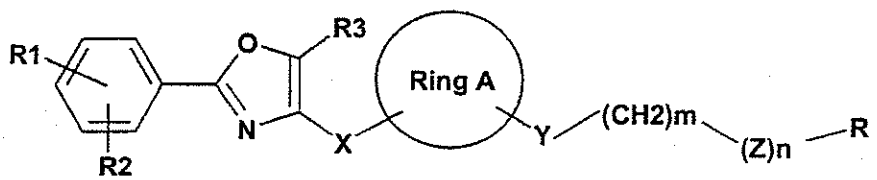
The invention relates to 1,3-substituted cycloalkyl derivatives having acidic, mostly heterocyclic groups, and to their physiologically acceptable salts and physiologically functional derivatives.

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

It was an object of the invention to provide compounds which allow a therapeutically exploitable, modulation of the 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 PPARalpha and PPARgamma, 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, (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, Cl, SF_5, S-(C_1-C_6)-alkyl, CF_3, OCF_3, (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, SCF_3, phenoxy, OCF_2CHF_2, OCF_2CF_3, (C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, O(C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, benzyloxy;

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

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

Y is S, O, a bond;

m is 1 to 3;

n is 0 or 1;

Z is O, S, CO or CO-NH;

R is H, OH, CH_2-CO-NH-OH, CH_2-CO-NH-(C_1-C_6)-alkyl, CH_2-CO-NH-(C_1-C_6)-alkoxy, NR4R5 or a 5- to 12-membered mono or bicyclic unsaturated, partially unsaturated or saturated ring which may contain one to four heteroatoms from the group consisting of N, O and S and which may be benzo-fused, where the 5- to 12-membered ring may further substituents such as F, Cl, Br, CN, SH, COOH, (C_1C_4)-alkyl, (C_1-C_6)-alkoxy, SO_2-(C_1-C_4)-alkyl, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-phenyl, phenoxy, $NHSO_2CF_3$ or $B(OH)_2$;

R4 is H, (C_1-C_6)-alkyl;

R5 is OH, NH_2, SO_2-CF_3, SO_2-phenyl-CF_3, CO-CF_3, (C_1-C_6)-alkoxy, phenyl which may be substituted by CH_3 and COOH;

R4 and R5 together with the nitrogen atom that carries them form a 5-membered aromatic heterocycle which in turn may be fused to an aromatic 5- to 7-membered ring which may have one to four nitrogen atoms and which may be substituted by: F,

Cl, Br, CF_3, OCF_3, COOH, SO_2CH_3, CN, $(C_1$-$C_4)$-alkoxy, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_6)$-alkyl-phenyl, $(C_1$-$C_6)$-alkyl-$(C_1$-$C_6)$-alkoxy, $(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkoxy, $(C_1$-$C_6)$-alkoxy-phenyl, phenoxy;

and physiologically acceptable salts thereof.

Preference is given to compounds of the formula I in which

ring A is $(C_3$-$C_8)$-cycloalkanediyl, where one carbon atom may be replaced by an oxygen atom, and

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

or to compounds of the formula I in which

ring A is cyclohexane-1,3-diyl and

X is CH_2-O;

or to compounds of the formula I in which

ring A is cyclohexane-1,3-diyl;

X is CH_2-O;

Y is O.

Particular preference is given to compounds of the formula I in which the central cycloalkane-1,3-diyl ring is attached cis

or to compounds of the formula I in which

R1/R2 are H, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy;

R3 is $(C_1$-$C_4)$-alkyl.

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

which

Y is O;

m is 3;

n is 0;

or to compounds of the formula I in which

Y is O;

m is 2;

n is 0;

or to compounds of the formula I in which

Y is O;

m is 2;

n is 1;

Z is O;

or to compounds of the formula I in which

Y is O;

m is 1;

n is 0;

or to compounds of the formula I in which

Y is a bond;

m is 1;

n is 0;

the compounds of the formula I in which

Y is a bond;

m is 1;

n is 1;

Z is O.

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

Y is O;

m is 3;

n is 0;

R is tetrazole, $NHSO_2CF_3$;

or to compounds of the formula I in which

Y is O;

m is 2;

n is 0;

R is tetrazole, $NHSO_2CF_3$ or NR4R5 which denotes indole or 6-azaindole and may be substituted by F, Br, CN, COOH, (C_1C_4)-alkyl, $(C_1$-$C_4)$-alkoxy, SO_2-CH_3, $(C_1$-$C_6)$-alkoxy-$(C_1$-$C_6)$-alkoxy or benzoxy;

or compounds of the formula I in which

Y is O;

m is 2;

n is 1;

Z is O;

R is phenyl or thiophene, which radicals may carry further substituents such as F, COOH, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, NO_2, CF_3, benzyloxy or $B(OH)_2$;

or to compounds of the formula I in which

Y is O;

m is 1;

n is 0;

R is phenyl $NHSO_2CF_3$, phenyl-$B(OH)_2$;

or to compounds of the formula I in which

Y is a bond;

m is 1;

n is 0;

R is NR4R5 which denotes pyrrole or indole and is substituted by COOH;

or to compounds of the formula I in which

Y is a bond;

m is 1;

n is 1;

Z is O;

R is thiophene or benzothiophene, which radicals may be substituted by COOH, Cl, CF_3.

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

The alkyl radicals in the substituents R, R1, R2, R3, R4 and R5 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 assymmetry 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), diethanolamine, lysine or ethylenediamine.

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

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

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

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

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

Use

This invention relates further to the use of compounds of the formula I and their pharmaceutical compositions as PPAR receptor ligands. The PPAR receptor ligands of the invention are suitable as modulators of 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, 18(5), 267-77).

There exist two variants of PPARgamma, $PPARgamma_1$ and $PPARgamma_2$, 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 are:
   - 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 1 ng 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, hydroxypropyl-methylcellulose 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 petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active compound is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Pharmaceutical compositions suitable for transdermal uses can be in the form of single plasters which are suitable for long-term close contact with the patient's epidermis. Such plasters suitably contain the active compound in an aqueous solution which is buffered where appropriate, dissolved and/or dispersed in an adhesive or

dispersed in a polymer. A suitable active compound concentration is about 1% to 35%, preferably about 3% to 15%. A particular possibility is for the active compound to be released by 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

Examples of suitable antidiabetics are those disclosed 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 WO01/04146, or else such as, for example, those disclosed in WO 98/08871 of Novo Nordisk A/S. The orally active hypoglycemic active compounds include, preferably, sulfonylureas, biguanides, 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 the alteration of the lipid compositions of 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 I are administered in combination with insulin.

In one embodiment of the invention, the compounds of the formula 1 are administered in combination with substances which influence the hepatic glucose production, such as, for example glycogen phosphorylase inhibitors (c.f.: 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 1 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 P93/01 (1-cyclopentyl-3-methyl-1-oxo-2-pentanammonium chloride), P-31/98, LAF237 (1-[2-[3-hydroxyadamant-1-ylamino)acetyl]pyrrolidine-2-(5)-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 1 are administered in combination with compounds with inhibitory activity 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 HMG-CoA reductase inhibitor such as lovastatin, fluvastatin, pravastatin, simvastatin, ivastatin, itavastatin, atorvastatin, rosuvastatin.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a bile acid adsorption inhibitor (see, for example, US 6,245,744, US 6,221,897, US 6,227,831, EP0683773, EP0683774).

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

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

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

In one embodiment, the compounds of the formula I are administered in combination with 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-methanesulfongloxyphenyl)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 1 are administered in combination with nicotinic acid or niacin.

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

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-hexahydropyrazolo-[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-tetra-hydronaphthalene-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 stable transfected HEK cell line (HEK = human embryo kidney) designated here as "PPARalpha reporter cell line" is used. It contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) which mediates expression of the luciferase reporter element depending on a PPARalpha ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPARalpha-LBD binds in the cell nucleus of the PPARalpha reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is stably integrated in the genome of the cell line. There is only little expression of the luciferase reporter gene without addition of a PPARalpha ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the 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 (Genbank Accession # V01175). The minimal MMTV promoter section contains a CCAAT box and a TATA element in order to enable efficient transcription by RNA polymerase II. The cloning and sequencing of the GAL4-MMTV construct took place in analogy to the description of Sambrook J. et. al. (Molecular cloning, Cold Spring Harbor Laboratory Press, 1989). Then the complete Photinus pyralis luciferase gene (Genbank Accession # M15077) was cloned in 3'-downstream of the GAL4-MMTV element. After sequencing, the luciferase reporter element consisting of five GAL4 binding sites, MMTV promoter and luciferase gene was recloned into a plasmid

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

In a second step, the PPARalpha fusion protein (GR-GAL4-humanPPARalpha-LBD) was introduced into the stable cell clone described. For this purpose, initially the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Genbank Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Genbank Accession # P04386). The cDNA of the ligand-binding domain of the human PPARalpha receptor (amino acids S167-Y468; Genbank Accession # S74349) was cloned in at the 3' end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPARalpha-LBD) was 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 zeocin (#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 (# 35 3112, 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 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 (zeocin, G418, penicillin and streptomycin) are added.
Test substances are tested at 11 different concentrations in the range from 10 µM to 100 µM. 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 EC_{50} 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 EC_{50} values for the compounds of Examples 1 to 31 are in the range from 0.1 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:

Table I

Example No.	EC50 PPARalpha [nM]
II	331
VII	469
XI	361
XIV	106
XV	519
XXIII	222
XXVI	24

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

Determination of EC50 values of PPAR agonists in the cellular PPARgamma 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 for 48 h in an incubator at 37°C and 5% CO_2.

Day 4

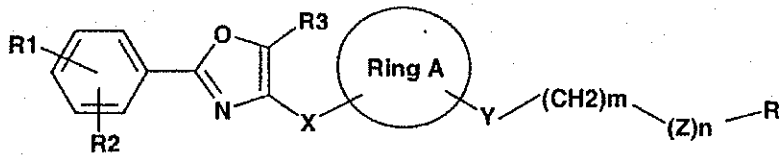
After removal of the medium by aspiration, 50 µl of Dual-Glo™ reagent (Dual-Glo™ Luciferase Assay System; Promega) are added to each well in accordance with the manufacturer's instructions in order to lyze the cells and provide the substrate for the firefly luciferase (Photinus pyralis) formed in the 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.

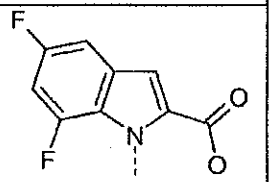
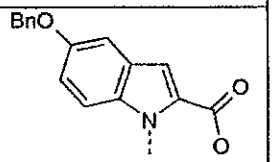
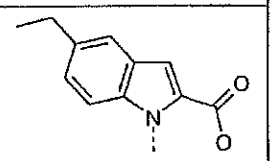
Evaluation

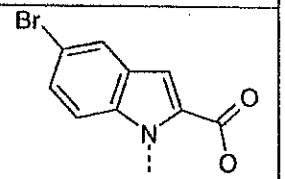
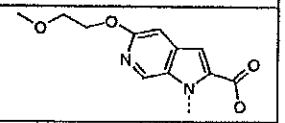
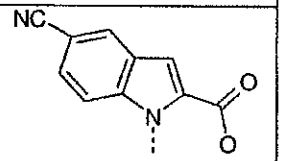
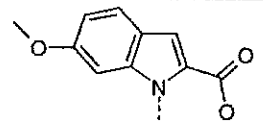
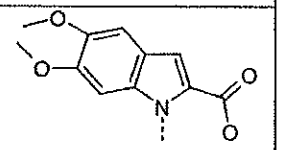
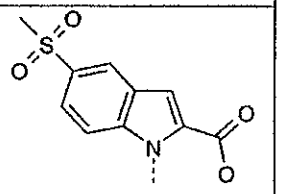
The crude data from the luminometer are transferred into a Microsoft Excel file. The firefly/Renilla luciferase activity ratio is determined for each measurement derived from one well of the microtiter plate. The dose-effect plots and EC50 values of PPAR agonists are calculated from the ratios by the XL.Fit program as specified by the manufacturer (IDBS).
PPARgamma EC50 values in the range from 6 nM to > 10 µM were measured for the PPAR agonists described in this application.

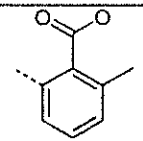
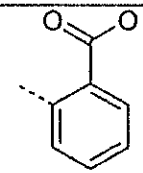
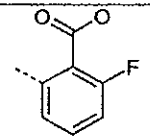
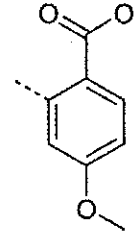
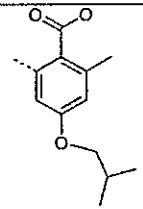
The examples given below serve to illustrate the invention, but without limiting it.

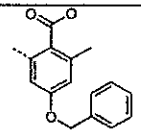
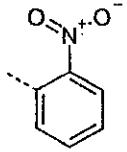
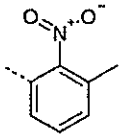
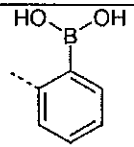
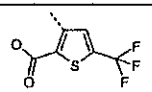
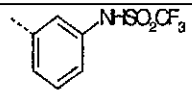
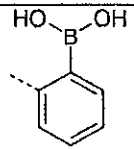


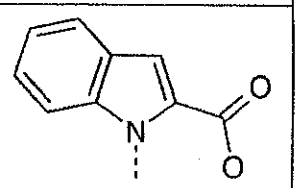
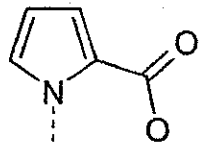
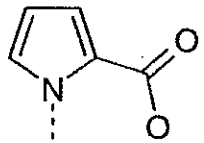
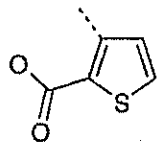
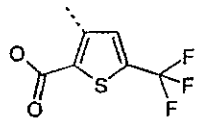
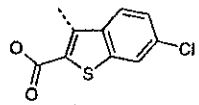
I

	R1	R2	R3	X	Y	ring A	m	n	Z	R
I	3-Me	H	Me	CH2O	O	1,3-Cy	3	0	-	5-tetrazole
II	3-Me	H	Me	CH2O	O	1,3-Cy	3	0	-	NH-SO2CF3
III	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	5-tetrazole
IV	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	NH-SO2CF3
V	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	
VI	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	
VII	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	

	R1	R2	R3	X	Y	ring A	m	n	Z	R
VIII	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	
IX	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	
X	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	
XI	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	
XII	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	
XIII	3-Me	H	Me	CH2O	O	1,3-Cy	2	0	-	

	R1	R2	R3	X	Y	ring A	m	n	Z	R
XIV	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XV	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XVI	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XVII	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XVIII	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	

	R1	R2	R3	X	Y	ring A	m	n	Z	R
XIX	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XX	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XXI	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XXII	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XXIII	3-Me	H	Me	CH2O	O	1,3-Cy	2	1	O	
XXIV	3-Me	H	Me	CH2O	O	1,3-Cy	1	0	-	
XXV	3-Me	H	Me	CH2O	O	1,3-Cy	1	0	-	

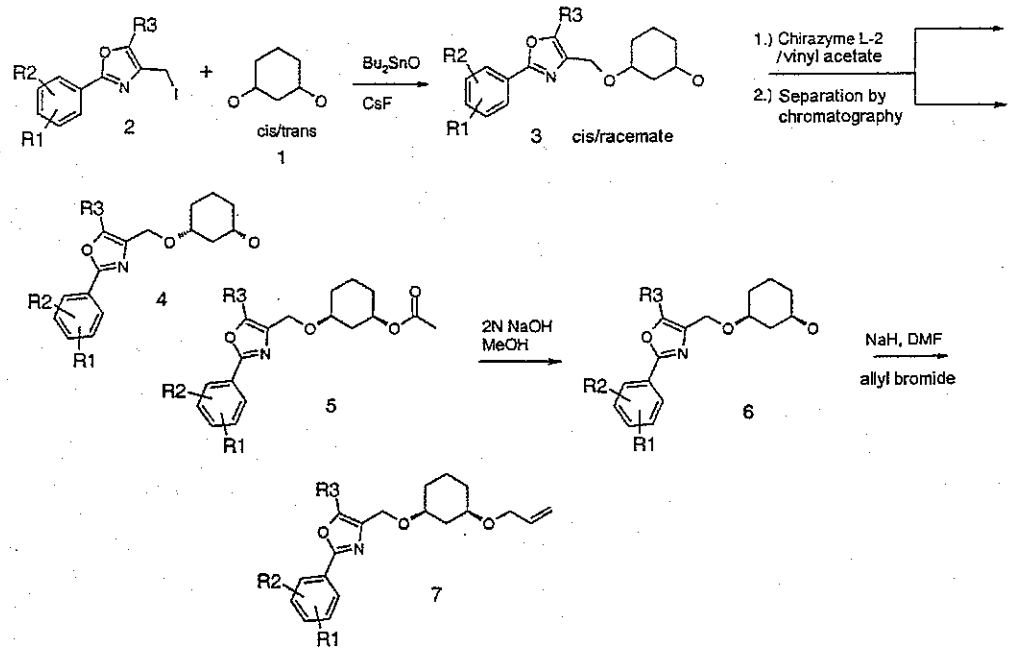
	R1	R2	R3	X	Y	ring A	m	n	Z	R
XXVI	4-Me	H	Me	CH2O	-	1,3-Cy	1	0	-	
XXVII	4-Me	H	Me	CH2O	-	1,3-Cy	1	0	-	
XXVIII	3-OMe	H	Me	CH2O	-	1,3-Cy	1	0	-	
XXIX	4-Me	H	Me	CH2O	-	1,3-Cy	1	1	O	
XXX	4-Me	H	Me	CH2O	-	1,3-Cy	1	1	O	
XXXI	4-Me	H	Me	CH2O	-	1,3-Cy	1	1	O	

Ring A: 1,3 Cy = cis-cyclohexane-1,3-diyl having the stereochemistry according to Cahn-Ingold-Prelog stated in the examples.

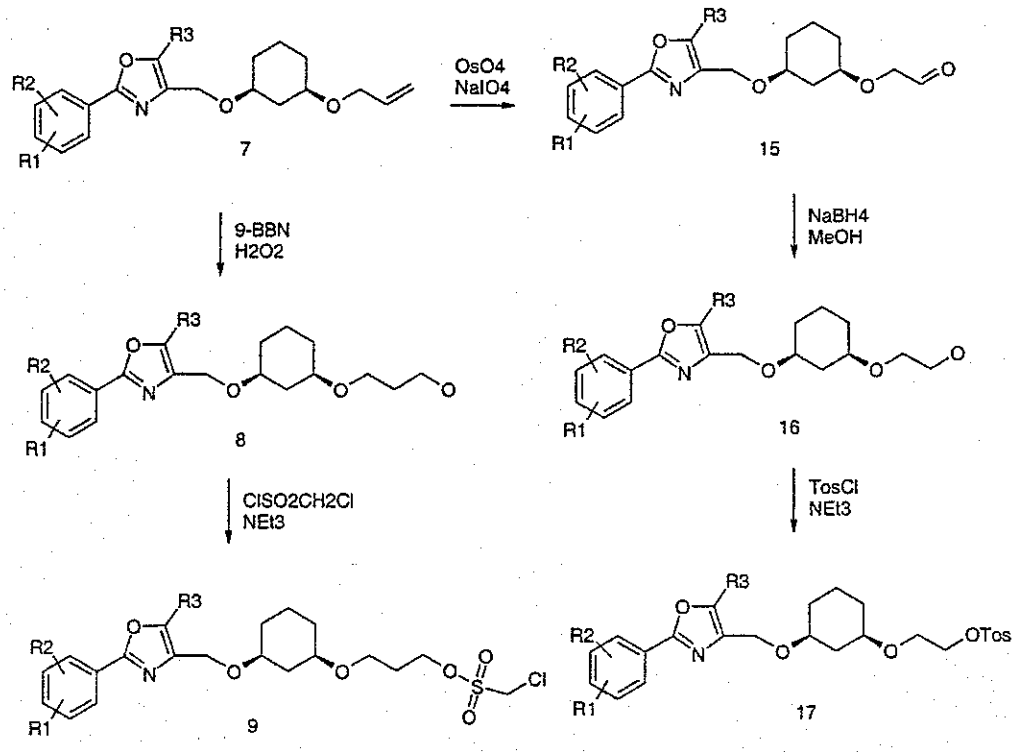
R: ----- denotes the point of attachment.

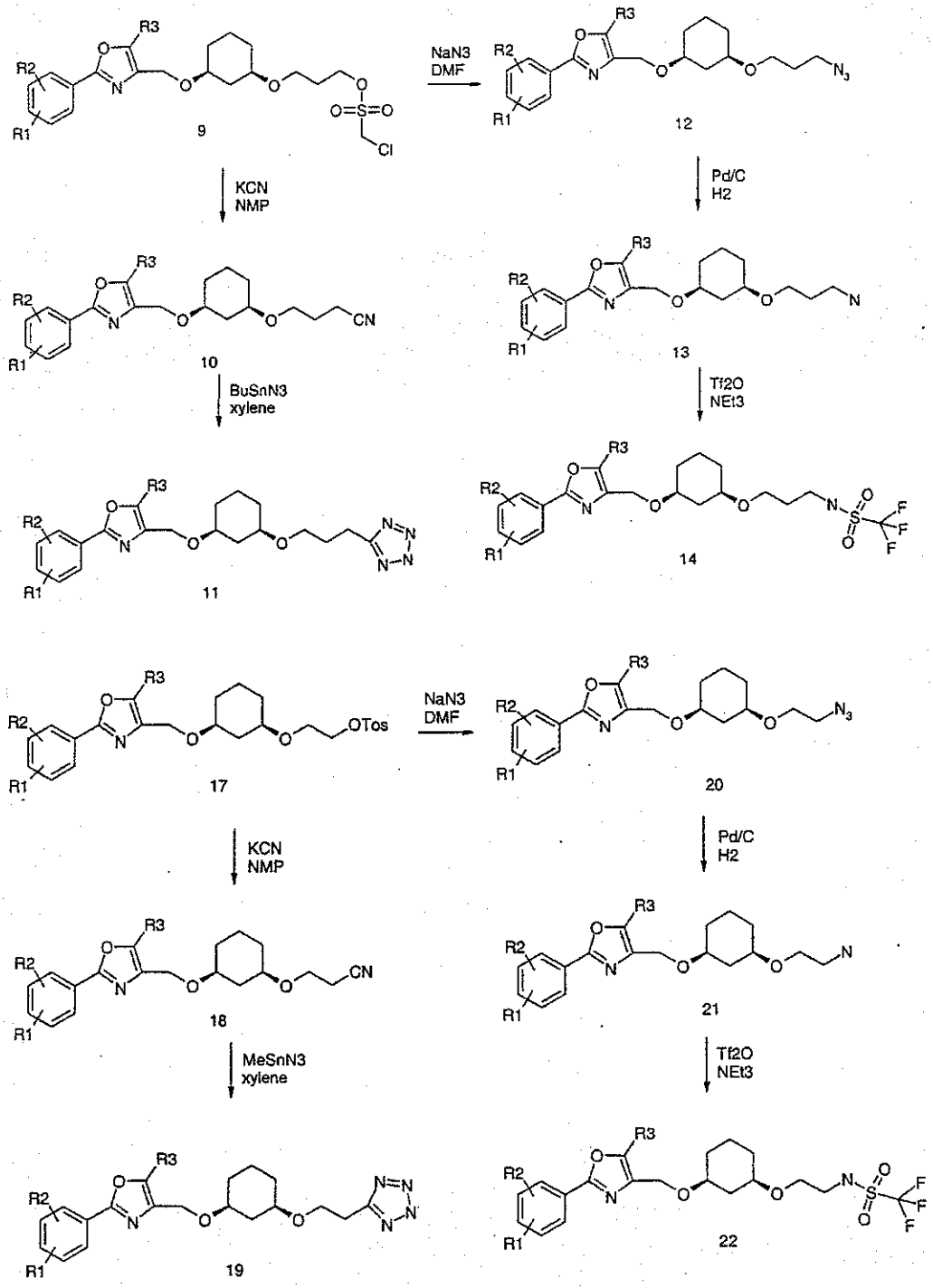
The compounds of the general formula I can be obtained in accordance with the reaction schemes below:

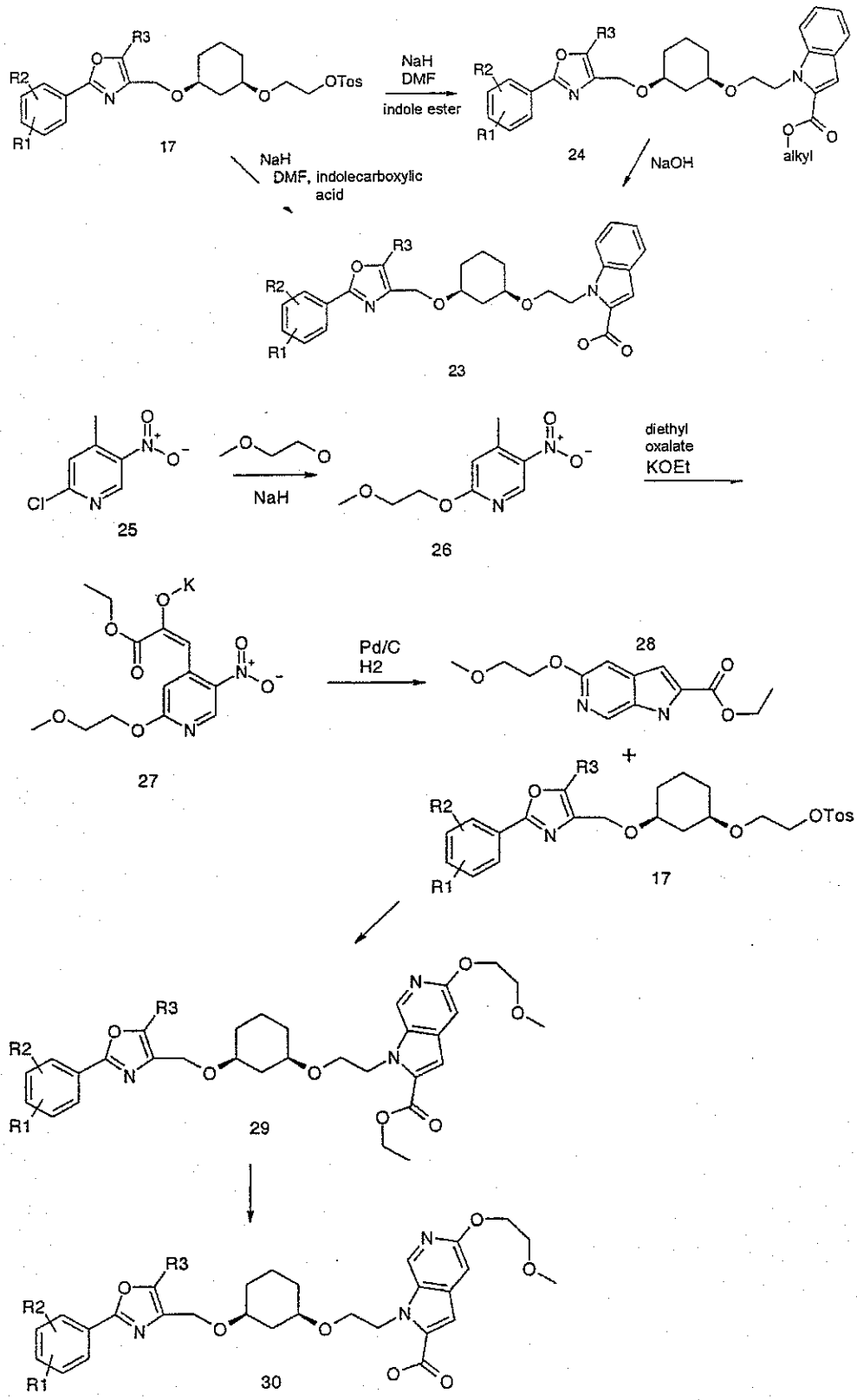
Synthesis scheme I: Preparation of the central intermediates **6** and **7**

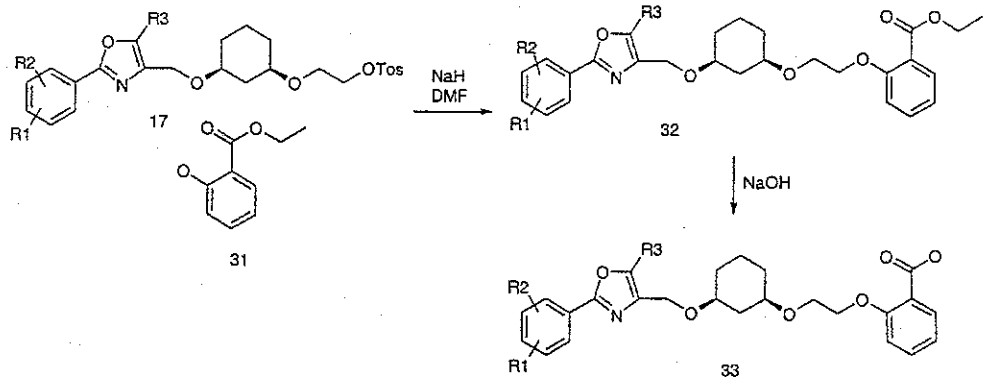


Synthesis scheme II: Functionalization of the allyl group in **7**

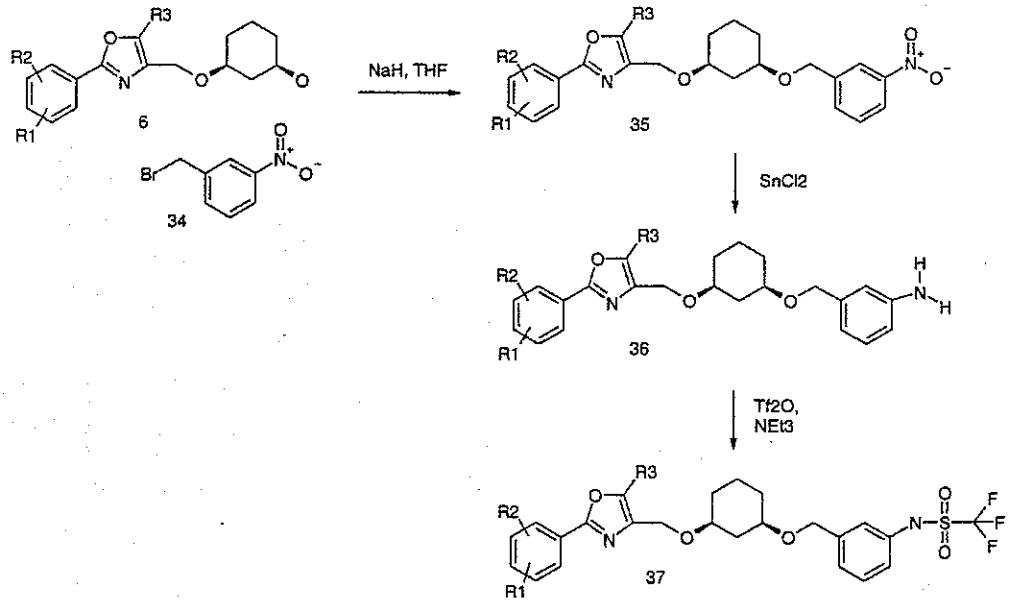



NaN3
DMF
KCN
NMP
Pd/C
H2
BuSnN3
xylene
Tf2O
NEt3
NaN3
DMF
KCN
NMP
Pd/C
H2
MeSnN3
xylene
Tf2O
NEt3

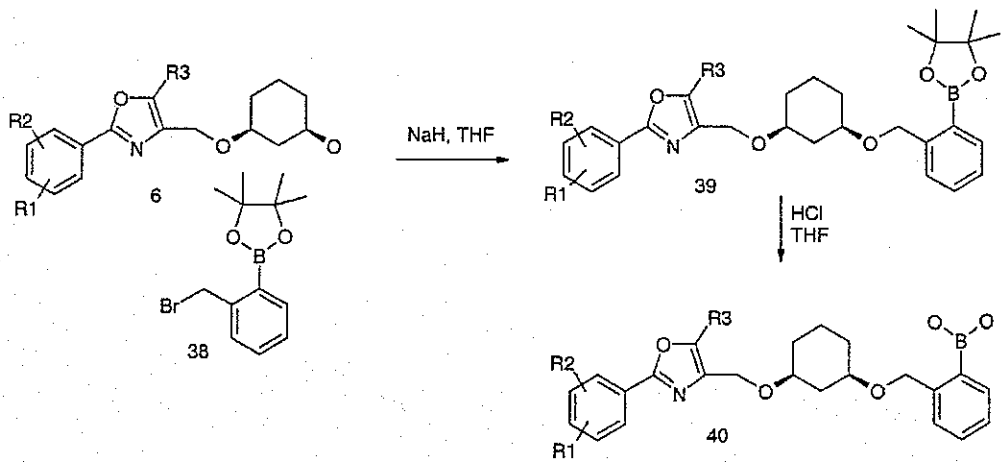

R3
R2
R1
OTos
17
NaH
DMF
indole ester
24
alkyl
NaOH
NaH
DMF, indolecarboxylic
acid
23
Cl
25
NaH
26
diethyl
oxalate
KOEt
K
27
Pd/C
H2
28
+
17
29
30



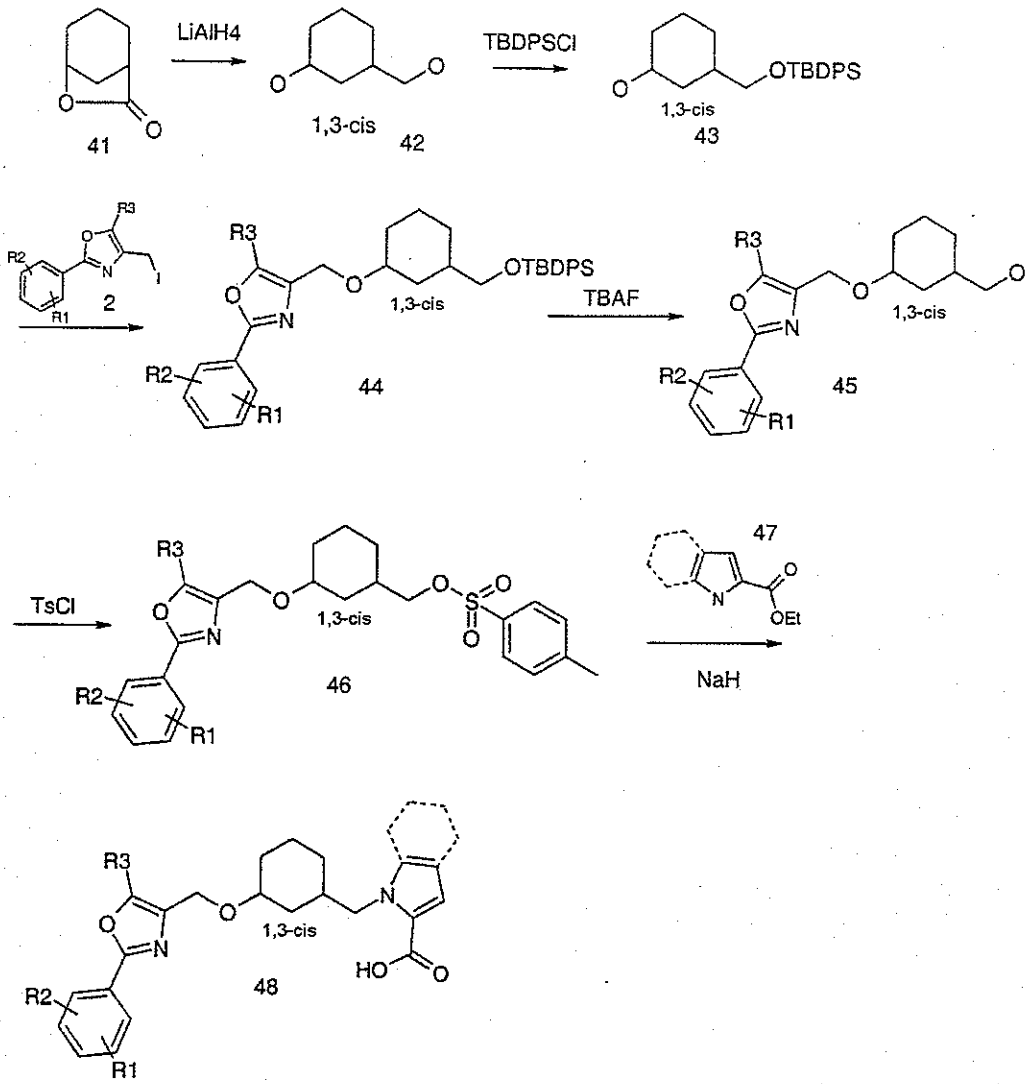
Synthesis scheme III: Reaction of **6** with functionalized benzyl bromides



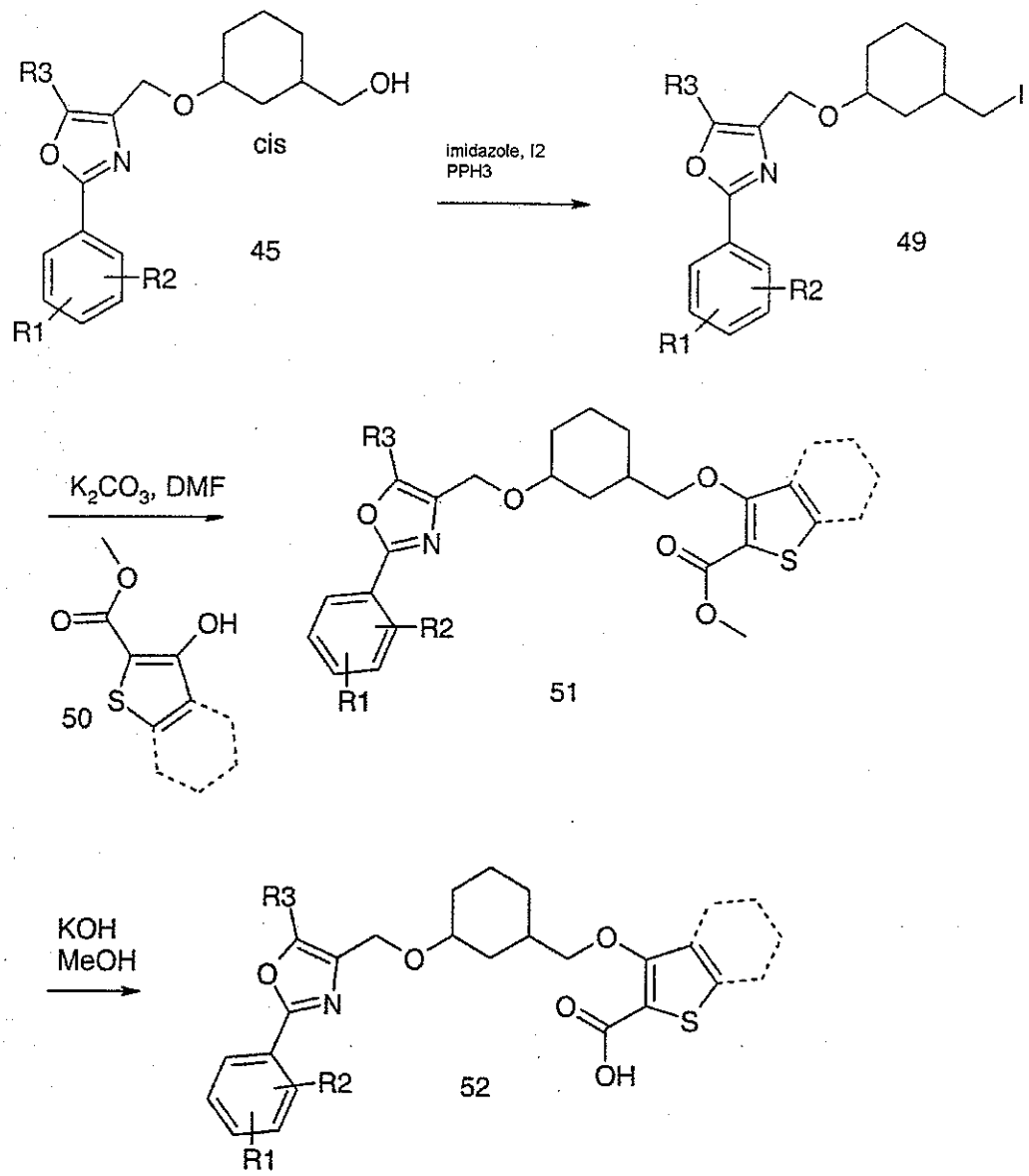
5



Synthesis scheme IV:



5



Here, component 1 is initially heated with dibutyltin oxide in toluene on a water separator for a plurality of hours and then, with addition of dimethylformamide, cesium fluoride and iodide 2, converted by stirring at room temperature for a number of hours into compounds of the general structure 3 in which R1, R2, R3 are as defined above.

The compound of the general formula 3 is reacted using Chirazyme L2 and vinyl acetate; this gives the compounds 4 and 5, of which 5, after separation, is reacted with alkali metal hydroxides to give compounds of the general structure 6 in which R1, R2, R3 are as defined above.

The compound of the general formula 6 is deprotonated using strong bases, for example sodium hydride in an aprotic solvent, and reacted with unsaturated bromides, for example allyl bromide, to give compounds of the general structure 7 in which R1, R2, R3 are as defined above.

The compound of the general formula 7 is, using hydroboration reagents, such as, for example, 9-BBN, and subsequent treatment with alkaline hydrogen peroxide, converted into compounds of the general structure 8, which is reacted with sulfonyl chlorides, for example chloromethylsulfonyl chloride, to give compounds of the general structure 9 in which R1, R2, R3 are as defined above.

Alternatively, the compound of the general formula 7 can be converted with osmium tetroxide and sodium periodate into the aldehyde of the general structure 15, which is reacted with complex hydrides, for example sodium borohydride, to give compounds of the general structure 16. The further conversion of compound of the general formula 16 with sulfonyl chlorides, for example toluenesulfonyl chloride, yields compounds of the general structure 17 in which R1, R2, R3 are as defined above.

Using sodium cyanide in aprotic solvents, such as, for example, NMP, the compound of the general formula 9 is converted into compounds of the general structure 10, which is reacted with a metal azide, for example tributyltin azide, to give compounds of the general structure 11 in which R1, R2, R3 are as defined above.

Alternatively, the compound of the general formula 9 can, using sodium azide in aprotic solvents, such as, for example, NMP, be converted into compounds of the general structure 12, which are, by catalytic hydrogenation using, for example, palladium-on-carbon, converted into the compounds of the general structure 13. The further reaction of compound of the general formula 13 with sulfonyl chlorides, for example trifluoromethanesulfonic anhyride, gives compounds of the general structure 14 in which R1, R2, R3 are as defined above.

The compound of the general formula 17 is, using sodium cyanide in aprotic solvents, such as, for example, NMP, converted into compounds of the general structure 18, which is reacted with a metal azide, for example

tributyltin azide, to give compounds of the general structure 19 in which R1, R2, R3 are as defined above.

Alternatively, using sodium azide in aprotic solvents, such as, for example, NMP, the compound of the general formula 17 can be converted into compounds of the general structure 20, which are converted by catalytic hydrogenation, for example with palladium-on-carbon, into the compounds of the general structure 21. Further reaction of compound of the general formula 21 with sulfonyl chlorides, for example trifluoromethanesulfonic anhyride, gives compounds of the general structure 22 in which R1, R2, R3 are as defined above.

Nitrogen-containing aromatic heterocycles, for example pyrrole, indole, azaindole, are converted by treatment with strong bases, for example sodium hydride, in polar aprotic solvents, such as, for example, DMF, into the corresponding sodium salts and reacted with a compound of the general formula 17 to give compounds of the general structure 23 and 24. The compound of the general formula 24 is, using alkali metal hydroxides, converted into compounds of the general structure 23 in which R1, R2, R3 are as defined above.

Azaindole-2-carboxylic esters of type 28 are prepared by nucloephilic aromatic substitution on 2-chloronitropyridines (25) with alkoxides and subsequent condensation with oxalic esters. Reductive cyclization under an atmosphere of hydrogen gives azaindole-2-carboxylic esters of type 28 which can be reacted as described above with a compound of the general formula 17 to give compounds of the general structure 29. Following hydrolysis of the ester compounds of the general structure 30 similar to compounds of the general structure 22.

Benzoic esters substituted by a hydroxyl group of the general formula 31 and heterocyclic carboxylic esters, for example thiophene and furan, are converted by treatment with strong bases, for example sodium hydride, in polar aprotic solvents, such as, for example, DMF, into the corresponding sodium salts and reacted with a compound of the general formula 17 to give compounds of the general structure 32. The compound of the general formula 32 is, using alkali metal hydroxides, converted into compounds of the general structure 33 in which R1, R2, R3 are as defined above.

The compound of the general formula 6 is deprotonated in an aprotic solvent using strong bases, for example sodium hydride, and reacted with benzyl bromides of the general formula 34 to give compounds of the general structure 35. The compound of the general formula 35 is, using a reducing agent, for example tin(II) chloride, in an aprotic solvent, converted into compounds of the general formula 36, which with trifluoromethanesulfonic anhydride into the sulfonamides of the general formula 37 in which R1, R2, R3 are as defined above.

The compound of the general formula 6 is deprotonated using strong bases, for example sodium hydride in an aprotic solvent, and reacted with benzyl bromides of the general formula 38 to give compounds of the general structure 39. The compound of the general formula 39 is reacted with aqueous acid to give compounds of the general formula 40 in which R1, R2, R3 are as defined above.

Using lithium aluminum hydride, the lactone 41 is reduced to diol 42 which can be protected by selective monosilylation (43). The compound of the general formula 43 is deprotonated using strong bases, for example sodium hydride in an aprotic solvent, and reacted with phenyloxazoyl iodides of the general formula 2 to give compounds of the general structure 44. The compound of the general formula 45 is desilylated with fluoride, for example TBAF, giving compounds of the general formula 45, which are reacted with sulfonyl chloride, for example toluenesulfonyl chloride, to give compounds of the general formula 46 in which R1, R2, R3 are as defined above.

Nitrogen-containing aromatic heterocycles of the general formula 47, for example pyrrole, indole, azaindole, are converted by treatment with strong bases, for example sodium hydride, in polar aprotic solvents, such as, for example, DMF, into the corresponding sodium salts and reacted with a compound of the general formula 48 in which R1, R2, R3 are as defined above.

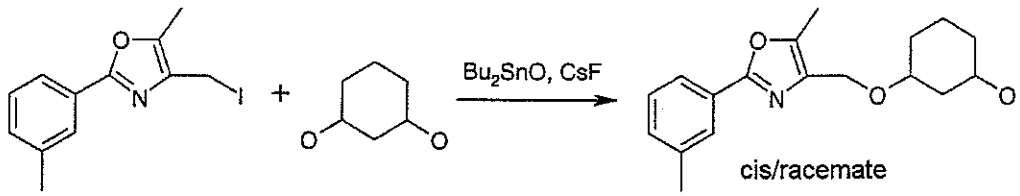
Heterocyclic carboxylic esters substituted by a hydroxyl group, for example thiophene and benzothiophene are in the deprotonated in the presence of weak bases, for example potassium carbonate, in polar aprotic solvents,

such as, for example, DMF, and reacted with a compound of the general formula 49 to give compounds of the general structure 51. The compound of the general formula 51 is converted using alkali metal hydroxides into compounds of the general structure 52 in which R1, R2, R3 are as defined above.

Other compounds of the formula I can be prepared accordingly or by known processes.

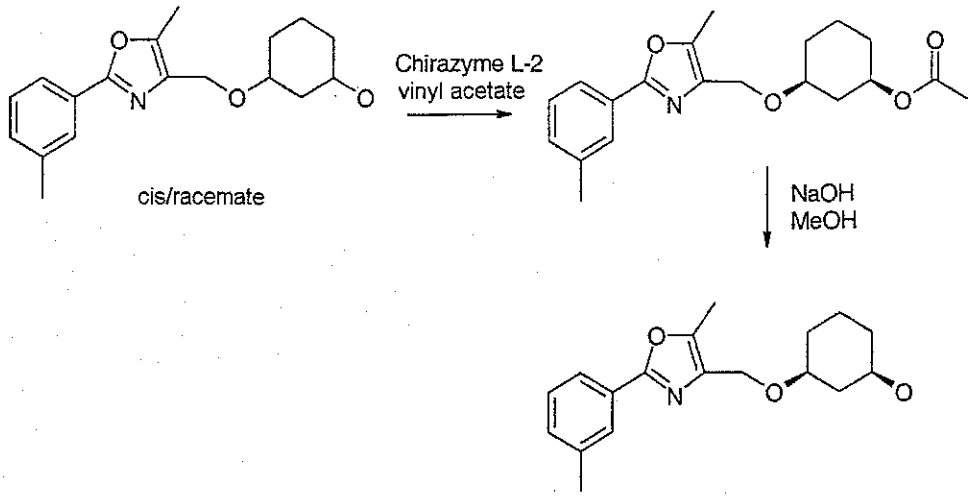
The examples and preparation methods given below serve to illustrate the invention, but without limiting it.

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



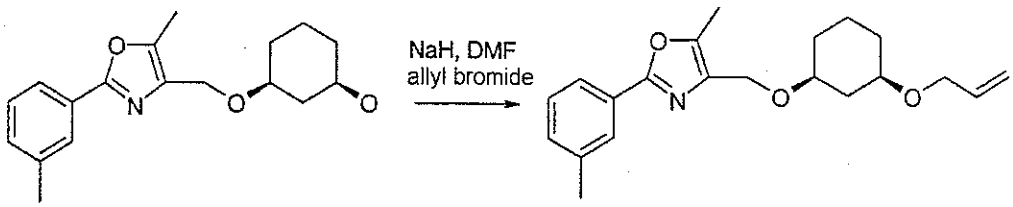
21.7 g of 1,3-cyclohexanediol and 30.3 g of dibutyltin oxide are dissolved in 450 ml of toluene and, under reflux on a water separator, heated at the boil. During the reaction time, the reaction volume is reduced by half. After three hours, the reaction mixture is cooled to room temperature and 300 ml of DMF, 29 g of 4-iodomethyl-5-methyl-2-m-tolyloxazole 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 NaCl 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 the *cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol racemate as a yellowish solid which is recrystallized from n-heptane/ethyl acetate. $C_{18}H_{23}NO_3$ (301.39), MS (ESI): 302 ($M + H^+$).

3-((1R,3S)-cis-5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol



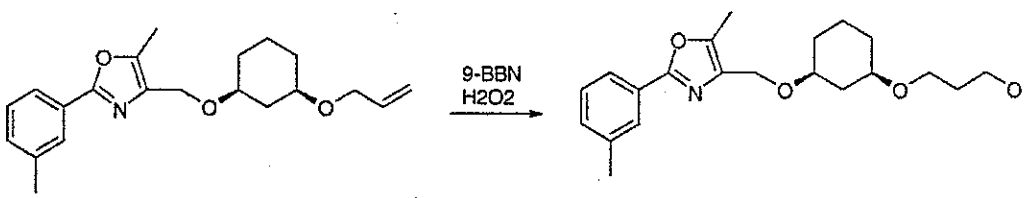
25 g of *racemic cis*-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol are dissolved in 320 ml of vinyl acetate and 1.3 g of chirazyme L-2 Lyo (Boehringer Mannheim) are added. After about three hours of stirring at room temperature (LC-MS control for a conversion of 40-45%) the enzyme is filtered 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 the (1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyl acetate as colorless oil. $C_{20}H_{25}NO_4$ (343.43), MS (ESI): 344 ($M + H^+$), the (1R,3S)-3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl acetate is taken up in 170 ml of methanol and, after addition of 27 ml of 2N NaOH, 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 org. phase is washed with NaCl solution. The organic phase is dried over magnesium sulfate, the solvent is removed under reduced pressure. This gives 6.7 g of 3-((1R,3S)-5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexanol as a yellowish solid. $C_{18}H_{23}NO_3$ (301.39), MS (ESI): 302 ($M + H^+$).

4-((1R,3S)-3-Allyloxycyclohexyloxymethyl)-5-methyl-2-m-tolyloxazole



At room temperature, 470 mg of a 60 percent strength suspension of sodium hydride are added to a solution of 2.2 g of 3-((1R,3S)-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol in 30 ml of dimethylformamide, and the mixture is stirred at room temperature for 20 min. 1.36 ml of allyl bromide are then added, the mixture is stirred at 40°C until the conversion is complete, and, if necessary, further sodium hydride and ally bromide are added. Once the conversion is complete (monitored by LC-MS), 100 ml of ethyl acetate and 150 ml of sat. NaCl solution are added. The organic phase is dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 3:1). This gives 2.3 g of 4-((1R,3S)-3-allyloxycyclohexyloxymethyl)-5-methyl-2-m-tolyloxazol 5 as a colorless oil. $C_{21}H_{27}NO_3$ (341.45), MS (ESI): 342 ($M + H^+$).

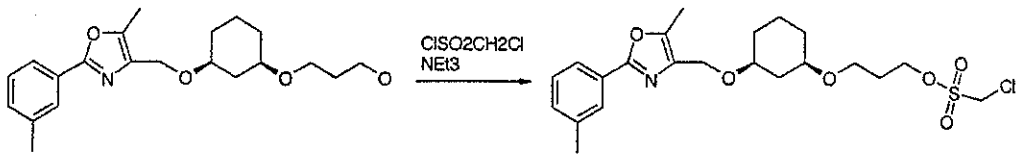
3-(1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propan-1-ol



3.3 g of 4-((1R,3S)-3-(Allyloxycyclohexyloxymethyl)-5-methyl-2-m-tolyloxazole are dissolved in 70 ml of dry THF and, at room temperature, 20 ml of 9-BBN, 0.5 M in THF, are added. The mixture is stirred at this temperature for 4 h and 10 ml of water, 10 ml of 2 N NaOH and 5 ml of 30% strength H_2O_2 are added successively. The mixture is stirred at room temperature for 18 h and then heated at 40°C for 1 h. After cooling, 50 ml of water are added, the mixture is extracted twice with 100 ml of methyl tert-butyl ether

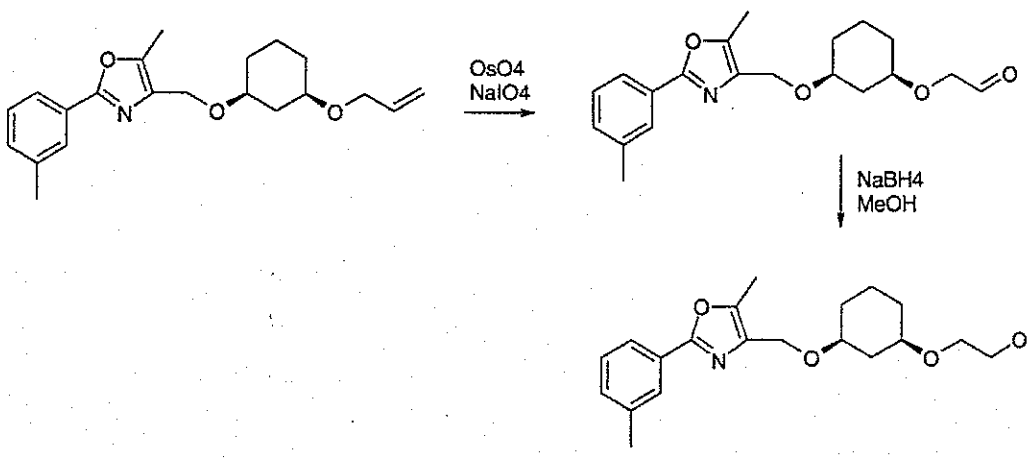
and the combined org. phases are washed with sat. NaCl solution. The organic phases are dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:2). This gives 1.56 g of 3-(1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propan-1-ol as a colorless oil. $C_{21}H_{29}NO_4$ (359.47), MS (ESI): 360 ($M + H^+$).

((1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propyl 4-chloromethanesulfonate



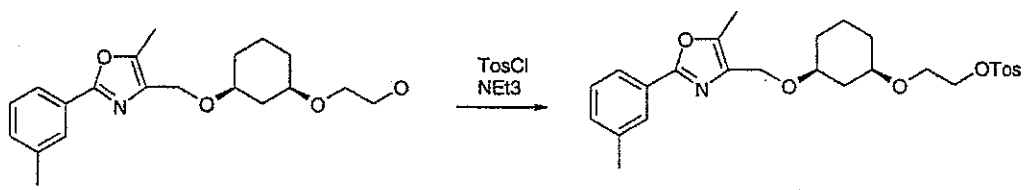
1.56 g of 3-(1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propan-1-ol are dissolved in 15 ml of dichloromethane, and, at 0°C, 0.7 ml of pyridine and 0.45 ml of chloromethanesulfonyl chloride are added. After five hours of stirring at this temperature, the mixture is poured onto ice/1 N HCl and extracted with dichloromethane. The extract is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:1). This gives 1.8 g of ((1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propyl 4-chloromethanesulfonate as a colorless oil. $C_{22}H_{30}ClNO_6S$ (472.00), MS (ESI): 473 ($M + H^+$),

2-((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethanol



2.3 g of 4-((1R,3S)-3-(allyloxycyclohexyloxymethyl)-5-methyl-2-m-tolyloxazole are dissolved in 65 ml of methyl tert-butyl ether and, at 0°C, 65 ml of water, 4.4 g of sodium metaperiodate and 3.3 ml of a 2.5% strength solution of osmium tetroxide in tert-butanol are added. After 20 min, the mixture is slowly warmed to 40°C. After 2 h, a further 700 mg of sodium metaperiodate were added and the mixture was stirred at 45°C for 2 h. 140 ml of sat. sodium thiosulfate solution were added and the mixture was extracted with methyl tert-butyl ether. The combined organic phases are dried over sodium sulfate and the solvent is removed under reduced pressure. This gives 2-((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]acetaldehyde as a colorless oil. $C_{20}H_{25}NO_4$ (343.43), MS (ESI): 344 ($M + H^+$). 2-((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]acetaldehyde is, as a crude product, taken up in 60 ml of dry methanol, and 300 mg of sodium borohydride are added. After 1.5 h, the mixture is quenched with 3 ml of acetone and concentrated. The residue is taken up in 50 ml of ethyl acetate/50 ml of sat. sodium bicarbonate solution, and the org. phase is dried over sodium sulfate. The solvent is removed under reduced pressure and the residue is then purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:3). This gives 1.6 g of 2-((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethanol as a colorless oil. $C_{20}H_{27}NO_4$ (345.44), MS (ESI): 346 ($M + H^+$).

((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate



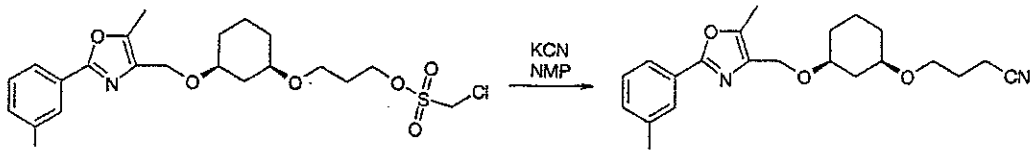
1.6 g of 2-((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethanol are dissolved in a mixture of 30 ml of dichloromethane and 3.6 ml of pyridine, and 1.2 g of 4-tosyl chloride and 50 mg of dimethylaminopyridine are added. The mixture is stirred at room temperature for 18 h and then poured into 2 N HCl/ice, and the aqueous

phase is extracted with 50 ml of dichloromethane. The combined organic phases are dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 2:1). This gives ((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate as a colorless oil. $C_{27}H_{33}NO_6S$ (513.66), MS (ESI): 514 ($M + H^+$).

Example I

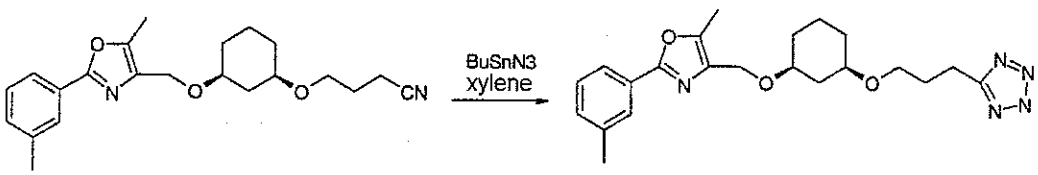
(IR,3S)-5-{3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-propyl}-2H-tetrazole

(1R,3S)-4-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]butyronitrile



472 mg of ((1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propyl 4-chloromethanesulfonate are dissolved in 3 ml of N-methylpyrrolidone, and 200 mg of potassium cyanide and 30 mg of tetrabutylammonium iodide are added. The mixture is stirred at 60°C for 3 h and, after cooling, taken up in 20 ml of ethyl acetate/20 ml with sat. NaCl solution. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:1). This gives (1R,3S)-4-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]butyronitrile as a colorless oil. $C_{22}H_{28}N_2O_3$ (368.48), MS (ESI): 369 ($M + H^+$).

(1R,3S)-5-{3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-propyl}-2H-tetrazole



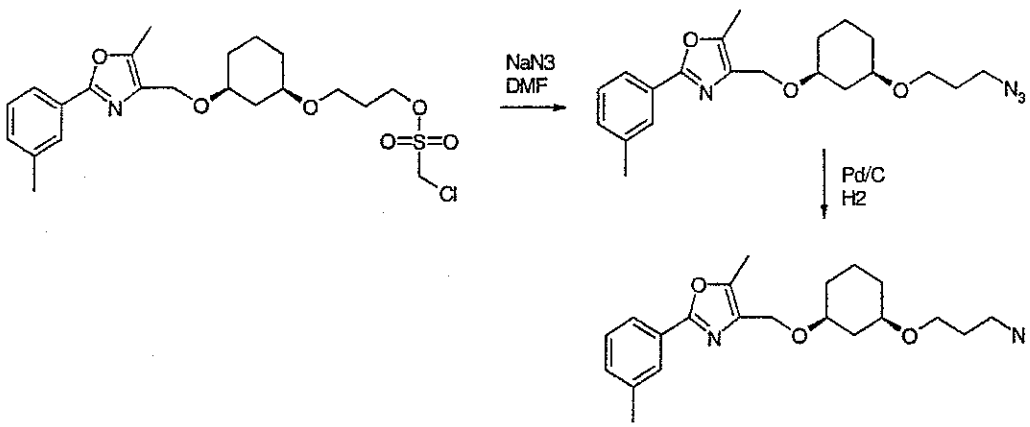
333 mg of (1R,3S)-4-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]butyronitrile are dissolved in 5 ml of xylene, and 919 mg of tributyltin

azide are added. The mixture is stirred at 120°C for 18 h and, after cooling, titurated with 0.5 ml of TFA. The solvent is removed under reduced pressure and the residue is purified by RP-HPLC. This gives (1R,3S)-5-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propyl}-2H-tetrazole as a colorless oil. $C_{22}H_{29}N_5O_3$ (411.51), MS (ESI): 412 ($M + H^+$).

Example II

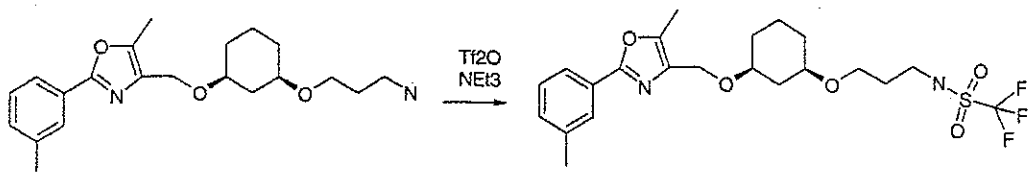
(1R,3S)-C,C,C-Trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propyl}methanesulfonamide

(1R,3S)-3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propyl-amine



472 mg of ((1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl-oxy]propyl 4-chloromethanesulfonate are dissolved in 3 ml of N-methylpyrrolidone, and 200 mg of sodium azide are added. The mixture is stirred at 60°C for 3 h and, after cooling, taken up in 20 ml of ethyl acetate/20 ml with sat. NaCl solution. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. This gives 4-((1R,3S)-[3-(3-azidopropoxy)cyclohexyloxymethyl]-5-methyl-2-m-tolyloxazole as a colorless oil. $C_{21}H_{28}N_4O_3$ (384.48), MS (ESI): 385 ($M + H^+$). The crude azide is taken up in 20 ml of methanol and hydrogenated with 50 mg of Pd/C 10% at a hydrogen atmosphere of 1 bar for 3 h. The catalyst is filtered off, giving (1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]propylamine as a colorless oil. $C_{21}H_{30}N_2O_3$ (358.48), MS (ESI): 359 ($M + H^+$).

(1R,3S)-C,C,C-Trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propyl}methanesulfonamide

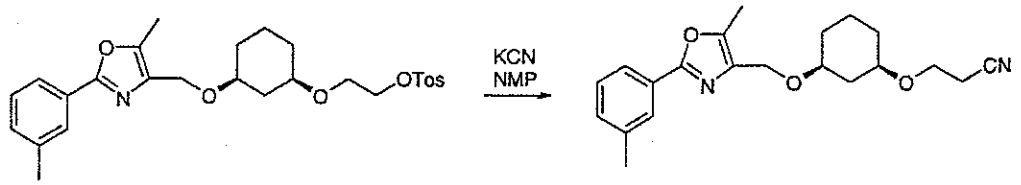


95 mg of (1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl-oxy]propylamine are dissolved in 2 ml of dichloromethane, 0.1 ml of triethylamine are added and the mixture is cooled to –78°C. 60 µl of trifluoromethanesulfonic anhydride are added, and the mixture is slowly allowed to warm to room temperature. After 3 h all volatile components were removed under reduced pressure and the residue was taken up in DMF and filtered. The compound is purified by RP-HPLC. This gives (1R,3S)-C,C,C-trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]propyl}methanesulfonamide as a colorless oil. $C_{22}H_{29}F_3N_2O_5S$ (490.55), MS (ESI): 491 ($M + H^+$).

Example III

(1R,3S)-5-{3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-ethyl}-2H-tetrazole

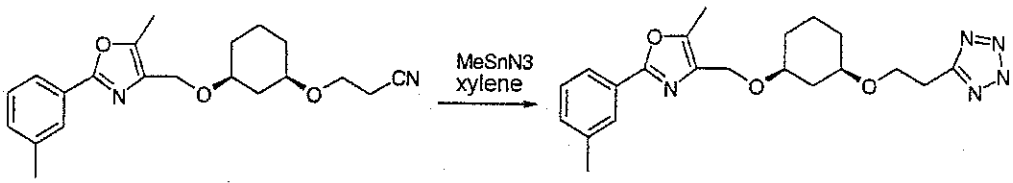
(1R,3S)-4-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-propionitrile



500 mg of ((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl-oxy]ethyl toluene-4-sulfonate are dissolved in 3 ml of N-methylpyrrolidone, and 200 mg of potassium cyanide and 30 mg of tetrabutylammonium iodide are added. The mixture is stirred at 50°C for 8 h and, after cooling, taken up in 20 ml of ethyl acetate/20 ml with sat. NaCl solution. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. This gives (1R,3S)-4-[3-(5-methyl-2-m-tolyloxazol-4-

ylmethoxy)cyclohexyloxy]propionitrile as a colorless oil. $C_{22}H_{28}N_2O_3$ (368.48), MS (ESI): 369 ($M + H^+$).

(1R,3S)-5-{3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-ethyl}-2H-tetrazole

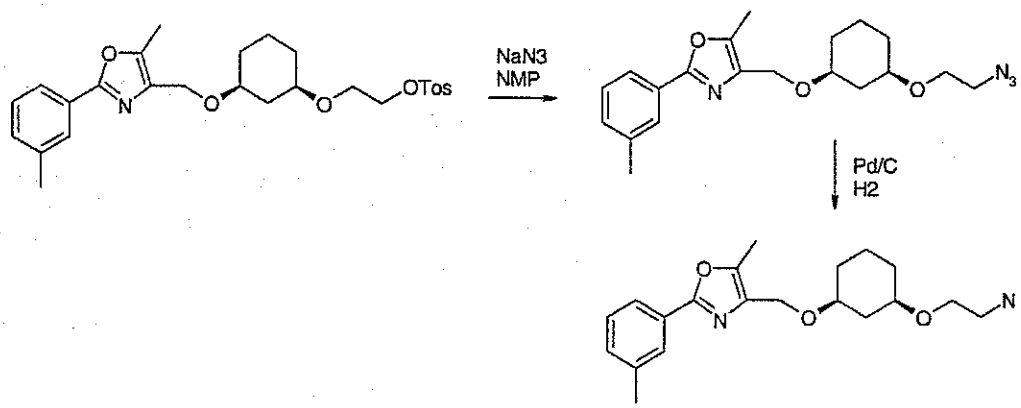


100 mg of (1R,3S)-4-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl-oxy]propionitrile are dissolved in 5 ml of xylene, and 82 mg of trimethyltin azide are added. The mixture is stirred at 130°C for 24 h and, after cooling, titurated with 0.5 ml of TFA. The solvent is removed under reduced pressure and the residue is purified by RP-HPLC. This gives (1R,3S)-5-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-2H-tetrazole as a colorless oil. $C_{21}H_{27}N_5O_3$ (397.48), MS (ESI): 398 ($M + H^+$).

Example IV

(1R,3S)-C,C,C-Trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]ethyl}-methanesulfonamide

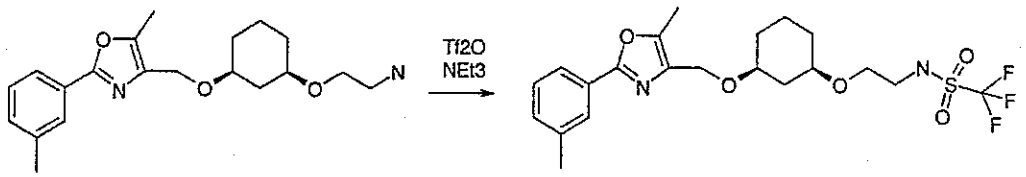
(1R,3S)-3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-ethylamine



500 mg of ((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl-oxy]ethyl toluene-4-sulfonate are dissolved in 5 ml of N-methylpyrrolidone,

and 200 mg of sodium azide are added. The mixture is stirred at 40°C for 5 h and, after cooling, taken up in 20 ml of ethyl acetate/20 ml with sat. NaCl solution. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. This gives (1S,3R)-4-[3-(2-azidoethoxy)cyclohexyloxymethyl)-5-methyl-2-m-tolyloxazole as a colorless oil. $C_{20}H_{26}N_4O_3$ (370.46), MS (ESI): 371 ($M + H^+$). The crude azide is taken up in 20 ml of methanol and hydrogenated with 50 mg of Pd/C 10% at a hydrogen atmosphere of 1 bar for 3 h. The catalyst is filtered off, giving (1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl-amine as a colorless oil. $C_{20}H_{28}N_2O_3$ (244.46), MS (ESI): 345 ($M + H^+$).

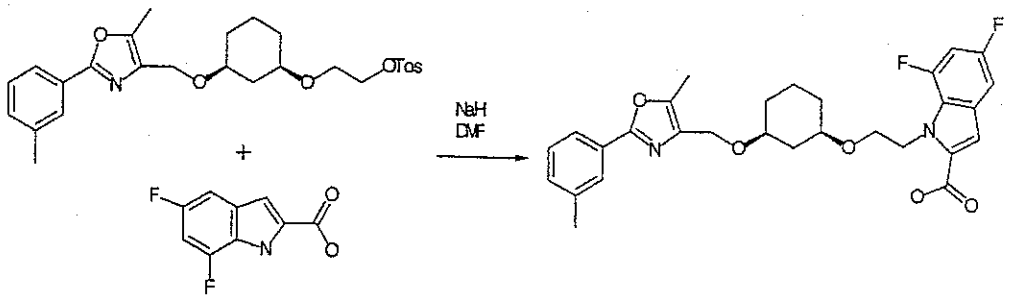
(1R,3S)-C,C,C-Trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]ethyl}-methanesulfonamide



95 mg of (1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl-oxy]ethylamine are dissolved in 2 ml of dichloromethane, 0.1 ml of triethylamine are added and the mixture is cooled to –78°C. 60 µl of trifluoromethanesulfonic anhydride are added and the mixture is allowed to slowly warm to room temperature. After 3 h, all volatile components were removed under reduced pressure and the residue was taken up in DMF and filtered. The compound is purified by RP-HPLC. This gives (1R,3S)-C,C,C-trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyl-oxy]ethyl}-methanesulfonamide as a colorless oil. $C_{21}H_{27}F_3N_2O_5S$ (476.52), MS (ESI): 477 ($M + H^+$).

Example V

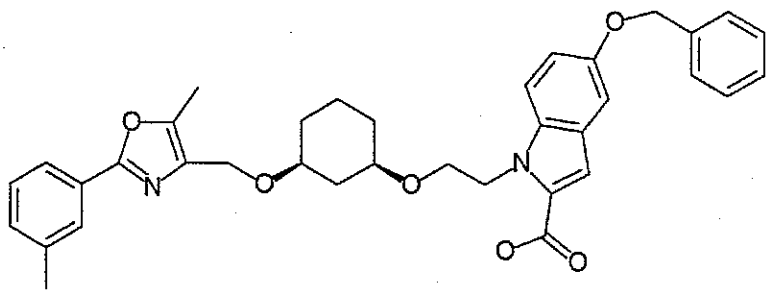
(1R,3S)-5,7-Difluoro-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclo-hexyloxy]ethyl}-1H-indole-2-carboxylic acid



79 mg of 5,7-difluoroindolecarboxylic acid are dissolved in 2 ml of dried DMF, and 34 mg of 60 percent strength sodium hydride suspension are added. After 30 min at room temperature, 100 mg of ((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy)ethyl toluene-4-sulfonate, dissolved in 2 ml of DMF, are added. The mixture is stirred at 65°C until the reaction has gone to completion (monitored by LC-MS). 50 µl of TFA are added, the mixture is filtered and the residue is purified by RP-HPLC. This gives 40 mg of (1R,3S)-5,7-difluoro-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid as a colorless oil. $C_{29}H_{30}F_2N_2O_5$ (524.56), MS (ESI): 525 ($M + H^+$).

Example VI

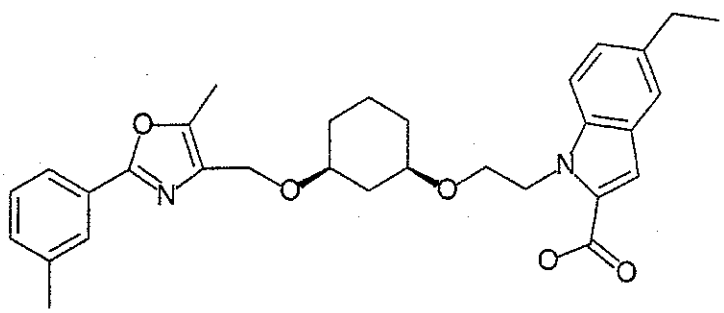
(1R,3S)-5-Benzyloxy-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and 5-benzyloxy-1H-indole-2-carboxylic acid give, analogously to Example V, (1R,3S)-5-benzyloxy-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid of molecular weight 594.71 ($C_{36}H_{38}N_2O_6$), MS (ESI): 595 ($M + H^+$).

Example VII

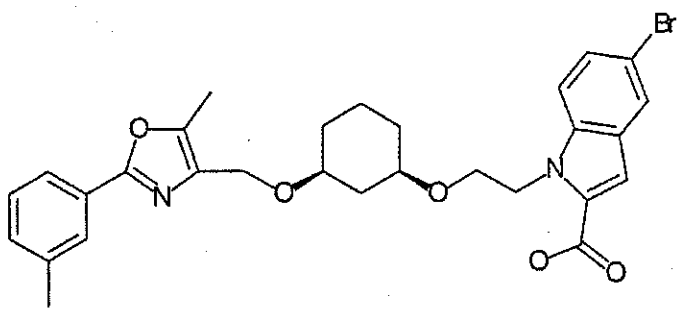
(1R,3S)-5-Ethyl-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and 5-ethyl-1H-indole-2-carboxylic acid give, analogously to Example V, (1R,3S)-5-ethyl-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid of molecular weight 516.64 ($C_{31}H_{36}N_2O_5$), MS (ESI): 517 ($M + H^+$).

Example VIII

(1R,3S)-5-Bromo-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid

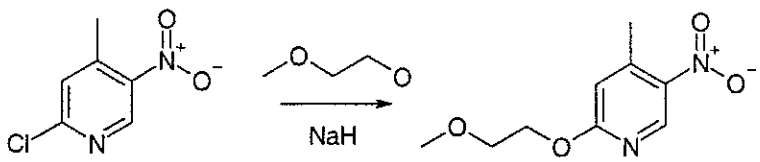


((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and 5-bromo-1H-indole-2-carboxylic acid give, analogously to Example I, (1R,3S)-5-bromo-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid of molecular weight 567.48 ($C_{29}H_{31}BrN_2O_5$), MS (ESI): 568 ($M + H^+$).

Example IX

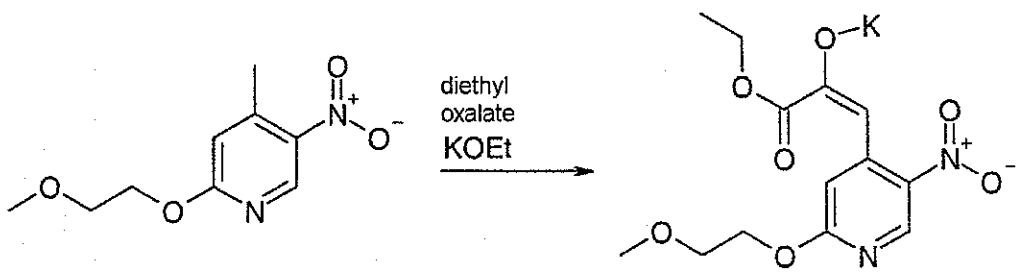
(1R,3S)-5-(2-Methoxyethoxy)-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-pyrrolo[2,3-c]pyridin-2-carboxylic acid

2-(2-Methoxyethoxy)-4-methyl-5-nitropyridine



60 percent strength sodium hydride suspension was introduced into 10 ml of ethylene glycol monomethyl ether, and the mixture was stirred until the evolution of hydrogen had ceased. 516 mg of 2-chloro-4-methyl-5-nitropyridine are added, and the mixture is stirred at room temperature until the reaction has gone to completion. 20 ml of water are added, and the mixture is extracted with methyl tert-butyl ether. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:3). This gives 2-(2-methoxyethoxy)-4-methyl-5-nitropyridine as a colorless oil. $C_9H_{12}N_2O_4$ (212.21), MS (ESI): 213 ($M + H^+$).

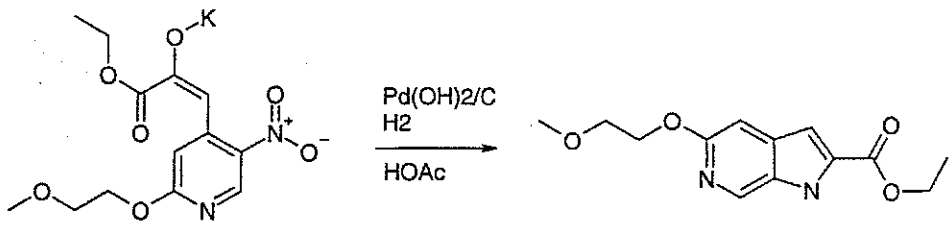
Ethyl 3-[2-(2-methoxyethoxy)-5-nitropyridin-4-yl]-2-oxopropionate potassium salt



1.86 g of potassium are initially charged in 120 ml of dry diethyl ether, and 15 ml of EtOH are added slowly. The mixture is cooled to 0°C. 5 g of 2-(2-methoxyethoxy)-4-methyl-5-nitropyridine are dissolved in 15 ml of dry ether and 3 ml of EtOH and added. 27.5 g of diethyl oxalate were dissolved in

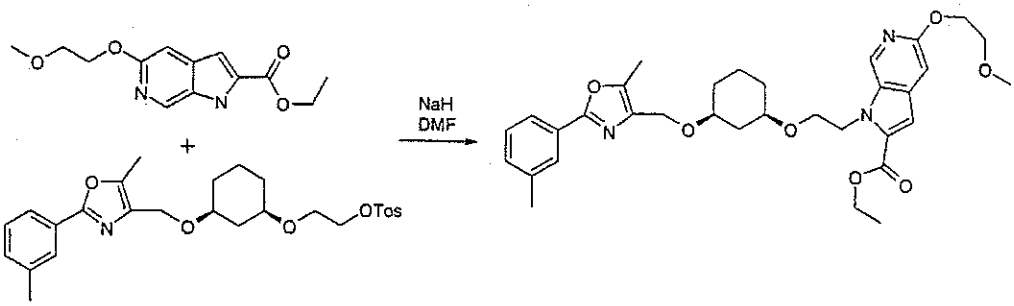
100 ml of toluene and, at 0°C, added dropwise over a period of 45 min. The mixture is stirred at room temperature for 24 h. The precipitate is allowed to settle, the mixture is filtered and the precipitate is washed with ether/n-heptane 1:1. The precipitate is dried under high vacuum. This gives ethyl 3-[2-(2-methoxyethoxy)-5-nitropyridin-4-yl]-2-oxopropionate potassium salt as a red solid. (LC-MS protonate form) $C_{13}H_{16}N_2O_7$ (312.28), MS (ESI): 313 ($M + H^+$).

Ethyl 5-(2-methoxyethoxy)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



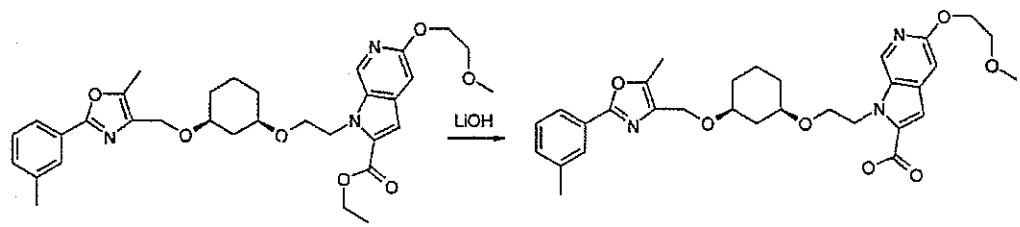
3.5 g of dried ethyl 3-[2-(2-methoxyethoxy)-5-nitropyridin-4-yl]-2-oxopropionate potassium salt are dissolved in 50 ml of MeOH, and 2 ml of acetic acid are added. After the addition of 500 mg of palladium hydroxide/C 20%, the mixture is stirred under 1 atm of hydrogen. After 5 h, a further 200 mg of catalyst and 0.75 ml of trifluoroethanol are added. After a further 3 h, all volatile components are removed under reduced pressure and 20 ml of sat. sodium bicarbonate solution are added and the mixture is extracted with ethyl acetate. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:2). This gives ethyl 5-(2-methoxyethoxy)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate as a yellowish solid. $C_{13}H_{16}N_2O_4$ (264.28), MS (ESI): 265 ($M + H^+$).

Ethyl 5-(2-methoxyethoxy)-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]ethyl}-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



66 mg of ethyl 5-(2-methoxyethoxy)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate are dissolved in 2 ml of dry DMF, and 12 mg of 60 percent strength sodium hydride suspension are added. After 30 min at room temperature, 100 mg of ((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate ((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]ethyl toluene-4-sulfonate in 2 ml of DMF are added. The mixture is stirred at 40°C until the reaction has gone to completion (monitored by LC-MS). After cooling, the mixture is diluted with sat. NaCl solution and ethyl acetate. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:2). This gives ethyl 5-(2-methoxyethoxy)-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-pyrrolo[2,3-c]pyridine-2-carboxylate as a yellowish solid. $C_{33}H_{41}N_3O_7$ (591.71), MS (ESI): 592 ($M + H^+$).

(1R,3S)-5-(2-Methoxyethoxy)-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-yl-methoxy)cyclohexyloxy]ethyl}-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

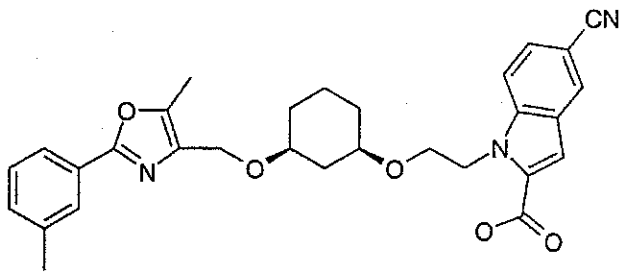


60 mg of ethyl 5-(2-methoxyethoxy)-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-pyrrolo[2,3-c]pyridine-2-carboxylate are dissolved in 2 ml of THF/methanol 3:1, and 0.15 ml of a 1 N lithium hydroxide solution is added. The mixture is stirred at room temperature for 24 h. All volatile components are removed under reduced pressure, the

residue is taken up in DMF/acetonitrile, 70 µl of TFA are added and the mixture is filtered and purified by RP-HPLC. This gives 14 mg of (1R,3S)-5-(2-methoxyethoxy)-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid as a colorless oil. $C_{31}H_{37}N_3O_7$ (563.66), MS (ESI): 564 ($M + H^+$).

Example X

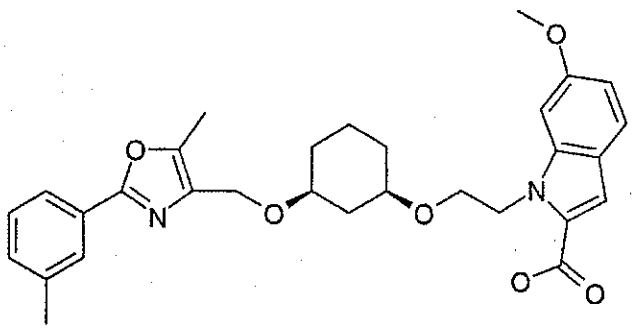
(1R,3S)-5-Cyano-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and ethyl 5-cyano-1H-indole-2-carboxylate give, analogously to Example IX, (1R,3S)-5-cyano-1-{2-[3-(5-methyl-2-m-tolyl-oxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid of molecular weight 513.60 ($C_{30}H_{31}N_3O_5$), MS (ESI): 514 ($M + H^+$).

Example XI

(1R,3S)-6-Methoxy-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid

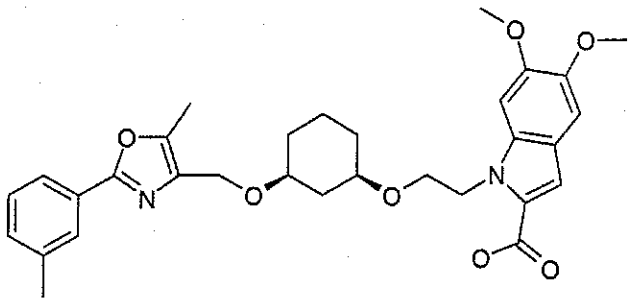


((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and methyl 6-methoxy-1H-indole-2-carboxylate give,

analogously to Example IX, (1R,3S)-6-methoxy-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid of molecular weight 518.62 ($C_{30}H_{34}N_2O_6$), MS (ESI): 519 ($M + H^+$).

Example XII

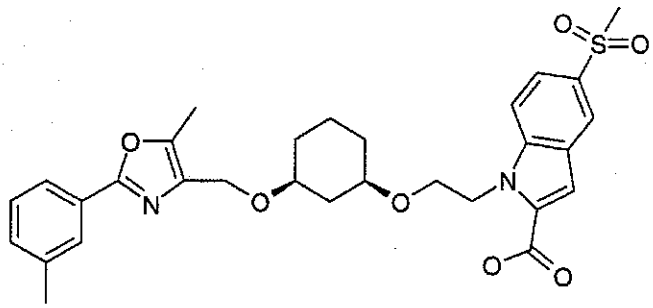
(1R,3S)-5,6-Dimethoxy-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and ethyl 5,6-dimethoxy-1H-indole-2-carboxylate give, analogously to Example IX, (1R,3S)-5,6-dimethoxy-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid of molecular weight 548.64 ($C_{31}H_{36}N_2O_7$), MS (ESI): 549 ($M + H^+$).

Example XIII

(1R,3S)-5-Methanesulfonyl-1-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid



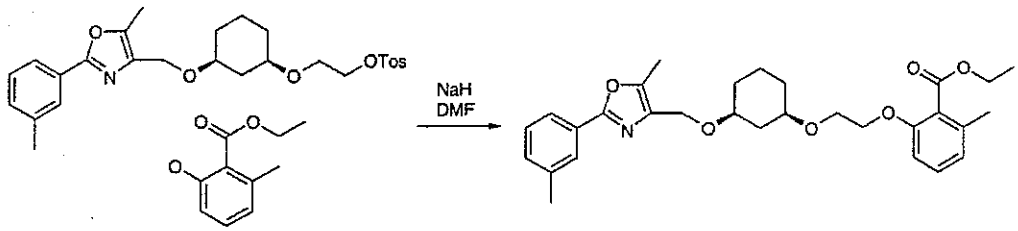
((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and methyl 5-methanesulfonyl-1H-indole-2-carboxylate give, analogously to Example IX, (1R,3S)-5-methanesulfonyl-1-{2-[3-(5-

methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl}-1H-indole-2-carboxylic acid of molecular weight 566.68 ($C_{30}H_{34}N_2O_7S$), MS (ESI): 567 ($M + H^+$).

Example XIV

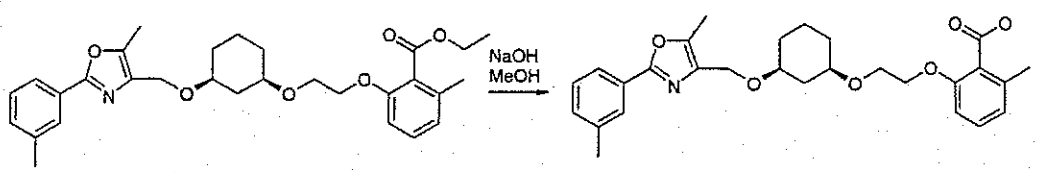
(1R,3S)-2-Methyl-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid

Ethyl (1R,3S)-2-methyl-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxy]ethoxy}benzoate



90 mg of ethyl 2-hydroxy-6-methylbenzoate are dissolved in 2 ml of dry DMF, and 23 mg of a 60 percent strength sodium hydride suspension are added. After 30 min at room temperature, 100 mg of ((1R,3S)-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate in 2 ml of DMF are added. The mixture is stirred at 40°C until the reaction has gone to completion (monitored by LC-MS). After cooling, the mixture is diluted with sat. NaCl solution and ethyl acetate. The organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. This gives ethyl (1R,3S)-2-methyl-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-yl-methoxy)cyclohexyloxy]ethoxy}benzoate as a yellowish oil. $C_{30}H_{37}NO_6$ (507.63), MS (ESI): 508 ($M + H^+$).

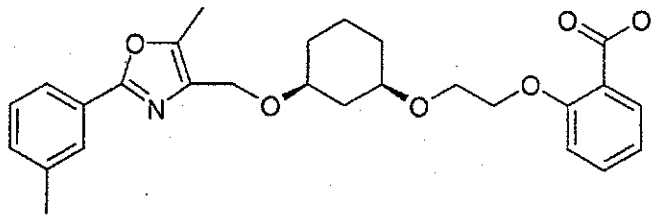
(1R,3S)-2-Methyl-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclo-hexyloxy]ethoxy}benzoic acid



Unpurified ethyl (1R,3S)-2-methyl-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoate are dissolved in 3 ml of methanol, and 0.25 ml of a 5 N sodium hydroxide solution are added. The mixture is stirred at 60°C for 8 h and at 80°C for 12 h. After cooling, the mixture is taken up in 2N HCl/ethyl acetate, the organic phase is dried over sodium sulfate and the solvent is removed under reduced pressure. The residue is purified by RP-HPLC. This gives (1R,3S)-2-methyl-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy)benzoic acid as a colorless oil. $C_{28}H_{33}NO_6$ (479.58), MS (ESI): 480 ($M + H^+$).

Example XV

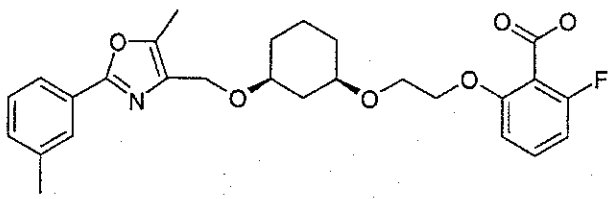
(1R,3S)-2-{2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-ethoxy}benzoic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and methyl 2-hydroxybenzoate give, analogously to Example XIV, (1R,3S)-2-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid of molecular weight 465.55 ($C_{27}H_{31}NO_6$), MS (ESI): 466 ($M + H^+$).

Example XVI

(1R,3S)-2-Fluoro-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid

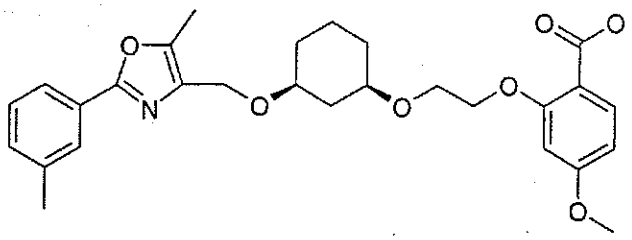


((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and methyl 2-fluoro-6-hydroxybenzoate give,

analogously to Example XIV, (1R,3S)-2-fluoro-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid of molecular weight 483.54 ($C_{27}H_{30}FNO_6$), MS (ESI): 484 ($M + H^+$).

Example XVII

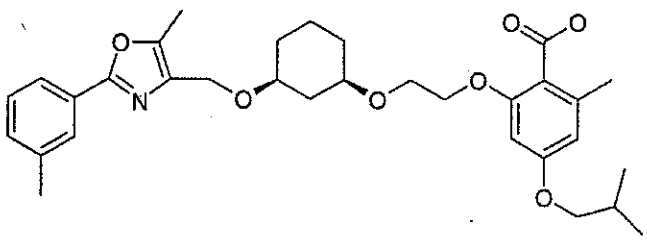
(1R,3S)-2-Fluoro-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and methyl 4-methoxy-2-hydroxybenzoate give, analogously to Example XIV, (1R,3S)-2-fluoro-6-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid of molecular weight 495.58 ($C_{28}H_{33}NO_7$), MS (ESI): 496 ($M + H^+$).

Example XVIII

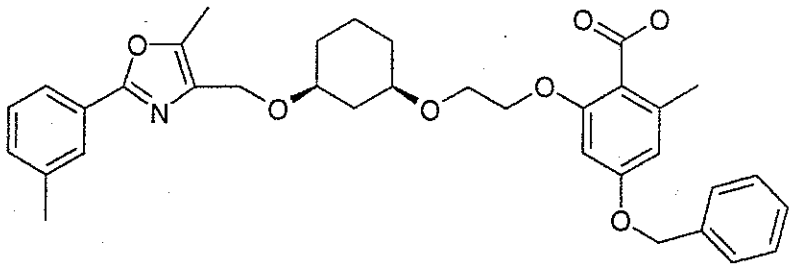
(1R,3S)-4-Isobutoxy-2-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and ethyl 4-isopropoxy-2-hydroxy-6-methylbenzoate give, analogously to Example XIV, (1R,3S)-4-isobutoxy-2-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid of molecular weight 551.69 ($C_{32}H_{41}NO_7$), MS (ESI): 552 ($M + H^+$).

Example XIX

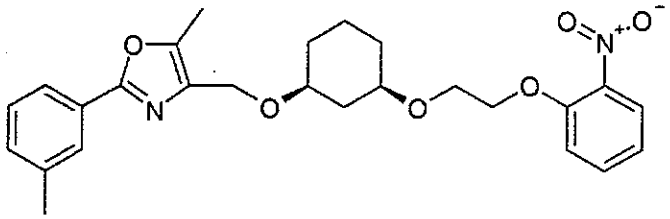
(1R,3S)-4-Benzyloxy-2-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and ethyl 4-benzyloxy-2-hydroxy-6-methylbenzoate give, analogously to Example XIV, (1R,3S)-4-benzyloxy-2-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}benzoic acid of molecular weight 585.70 ($C_{35}H_{39}NO_7$), MS (ESI): 586 ($M + H^+$).

Example XX

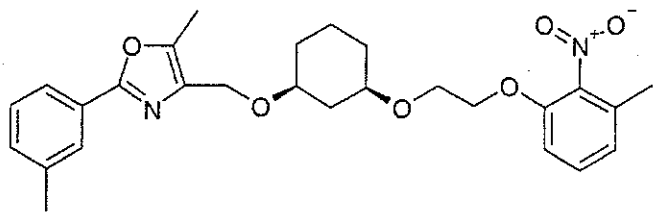
(1S,3R)-5-Methyl-4-{3-[2-(2-nitrophenoxy)ethoxy]cyclohexyloxymethyl}-2-m-tolyloxazole



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and 2-hydroxynitrobenzene give, analogously to Example XIV, (1S,3R)-5-methyl-4-{3-[2-(2-nitrophenoxy)ethoxy]cyclohexyloxymethyl}-2-m-tolyloxazole of molecular weight 466.54 ($C_{26}H_{30}N_2O_6$), MS (ESI): 467 ($M + H^+$).

Example XXI

(1S,3R)-5-Methyl-4-{3-[2-(3-methyl-2-nitrophenoxy)ethoxy]cyclohexyloxymethyl}-2-m-tolyloxazole

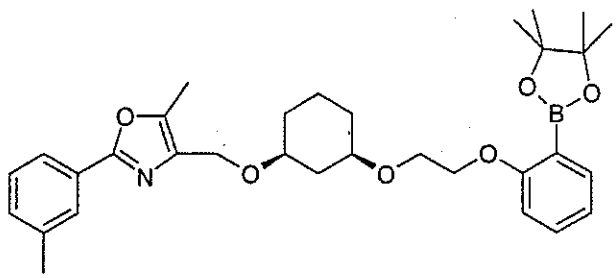


((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and 6-methyl-2-hydroxynitrobenzene give, analogously to Example XIV, (1S,3R)-5-methyl-4-{3-[2-(3-methyl-2-nitrophenoxy)-ethoxy]cyclohexyloxymethyl}-2-m-tolyloxazole of molecular weight 480.57 ($C_{27}H_{32}N_2O_6$), MS (ESI): 481 ($M + H^+$).

Example XXII

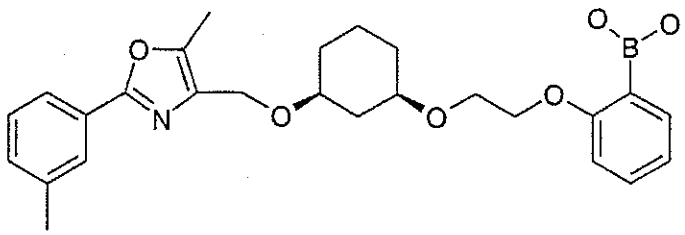
(1R,3S)-2-{2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-ethoxy}phenylboronic acid

(1S,3R)-5-Methyl-4-(3-{2-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]ethoxy}cyclohexyloxymethyl)-2-m-tolyloxazole



((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and 2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl) phenol give, analogously to Example XIV, (1S,3R)-5-methyl-4-(3-{2-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]ethoxy}cyclohexyl-oxymethyl)-2-m-tolyloxazole of molecular weight 547.51 ($C_{32}H_{42}BNO_6$), MS (ESI): 548 ($M + H^+$).

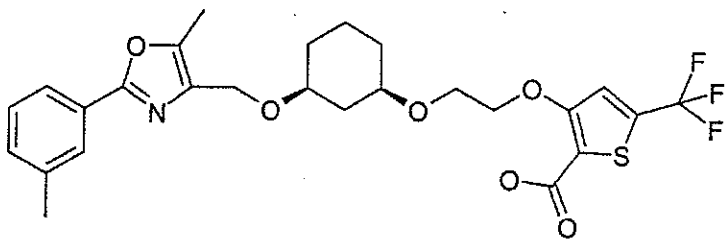
(1R,3S)-2-{2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-ethoxy}phenylboronic acid



Unpurified (1S,3R)-5-methyl-4-(3-{2-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenoxy]ethoxy}cyclohexyloxymethyl)-2-m-tolyloxazole is taken up in 6 ml of THF, and 0.75 ml of 1N HCl is added. After 3 h of stirring at room temperature, the solvent is evaporated and the residue is taken up in DMF then purified by RP-HPLC. This gives (1R,3S)-2-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}phenylboronic acid as a colorless oil. 465.36 ($C_{26}H_{32}BNO_6$), MS (ESI): 466 ($M + H^+$).

Example XXIII

(1R,3S)-3-{2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]-ethoxy}-5-trifluoromethylthiophene-2-carboxylic acid

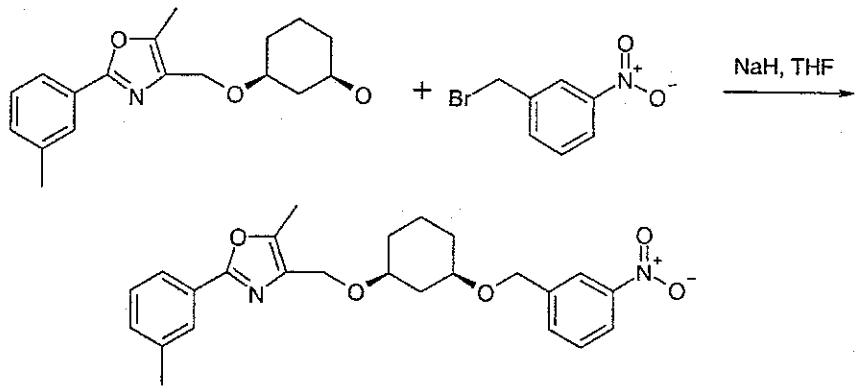


((1R,3S)-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethyl toluene-4-sulfonate and methyl 3-hydroxy-5-trifluoromethylthiophene-2-carboxylate give, analogously to Example XIV, (1R,3S)-3-{2-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxy]ethoxy}-5-trifluoromethylthiophene-2-carboxylic acid of molecular weight 539.58 ($C_{26}H_{28}F_3NO_6S$), MS (ESI): 540 ($M + H^+$).

Example XXIV

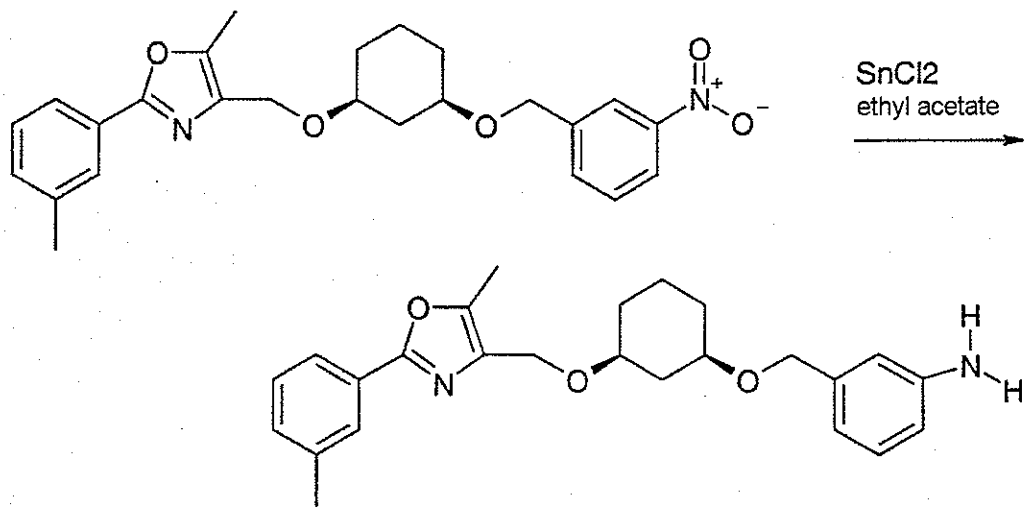
(1R,3S)-C,C,C-Trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxymethyl]phenyl}methanesulfonamide

(1S,3R)-5-Methyl-4-[3-(3-nitrobenzyloxy)cyclohexyloxymethyl]-2-m-tolyloxazole



530 µl of 1M NaHMDS in THF are added to 150 mg of 3-((1R,3S)-cis-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol in 3 ml of THF, and the mixture is stirred at RT for 10 min. 121 mg of 3-nitrobenzyl bromide are added, and the mixture is stirred at 60°C for 5 h. After addition of further 3-nitrobenzyl bromide the mixture is stirred overnight. The mixture is taken up in sat. NaCl solution/ethyl acetate. The org. phase is dried over sodium sulfate and evaporated. The residue is purified by chromatography on silica gel. This gives (1S,3R)-5-methyl-4-[3-(3-nitrobenzyloxy)cyclohexyloxy-methyl]-2-m-tolyloxazole as a colorless oil of molecular weight 436.51 ($C_{25}H_{28}N_2O_5$), MS (ESI): 437 ($M + H^+$).

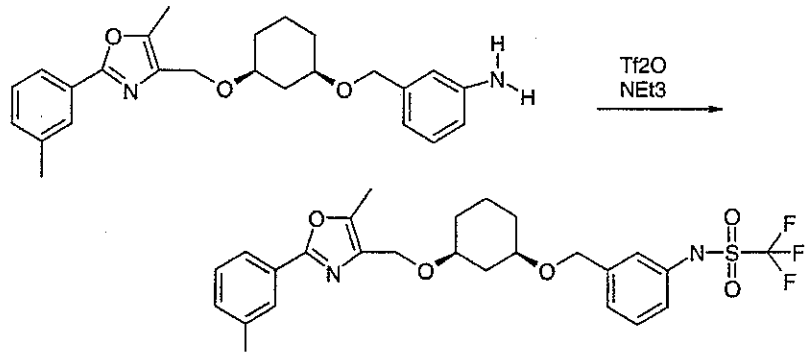
(1R,3S)-3-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-phenylamine



400 mg of tin(II) chloride dihydrate are added to 150 mg of (1S,3R)-5-methyl-4-[3-(3-nitrobenzyloxy)cyclohexyloxymethyl]-2-m-tolyloxazole in

24 ml of ethyl acetate, and the mixture is stirred at room temperature. After every 8 h, 400 mg of tin(II) chloride dihydrate are added, until the reaction has gone to completion. The mixture is diluted with ethyl acetate and washed with water. The org. phase is dried over sodium sulfate and evaporated. The residue is used for the next reaction without purification. This gives (1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]phenylamine as a colorless oil of molecular weight 406.53 ($C_{25}H_{30}N_2O_3$), MS (ESI): 407 ($M + H^+$).

(1R,3S)-C,C,C-Trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)-cyclohexyloxymethyl]phenyl}methanesulfonamide

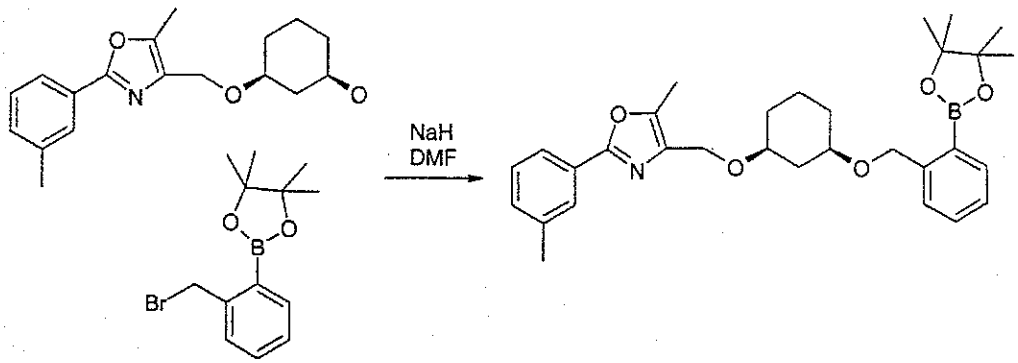


55 mg of (1R,3S)-3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]phenylamine are dissolved in 2 ml of dichloromethane and cooled to -78°C. 100 µl of triethylamine and then 42 µl of trifluoromethanesulfonic anhydride are added. After 1 h, 200 µl of water are added and the mixture is allowed to warm to room temperature. The mixture is diluted with dichloromethane and washed with 1N HCL and sat. NaCl solution. The org. phase is dried over sodium sulphate and evaporated. The residue is purified by RP-HPLC. This gives (1R,3S)-C,C,C-trifluoro-N-{3-[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]phenyl}methanesulfonamide as a colorless oil of molecular weight 538.59 ($C_{26}H_{29}F_3N_2O_5S$), MS (ESI): 539 ($M + H^+$).

Example XXV

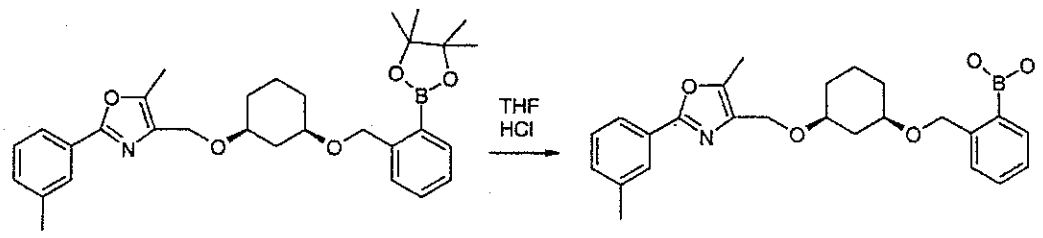
(1R,3S)-2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-benzeneboronic acid

(1S,3R)-5-Methyl-4-{3-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyloxy]cyclohexyloxymethyl}-2-m-tolyloxazole



60 mg (1.6 mmol) of NaH were added to 300 mg of 3-((1R,3S)-cis-5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexanol in 5 ml of DMF, and the mixture is stirred at RT for 10 min. After addition of 335 mg of 2-(2-bromomethylphenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolan, the mixture is stirred until maximum conversion has been achieved and quenched with MeOH. The mixture is taken up in sat. NaCl solution/ethyl acetate, the organic phase is dried over sodium sulfate and filtered and the solvent is removed under reduced pressure. The residue is purified by flash chromatography on silica gel (n-heptane/ethyl acetate = 1:1). This gives (1S,3R)-5-methyl-4-{3-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzyloxy]cyclohexyloxymethyl}-2-m-tolyloxazole as a colorless oil. $C_{31}H_{40}BNO_5$ (517.48), MS (ESI): 518 ($M + H^+$).

(1R,3S)-2-[3-(5-Methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-benzeneboronic acid



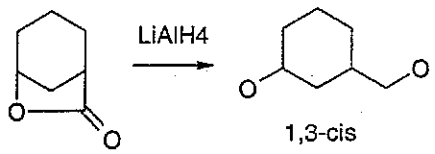
1 ml of 1 N HCl is added to 300 mg of (1S,3R)-5-methyl-4-{3-[2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzyloxy]cyclohexyloxymethyl}-2-m-tolyloxazole in 5 ml of THF, and the mixture is stirred at RT until the reaction has gone to completion. The solvent is removed under reduced pressure and the compound is purified by RP-HPLC. This gives (1R,3S)-2-

[3-(5-methyl-2-m-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzene-boronic acid as a colorless oil. $C_{25}H_{30}BNO_5$ (435.33), MS (ESI): 436 ($M + H^+$).

Example XXVI

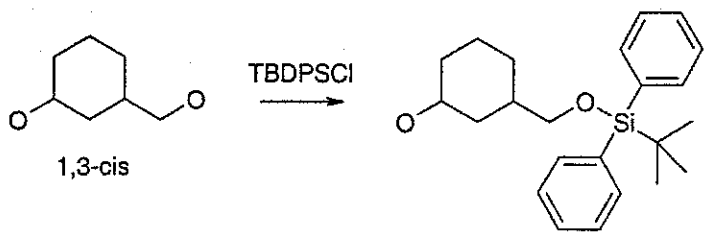
1-[(1S,3R)/(1R,3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl-methyl]-1H-indole-2-carboxylic acid

cis-3-Hydroxymethylcyclohexanol



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, saturated ammonium chloride solution is added and the pH is adjusted to neutral by addition of a 5% strength solution of citric acid. 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 MgSO4 and the solvent is then removed under reduced pressure. This gives 10.5 g of (1S,3R)/(1R,3S)-3-hydroxymethylcyclohexanol as a colorless oil. C7H14O2 (130.13), Rf(ethyl acetate) = 0.14.

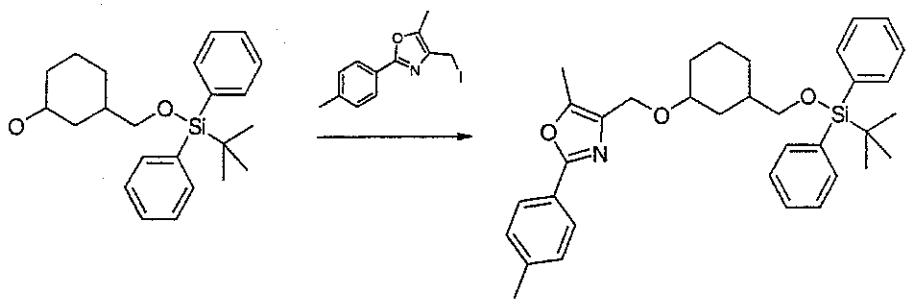
(1S,3R)/(1R,3S)-3-(tert-Butyldiphenylsilanyloxymethyl)cyclohexanol



10.5 g of (1S,3R)/(1R,3S)-3-hydroxymethylcyclohexanol are dissolved in 300 ml of dimethylformamide, and 23 ml of tert-butyldiphenylsilanyl chloride, 8.0 g of imidazole and 200 mg of dimethylaminopyridine are added. The mixture is stirred at room temperature for 12 hours. The

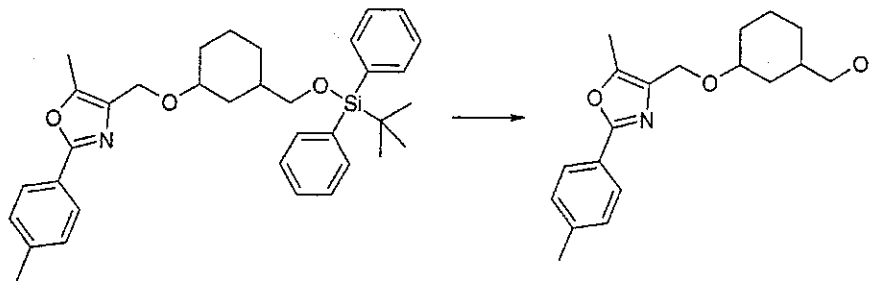
dimethylformamide is removed under reduced pressure and the residue is dissolved in 300 ml of ethyl acetate and washed five times with in each case 100 ml of water. The organic phase is dried over MgSO4 and the solvent is then removed under reduced pressure. This gives 27.0 g of (1S,3R)/(1R,3S)-3-(tert-butyldiphenylsilanyloxymethyl)cyclohexanol as an oil. C23H32O2Si (368.6), Rf(n-heptane:ethyl acetate = 1:1) = 0.42.

4-[(1S,3R)/(1R,3S)-3-(tert-Butyldiphenylsilanyloxymethyl)cyclohexyloxy-methyl]-5-methyl-2-p-tolyloxazole



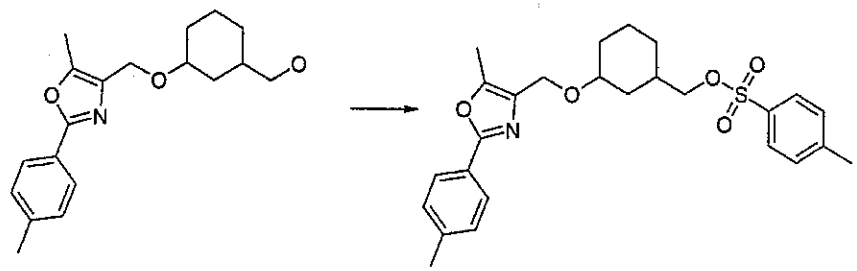
6.4 g of (1S,3R)/(1R,3S)-3-(tert-butyldiphenylsilanyloxymethyl)cyclohexanol and 6.5 g of 4-iodomethyl-5-methyl-2-p-tolyloxazole are dissolved in 200 ml of dimethylformamide, and 1 g of sodium hydride (60% strength suspension in mineral oil) is added. After 1 hour of stirring at room temperature, another 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 is dried over MgSO4 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-[(1S,3R)/(1R,3S)-3-(tert-butyldiphenylsilanyloxymethyl)cyclohexyloxy-methyl]-5-methyl-2-p-tolyloxazole as an oil. C35H43NO3Si (553.28), Rf(n-heptane:ethyl acetate = 2:1) = 0.50.

[(1S,3R)/(1R,3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]-methanol



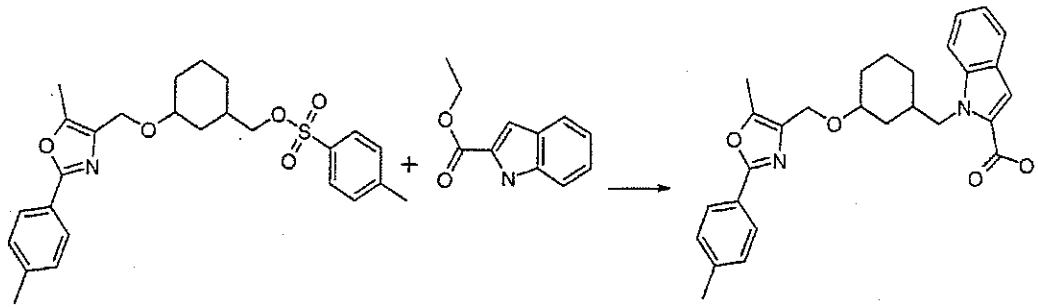
6.8 g of 4-[(1S,3R)/(1R,3S)-3-(tert-butyldiphenylsilanyloxymethyl)cyclohexyloxymethyl]-5-methyl-2-p-tolyloxazole are dissolved in 40 ml of tetrahydrofuran, and 40 ml of a 1M solution of tetrabutylammonium fluoride are added. The mixture is warmed at 50°C for 1 hour and the solvent is then removed under 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 [(1S,3R)/(1R,3S)-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.

(1S,3R)/(1R,3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethyl toluene-4-sulfonate



1 g of [(1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl]methanol together with 730 mg of p-toluenesulfonyl chloride, 0.7 ml of triethylamine and 50 mg of a dimethylaminopyridine are dissolved in 20 ml of dichloromethane and stirred at room temperature for 24 h. The mixture is washed with water and saturated sodium bicarbonate solution, the organic phase is dried over MgSO4 and the solvent is then removed under reduced pressure. This gives 1.5 g of (1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethyl toluene-4-sulfonate as a brown oil which is reacted further without purification. C26H31NO5S (469.60), Rf(n-heptane:ethyl acetate = 1:1) = 0.50.

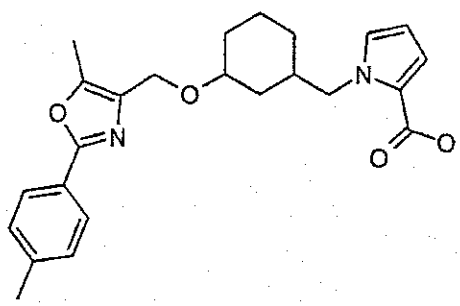
1-[(1S,3R)/(1R,3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl-methyl]-1H-indole-2-carboxylic acid



120 mg of ethyl 1H-indole-2-carboxylate are dissolved in 5 ml of dimethylformamide, and 25 mg of sodium hydride (60% strength suspension in mineral oil) are added. After 30 minutes, 100 mg of (1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethyl toluene-4-sulfonate, dissolved in 1 ml of dimethylformamide, are added dropwise. Another 25 mg of sodium hydride (60% strength suspension in mineral oil) are added, and the reaction mixture is warmed at 60°C for 3 hours. The mixture is diluted by addition of 50 ml of methyl tert-butyl ether and washed three times in each case with 20 ml of water. The organic phase is dried over MgSO4 and the solvent is then removed under reduced pressure. The residue is purified by RP-HPLC. Freeze-drying gives 36 mg of the racemate 1-[(1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl-methyl]-1H-indole-2-carboxylic acid as a lyophilisate. C28H30N2O4 (458.56), MS (ESI) = 459 ($M + H^+$).

Example XXVII

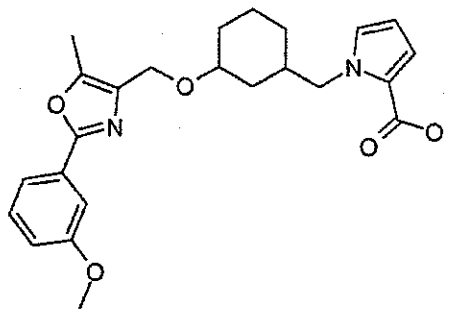
1-[(1S,3R)/(1R,3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl-methyl]-1H-pyrrole-2-carboxylic acid



Analogously to **Example XXVI**, (1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethyl toluene-4-sulfonate and ethyl 1H-pyrrole-2-carboxylate gave the racemate 1-[(1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethyl]-1H-pyrrole-2-carboxylic acid, $C_{24}H_{28}N_2O_4$ (408.50), MS (ESI) = 409 ($M + H^+$).

Example XXVIII

1-{(1S,3R)/(1R,3S)-3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]-cyclohexylmethyl}-1H-pyrrole-2-carboxylic acid

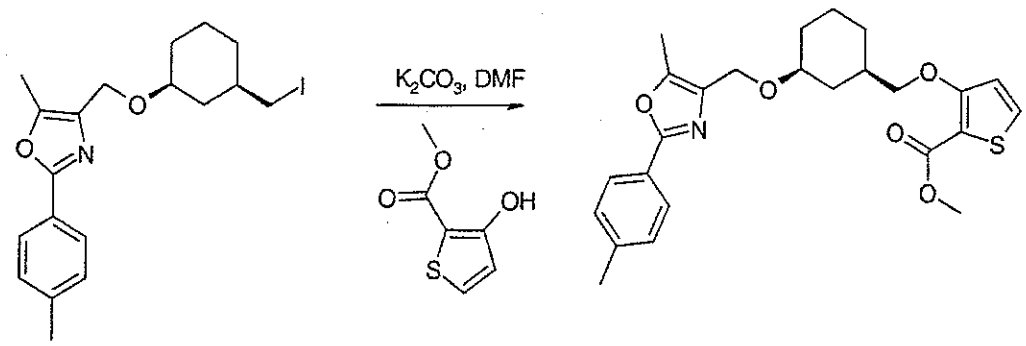


Analogously to **Example XXVI**, 4-iodomethyl-2-(3-methoxyphenyl)-5-methyloxazole, (1S,3R)/(1R,3S)-3-(tert-butyldiphenylsilanyloxymethyl)-cyclohexanol and ethyl 1H-pyrrole-2-carboxylate gave the racemate 1-{(1S,3R)/(1R,3S)-3-[2-(3-methoxyphenyl)-5-methyloxazol-4-ylmethoxy]-cyclohexylmethyl}-1H-pyrrole-2-carboxylic acid, $C_{24}H_{28}N_2O_5$ (424.50), MS (ESI) = 425 ($M + H^+$).

Example XXIX

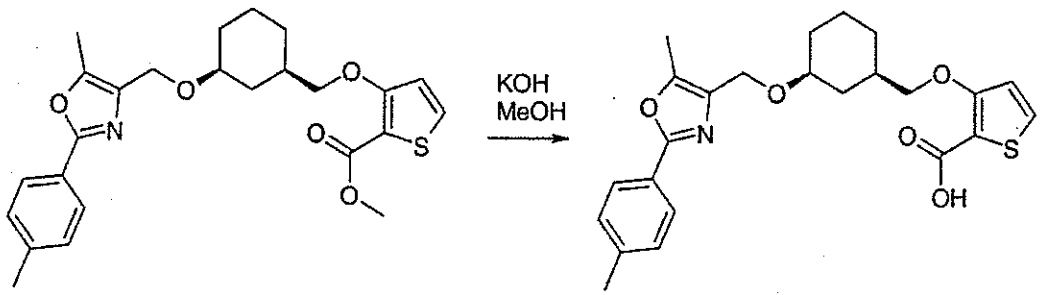
(1S,3R)/(1R,3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl-methyloxy]thiophen-2-carboxylic acid:

(1S,3R)/(1R,3S) Methyl 3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclo-hexylmethyloxy]thiophene-2-carboxylate:



27 mg of methyl 3-hydroxythiophene-2-carboxylate and 67 mg of potassium carbonate are added to 50 mg of 4-((1S,3R)/(1R,3S)-3-iodomethylcyclohexyloxymethyl)-5-methyl-2-p-tolyloxazole in 2 ml of DMF, and the mixture is stirred at 90°C for 2 h. Water and MTBE are added and the phases are then separated. The organic phase is dried over $MgSO_4$ and concentrated. Chromatography of the residue on silica gel (heptane/ethyl acetate 5/1) gives 12 mg of the racemate methyl (1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethyl-oxy]thiophene-2-carboxylate as a yellow oil. C25H29NO5S (455.58); LCMS (ESI): 456.1 (MH^+).

(1S,3R)/(1R,3S)-3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl-methyloxy]thiophene-2-carboxylic acid:

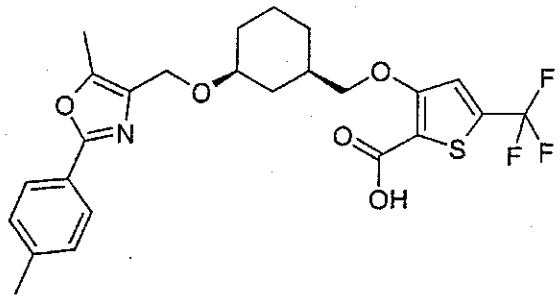


12 mg of methyl (1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-yl-methoxy)cyclohexylmethyloxy]thiophene-2-carboxylate methyl 3-(5-methyl-2-p-tolyoxazol-4-ylmethoxy) cyclohexylmethyloxy]thiophene-2-carboxylate are dissolved in 1 ml of methanol, 10 drops of 2N KOH are added and the mixture is stirred at RT for 1 h. 2 ml of saturated NH4Cl solution and MTBE are then added, and the phases are separated. The organic phase is dried over MgSO4 and concentrated, which gives 9.4 mg of (1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethyloxy]thiophene-2-

carboxylic acid as a racemate. C24H27NO5S (441.55); LCMS (ESI): 442.1 (MH^+).

Example XXX

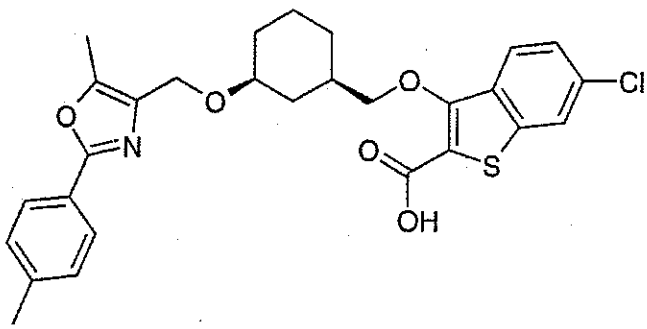
(1S,3R)/(1R,3S)-3-[3-(5-Methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-5-trifluoromethylthiophene-2-carboxylic acid



Analogously to **Example XXIX**, 4-((1S,3R)/(1R,3S)-3-iodomethyl-cyclohexyloxymethyl)-5-methyl-2-p-tolyloxazole and methyl 3-hydroxy-5-trifluoromethylthiophene-3-carboxylate give (1S,3R)/(1R,3S)-3-[3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexylmethoxy]-5-trifluoromethyl-thiophene-2-carboxylic acid as a racemate. C25H26F3NO5S (509.55), LCMS (ESI) = 510.1 (MH^+).

Example XXXI

6-Chloro-3-[1S,3R)/(1R,3S)-3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)-cyclohexylmethoxy]benzo[b]thiophene-2-carboxylic acid

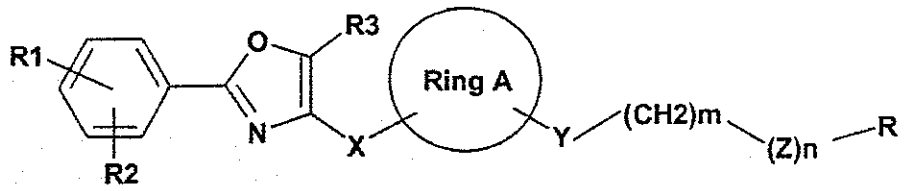


Analogously to **Example XXIX**, 4-((1S,3R/(1R,3S)-3-iodomethyl-cyclohexyloxymethyl)-5-methyl-2-p-tolyloxazole and methyl 6-chloro-3-hydroxybenzo[b]thiophene-2-carboxylate give 6-chloro-3-[(1S,3R)/(1R,3S)-

3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyl-methoxy]benzo[b]-thiophene-2-carboxylic acid as a racemate. C28H28ClNO5S (526.06), LCMS (ESI): 526.1 (MH^+).

We claim:

1. A compound of the formula I



I

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 atoms may be replaced by oxygen atoms;
	R1, R2	independently of one another are H, F, Br, Cl, SF_5, S-$(C_1$-$C_6)$-alkyl, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, SCF_3, phenoxy, OCF_2CHF_2, OCF_2CF_3, $(C_1$-$C_6)$-alkyl-$(C_1$-$C_6)$-alkoxy, O$(C_1$-$C_6)$-alkyl-$(C_1$-$C_6)$-alkoxy, benzyloxy;
	R3	is H, CF_3, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, phenyl;
	X	is $(C_1$-$C_6)$-alkanediyl, where in the alkanediyl group one or more carbon atoms may be replaced by oxygen atoms;
	Y	is S, O, a bond;
	m	is 1 to 3;
	n	is 0 or 1;
	Z	is O, S, CO or CO-NH;

R is H, OH, CH_2-CO-NH-OH, CH_2-CO-NH-(C_1-C_6)-alkyl, CH_2-CO-NH-(C_1-C_6)-alkoxy, NR4R5 or a 5- to 12-membered mono or bicyclic unsaturated, partially unsaturated or saturated ring which may contain one to four heteroatoms from the group consisting of N, O and S and which may be benzo-fused, where the 5- to 12-membered ring may further substituents such as F, Cl, Br, CN, SH, COOH, (C_1C_4)-alkyl, (C_1-C_6)-alkoxy, SO_2-(C_1-C_4)-alkyl, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-phenyl, phenoxy $NHSO_2CF_3$ or $B(OH)_2$;

R4 is H, (C_1-C_6)-alkyl;

R5 is OH, NH_2, SO_2-CF_3, SO_2-phenyl-CF_3, CO-CF_3, (C_1-C_6)-alkoxy, phenyl which may be substituted by CH_3 and COOH;

R4 and R5 together with the nitrogen atom that carries them form a 5-membered aromatic heterocycle which in turn may be fused to an aromatic 5- to 7-membered ring which may have one to four nitrogen atoms and which may be substituted by: F, Cl, Br, CF_3, OCF_3, COOH, SO_2CH_3, CN, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl, (C_1-C_6)-alkyl-phenyl, (C_1-C_6)-alkyl-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy, (C_1-C_6)-alkoxy-phenyl, phenoxy;

and physiologically acceptable salts thereof.

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

ring A is (C_3-C_8)-cycloalkanediyl, where one carbon atom may be replaced by an oxygen atom, and

X is (C_1-C_6)-alkanediyl, where one carbon atom may be replaced by an oxygen atom.

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

ring A is cyclohexane-1,3-diyl and

X is CH_2-O.

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;

X is CH_2-O;

Y is O.

5. A compound of the formula I as claimed in any of claims 1 to 4, in which the central cycloalkane-1,3-diyl ring is attached cis.

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

R1/R2 are H, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy;

R3 is (C_1-C_4)-alkyl.

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

Y is O;

m is 3;

n is 0.

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

Y is O;

m is 2;

n is 0.

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

Y is O;

m is 2;

n is 1;

Z is O.

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

Y is O;

m is 1;

n is 0;

11. A compound of the formula I as claimed in any of claims 1, 2, 3, 5 and 6, in which

Y is a bond;

m is 1;

n is 0.

12. A compound of the formula I as claimed in any of claims 1, 2, 3, 5 and 6, in which

Y is a bond;

m is 1;

n is 1;

Z is O.

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

Y is O;

m is 3;

n is 0;

R is tetrazole, $NHSO_2CF_3$.

14. A compound of the formula I as claimed in any of claims 1 to 6 and 8, in which

Y is O;

m is 2;

n is 0;

R is tetrazole, $NHSO_2CF_3$ or NR4R5 which denotes indole or 6-azaindole and may be substituted by F, Br, CN, COOH, (C_1C_4)-alkyl, (C_1-C_4)-alkoxy, SO_2-CH_3, (C_1-C_6)-alkoxy-(C_1-C_6)-alkoxy or benzoxy.

15. A compound of the formula I as claimed in any of claims 1 to 6 and 9, in which

Y is O;

m is 2;

n is 1;

Z is O;

R is phenyl or thiophene, which radicals may carry further substituents such as F, COOH, $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, NO_2, CF_3, benzyloxy or $B(OH)_2$.

16. A compound of the formula I as claimed in any of claims 1 to 6 and 10, in which

Y is O;

m is 1;

n is 0;

R is phenyl $NHSO_2CF_3$, phenyl-$B(OH)_2$ may carry.

17. A compound of the formula I as claimed in any of claims 1, 2, 3, 5, 6 and 11, in which

Y is a bond;

m is 1;

n is 0;

R is NR4R5 which denotes pyrrole or indole and is substituted by COOH.

18. A compound of the formula I as claimed in any of claims 1, 2, 3, 5, 6 and 12, in which

Y	is a bond;	
m	is 1;	
n	is 1;	
Z	is O;	
R	is thiophene or benzothiophene, which radicals may be substituted by COOH, Cl, CF_3.	

19. A pharmaceutical comprising one or more of the compounds of the formula I as claimed in one or more of claims 1 to 18.

20. A pharmaceutical comprising one or more of the compounds of the formula I as claimed in one or more of claims 1 to 18 and one or more active compounds which act favorably on metabolic disorders or associated sequelae.

21. A pharmaceutical, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 18 and one or more antidiabetics.

22. A pharmaceutical comprising one or more of the compounds of the formula I as claimed in one or more of claims 1 to 18 and one or more lipid modulators.

23. The use of the compounds of the formula I as claimed in one or more of claims 1 to 18 for the treatment and/or prevention of disorders of the fatty acid metabolism and disorders of glycose utilization.

24. The use of the compounds of the formula I as claimed in one or more of claims 1 to 18 for the treatment and/or prevention of disorders in which insulin resistance plays a role.

25. The use of the compounds of the formula I as claimed in one or

more of claims 1 to 18 for the treatment and/or prevention of diabetes mellitus and the associated sequelae.

26. The use of the compounds of the formula I as claimed in one or more of claims 1 to 18 for the treatment and/or prevention of dyslipidemias and their sequelae.

27. The use of the compounds of the formula I as claimed in one or more of claims 1 to 18 for the treatment and/or prevention of conditions associated with metabolic syndrome.

28. The use of the compounds as claimed in one or more of claims 1 to 18 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.

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

30. A process for preparing a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 18, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.