DIARYL CYCLOALKYL DERIVATIVES, METHOD FOR PRODUCING THE SAME AND THE USE THEREOF AS PPAR-ACTIVATORS

Description

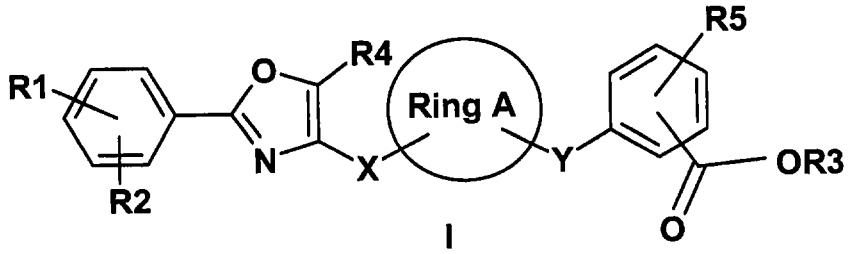
Diarylcycloalkyl derivatives, process for their preparation and their use as pharmaceuticals

The invention relates to diarylcycloalkyl derivatives and to their physiologically acceptable salts and physiologically functional derivatives.

Compounds of a similar structure have already been described in the prior art for the treatment of hyperlipidemia and diabetes (PCT/US/00/11490).

It was an object of the invention to provide compounds having a therapeutically exploitable triglyceride-lowering action and a favorable effect on lipid and carbohydrate metabolism, in particular for syndromes of dyslipidemias, type II diabetes and the metabolic syndrome/syndrome X. It was a particular object to provide compounds having improved action compared with the compounds of PCT/US14490. This was to be achieved, in particular, by activating the PPARα receptor.

Accordingly, the invention relates to compounds of the formula I



I

in which

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

G00002

R1, R2, R4, R5 independently of one another are H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl or O-$(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

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

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

and their physiologically acceptable salts.

Preference is given to compounds of the formula I in which

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

R1, R2, R4 independently of one another are H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, $(C_1$-$C_6)$-alkyl or O-$(C_1$-$C_6)$-alkyl;

R5 is $(C_1$-$C_6)$-alkyl;

R3 is H or $(C_1$-$C_6)$-alkyl;

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

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

and their physiologically acceptable salts.

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

Ring A is (C_3-C_8)-cycloalkyl or (C_3-C_8)-cycloalkenyl;

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

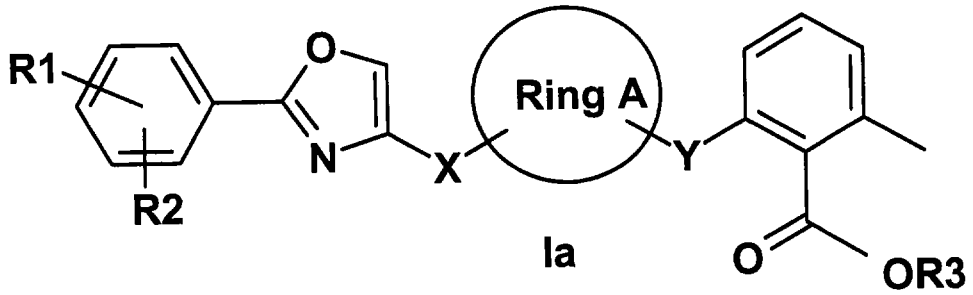
R3 is H or (C_1-C_6)-alkyl;

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

Y is (C_1-C_6)-alkyl, where in the alkyl group one or more carbon atoms are replaced by oxygen atoms;

and their physiologically acceptable salts.

Very particular preference is given to compounds of the formula I having the structure Ia



Ia

wherein

Ring A is cyclohexyl;

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

R3 is H or (C_1-C_6)-alkyl;

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

Y is (C_1-C_6)-alkyl, where in the alkyl group one or more carbon atoms are replaced by oxygen atoms;

and their physiologically acceptable salts.

The invention embraces compounds of the formula I in the form of their racemates, racemic mixtures and pure enantiomers, and also their diastereomers and mixtures thereof.

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

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).

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.

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 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active compound. Thus, ampoules for injections may contain, for example,

from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, capsules or tablets, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active compound. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

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

Suitable pharmaceutical compounds 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.

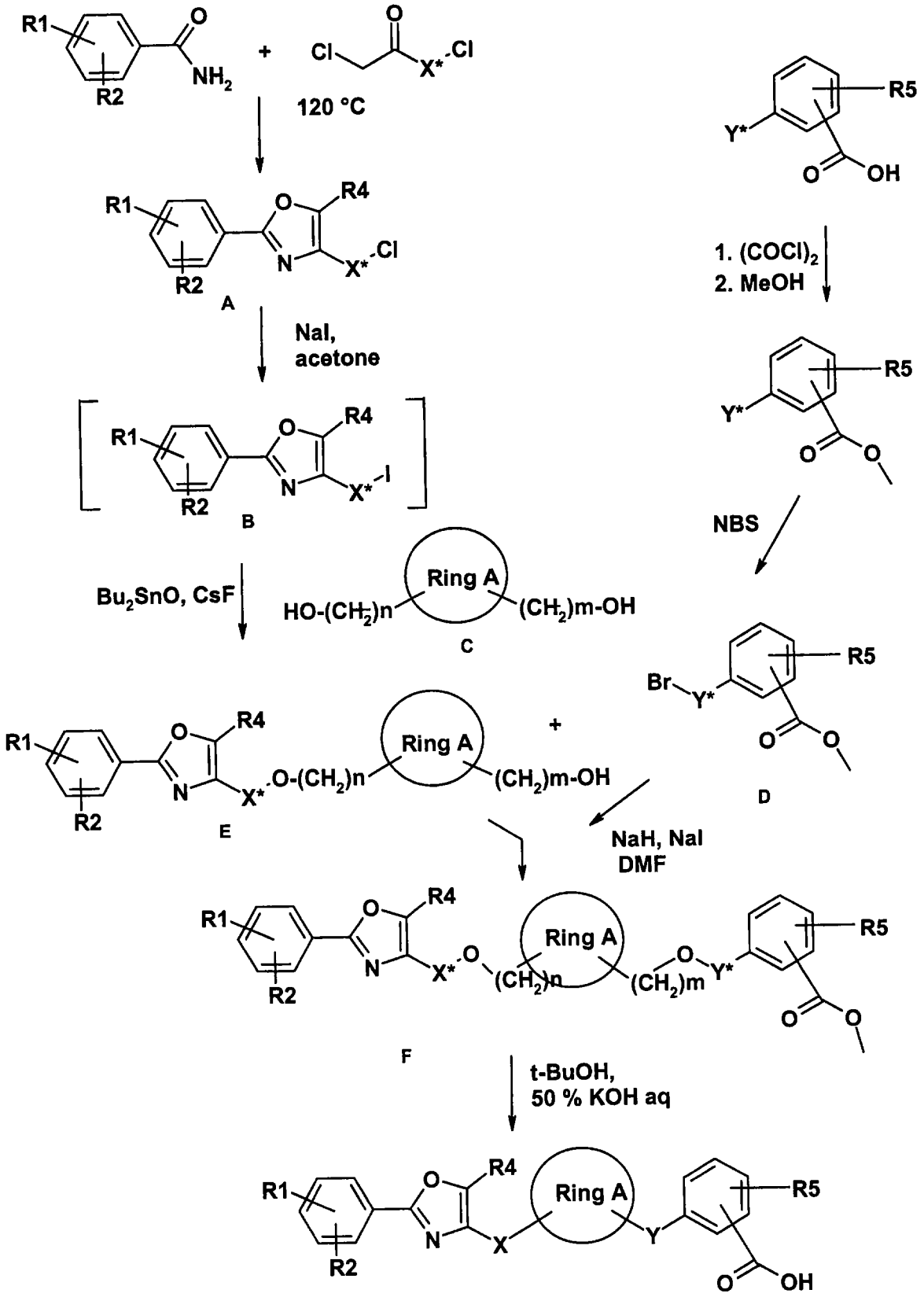
The pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration 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 invention furthermore provides a process for preparing the compounds of the formula I which comprises obtaining the compounds of the formula I by proceeding in accordance with the reaction scheme below:


R1
R2
NH2
O
+
Cl
X*
Cl
120 °C
A
NaI,
acetone
B
Bu2SnO, CsF
HO-(CH2)n
Ring A
(CH2)m-OH
C
R4
R5
Y*
OH
1. (COCl)2
2. MeOH
NBS
Br
D
E
F
NaH, NaI
DMF
t-BuOH,
50 % KOH aq
X
Y

To this end, compounds of the formula A in which R1, R2, R4 and X have the meanings given above are reacted with NaI in acetone with heating at reflux for 12 to 24 hours, giving a compound of the formula B.

The compound of the formula B is reacted with a compound of the formula C in which n and m are each 0-5, giving a compound of the formula E in which R1, R2, R4, m, n and X have the meanings described above. Here, a) C is deprotonated at room temperature in an inert solvent such as dimethylformamide or tetrahydrofuran using sodium hydride and then reacted at about 70°C with the halide, or b) component C is initially heated with dibutyltin oxide in toluene on a water separator for a number of hours and then, with addition of dimethylformamide, cesium fluoride and iodide B, converted into E by stirring at room temperature for a number of hours.

The compound of the formula E is, using a compound of the formula D in which Y is as described above, converted into a compound of the formula F in which R1, R2, R4, R5, X and Y have the meanings described above. To form an ether bond, E is deprotonated, for example in a mixture of dimethylformamide and tetrahydrofuran using a strong base such as Na hydride at room temperature, and then alkylated with a component D, preferably with addition of Na iodide.

The compound of the formula F is converted into compounds of the formula I by hydrolyzing the ester function, for example by heating with potassium hydroxide in an alcohol (ethanol, tert-butanol) and releasing the carboxylic acid group of the formula I by acidification. This carboxylic acid group can be derivatized by customary methods to the group of the formula -(C=O)-OR3, where R3 has the meaning described above.

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.

The compounds can be administered alone or in combination with one or more

further pharmacologically active substances which, for example, act favorably on metabolic disorders and are selected, for example, from antidiabetics, antiadipose agents, antihypertensives and active compounds for treating and/or preventing complications caused by or associated with diabetes.

Particularly suitable further pharmacologically active substances are:

All antidiabetics mentioned in chapter 12 of the Rote Liste 2001. 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. Most of the active compounds listed below are disclosed in USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives such as, for example, Lantus® (see www.lantus.com) or HMR 1964, fast-acting insulins (see US 6,221,633), GLP-1 derivatives such as, for example, those disclosed in WO 98/08871 of Novo Nordisk A/S, and orally active hypoglycemic active compounds.

The orally active hypoglycemic active compounds include, preferably, sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers such as, for example, those disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S, insulin sensitizers, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds which alter lipid metabolism, such as antihyperlipidemic active compounds and antilipidemic active compounds, compounds which reduce food intake, PPAR and PXR agonists 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 an HMG-CoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin.

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

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, JTT-501, GI 262570.

In one embodiment of the invention, the compounds of the formula I are administered in combination with PPAR alpha agonist such as, for example, GW 9578, GW 7647.

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, GW 1536, AVE 8042, AVE 8134, AVE 0847, or as described in PCT/US 11833, PCT/US 11490, DE 10142734.4.

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

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, BMS-201038, R-103757.

In one embodiment of the invention, the compounds of the formula I are administered in combination with bile acid adsorption inhibitor (see, for example, US 6,245,744 or US 6,221,897) such as, for example, HMR 1741.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor such as, for example, JTT-705.

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 an LDL receptor inducer (see US 6,342,512) such as, for example, HMR1171, HMR1586.

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant such as, for example, OPC-14117.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor such as, for example, NO-1886.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an ATP citrate lyase inhibitor such as, for example, SB-204990.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a squalene synthetase inhibitor such as, for example, BMS-188494.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein(a) antagonist such as, for example, CI-1027 or nicotinic acid.

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

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 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, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 of Dr. Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.

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

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-hexa-hydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxamide (WO 01/91752)), orexin antagonists (for example 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A)), H3 agonists (for example 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; see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy

(2001), 2(10), 1615-1622.

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

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

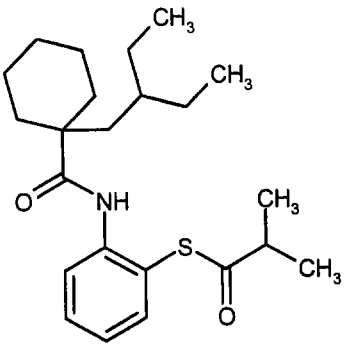
In a further embodiment, the other active compound is sibutramine.

In one embodiment, the other active compound is orlistat.

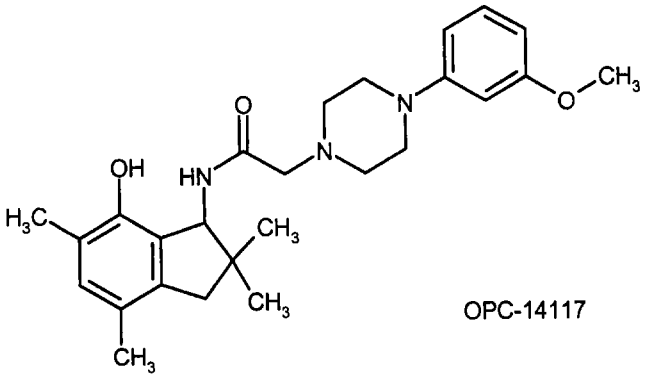
In one embodiment, the other active compound is mazindol or phentermine.

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.

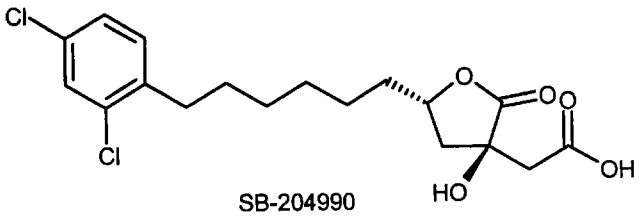
It is self-evident that any suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is regarded as falling within the protection conferred by the present invention.



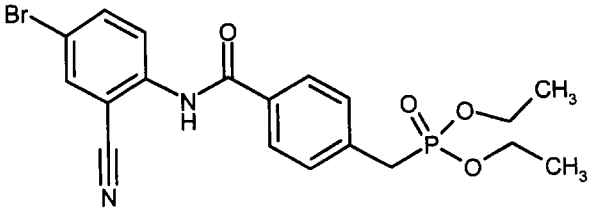
JTT-705



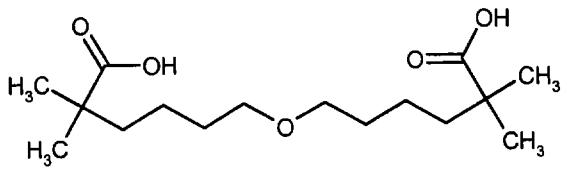
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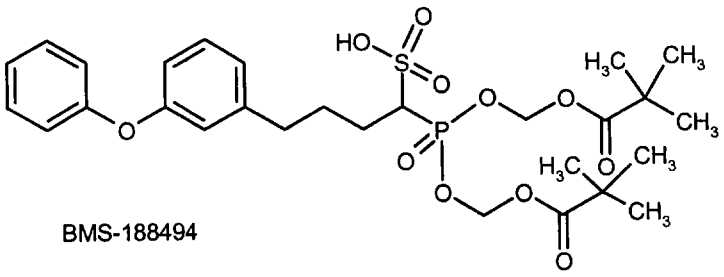
SB-204990



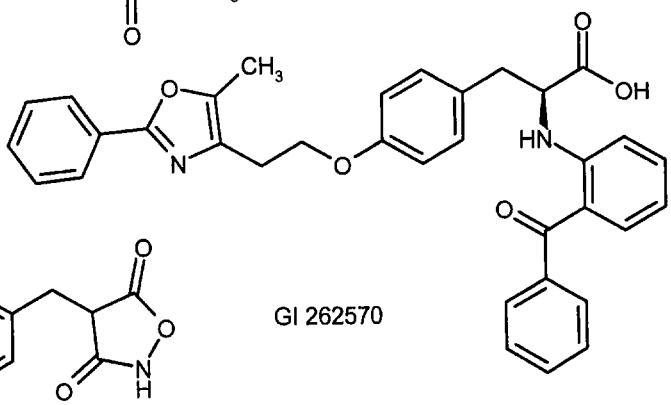
NO-1886



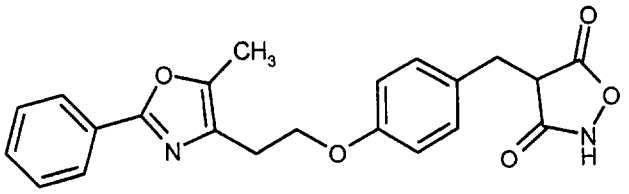
Cl-1027



BMS-188494



GI 262570



JTT-501

This invention furthermore relates to the use of compounds of the formula I and their pharmaceutical compositions as PPAR ligand receptor binders. The PPAR ligand receptor binders according to the invention are suitable for use as agonists or antagonists of the PPAR receptor.

Peroxisome-proliferator-activated receptors (PPAR) can be divided into the three subtypes PPARα, PPARδ and PPARγ. These are encoded by different genes (Motojima, Cell Structure and Function, 18:267-277, 1993). In addition, there are two isotopes of PPARγ, PPARγ$_1$ and γ$_2$. These two proteins differ in the 30 NH_2-terminal amino acids and are the result of an alternative use of promoters and different mRNA splicing (Vidal-Puig, Jiminez, Linan, Lowell, Hamann, Hu, Spiegelman, Flier, Moller, J. Clin. Invest., 97:2553-2561, 1996).

PPAR-modulated biological processes are processes modulated by receptors or combinations of receptors which react to the PPAR receptor ligands described in this patent. These processes include, for example, plasma lipid transport and fatty acid catabolism, regulation of insulin sensitivity and blood glucose levels involved in hypoglycemia/hyperinsulinism (caused, for example, by functional disorders of the pancrease beta-cells, insulin-secreting tumors and/or autoimmune hypoglycemia owing to autoantibodies against insulin, the insulin receptor or autoantibodies having a stimulating action on pancrease beta-cells), macrophage differentiation resulting in the formation of atherosclerotic plaques, in inflammable reactions, carcinogenesis, hyperplasia or adipocyte differentiation.

Adiposity is an excessive buildup of fatty tissue. Recent investigations in this field have shown that PPARγ plays a central role in gene expression and differentiation of adipocytes. Excess fatty tissue is associated with the development of serious disorders such as, for example, non-insulin-dependent diabetis mellitus (NIDDM), hypertension, disorders of the coronary arteries, hyperlipidemia, adiposity and certain malignant syndromes. The adipocytes can, by forming tumor necrosis factor α (TNFα) and other molecules, also have an effect on glucose homeostasis.

Non-insulin-dependent diabetes mellitus (NIDDM) or type II diabetes is the more frequent form of diabetes. About 90-95% of hyperglycemia patients suffer from this form of the disease. What is present in NIDDM is apparently a reduction of the mass of the beta cells of the pancreas, a number of different disorders of insulin secretion or reduced insulin sensitivity of the tissue. The symptoms of this form of

diabetes include tiredness, frequent urination, thirst, blurred vision, frequent infections and slow healing of wounds, diabetic nerve damage and kidney diseases.

Resistance against the metabolic effects of insulin is one of the main features of non-insulin-dependent diabetes (NIDDM). Insulin resistance is characterized by reduced uptake and conversion of glucose in insulin-sensitive target organs such as, for example, adipocytes and skeletal muscles, and by reduced inhibition of hepatic gluconeogenesis. Functional insulin deficiency and the absent suppression of hepatic gluconeogenesis by insulin leads to hyperglycemia in the fasting state. The pancreas beta-cells compensate insulin resistance by increased secretion of insulin. However, the beta-cells are not able to maintain this high insulin output, so that the glucose-induced insulin secretion decreases, resulting in a deterioration of glucose homeostasis and finally in the development of manifest diabetes. Hyperinsulinemia is likewise associated with insulin resistance, hypertriglyceridemia and increased plasma concentrations of low-density lipoproteins. Insulin resistance and hyperinsulinemia combined with these metabolic disorders is called "syndrome X" and is strongly associated with an increased risk of hypertension and disorders of the coronary arteries.

Metformin is known to the person skilled in the art as an agent for treating diabetes in humans (US patent No. 3,174,901). The primary action of metformin is reduced formation of glucose in the liver. As is known, Troglitazone® acts primarily by improving the ability of skeletal muscles to react to insulin and to take up glucose. It is known that a combination therapy of metformin and Troglitazone can be used for treating diabetes-associated disorders (DDT 3:79-88, 1998).

It has been observed that PPARγ activators, in particular Troglitazone®, convert cancerous tissue in liposarcoma (fat tumors) into normal cells (PNAS 96:3951-3956, 1999). Furthermore, it has been proposed that PPARγ activators may be of benefit in the treatment of breast cancer and intestinal cancer (PNAS 95:8806-8811, 1998, Nature Medicine 4:1046-1052, 1998).

In addition, PPARγ activators such as, for example, Troglitazone® have also been used for treating polycystic ovarial syndrome (PCO). This syndrome, which occurs in women, is characterized by chronic anovulation and hyperandrogenism. Women with this syndrome frequently also suffer from insulin resistance and an increased

risk of developing non-insulin-dependent diabetes mellitus (Dunaif, Scott, Finegood, Quintana, Whitcomb, J. Clin. Endocrinol. Metab., 81:3299, 1996). Furthermore, it has recently been discovered that PPARγ activators increase the formation of progesterone and inhibit steroid genesis in granulosa cell cultures and may therefore be suitable for treating climacterium (US patent No. 5,814,647, Urban et al., 29 September 1998; B. Lorke et al., Journal of Endocrinology, 159, 429-39, 1998). Climacterium is defined as the syndrome of the endocrine, somatic and psychological changes which occur in women at the end of the reproductive phase.

Peroxisomes are cellular organelles involved in the control of the redox potential and oxidative stress in cells by metabolizing a large number of substrates such as, for example, hydrogen peroxide. A number of disorders are associated with oxidative stress. Thus, for example, inflammable reactions to tissue damage, pathogenesis of emphysemia, ischemia-associated organ damage (shock), doxorubicin-induced heart damage, drug-induced hepatotoxicity, atherosclerosis and lung damage caused by hyperoxia are in each case associated with the formation of reactive oxygen species and changes of the reductive capability of the cell. Accordingly, it has been proposed that PPARα activators regulate inter alia the redox potential and the oxidative stress in cells and may be useful for treating these disorders (Poynter et al., J. Biol. Chem. 273, 32833-41, 1998).

It has also been found that PPARα agonists inhibit NF_KB-mediated transcription and thus modulate various inflammatory reactions, such as, for example, the enzyme paths of inducible nitrous oxide synthase (NOS) and cyclooxygenase-2 (COX-2) (Pineda-Torra, I. et al., 1999, Curr. Opinion in Lipidology, 10, 151-9) and can therefore be used for therapeutic interventions in a large number of different inflammatory diseases and other pathological conditions (Colville-Nash et al., Journal of Immunology, 161, 978-84, 1998; Staels et al, Nature, 393, 790-3, 1998).

Peroxisome proliferators activate PPAR which, in turn, act as transcription factors and cause differentiation, cell growth and proliferation of peroxisomes. It is also presumed that PPAR activators play a role in hyperplasia and carcinogenesis and change the enzymatic properties of animal cells such as, for example, rodent cells; however, these PPAR activators appear to have only minimal negative effects on human cells (Green, Biochem. Pharm. 43(3):393, 1992). Activation of PPAR leads

to a rapid increase of gamma-glutamyl transpeptidase and -catalase.

PPARα is activated by a number of medium-chain fatty acids and long-chain fatty acids and is involved in the stimulation of β-oxidation of fatty acids in tissues such as liver, heart, skeletal muscle and brown fatty tissue (Issemann and Green, ibid.; Beck et al., Proc. R. Soc. Lond. 247:83-87, 1992; Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657, 1992). Pharmacological PPARα activators such as, for example, fenofibrate, clofibrate, genfibrozil and bezafibrate are likewise involved in the considerable reduction of plasma triglycerides and a moderate reduction of LDL cholesterol, and they are used, in particular, for treating hypertriglyceridemia, hyperlipidemia and adiposity. It is known that PPARα is also involved in inflammatory disorders (Schoonjans, K., Current Opinion in Lipidology, 8, 159-66, 1997).

The human nuclear receptor PPARδ has been cloned from a cDNA library of human osteosarcoma cells and is described completely in A. Schmidt et al., Molecular Endocrinology, 6:1634-1641 (1992). The contents of this article are hereby incorporated by reference into the present patent application. It may be pointed out that in the literature PPARδ is also referred to as PPARβ and as NUC1, but all of these names refer to the same receptor. Thus, in A. Schmidt et al., Molecular Endocrinology, 6:1634-1641, 1992, for example, the receptor is referred to as NUC1. PPARδ is found both in embryonal and in adult tissue. It has been reported that this receptor is involved in the regulation of the expression of some fat-specific genes and therefore plays a role in the process of adipogenesis (Amri, E. et al., J. Biol. Chem. 270, 2367-71, 1995).

It is known that atherosclerotic disorders are caused by a number of factors such as, for example, hypertension, diabetes, low concentrations of high-density lipoproteins (HDL) and high concentrations of low-density lipoproteins (LDL). In addition to reducing the risks by acting on the concentration of the plasma lipids and other risk factors, PPARα agonists have direct atheroprotective actions (Frick, M.H. et al., 1997, Circulation 96:2137-2143, de Faire et al., 1997, Cardiovasc. Drugs Ther. 11 Suppl. 1:257-63).

It has recently been found that PPARδ agonists are useful for increasing HDL level and are therefore suitable for treating atherosclerotic disorders (Leibowitz et al., WO/9728149). Atherosclerotic disorders include vascular disorders, coronary

heart disease, cerebrovascular disorders and disorders of the peripheral vessels. Coronary heart disease includes death by coronary heart disease, myocardial infarction and coronary revascularization. Cerebrovascular diseases include ischemic and hemorrhagic infarcts and transient ischemic attacks.

PPARγ subtypes are involved in the activation of adipocyte differentiation and do not play any role in the stimulation of peroxysome proliferation in the liver. Activation of PPARγ contributes to adipocyte differentiation by activating the adipocyte-specific gene expression (Lehmann, Moore, Smith-Oliver, Wilkison, Willson, Kliewer, J. Biol. Chem., 270:12953-12956, 1995). The DNA sequences of the PPARγ subtypes are described in Elbrecht et al., BBRC 224; 431-437 (1996). Although peroxysome proliferators including fibrates and fatty acids activate the transciptory activity of PPARs, only prostaglandin J_2 derivatives such as the arachidonic metabolite 15-deoxy-delta^{12}, 14-prostaglandin J_2 (15d-PGJ_2) have been identified as natural ligands specific for the PPARγ subtype which also binds to thiazolidinediones. This prostaglandin activates PPARγ-dependent adipogenesis, but activates PPARα only at high concentrations (Formann, Tontonoz, Chen, Brun, Spiegelman, Evans, Cell, 83:803-812, 1995; Kliewer, Lenhard, Wilson, Patel, Morris, Lehmann, Cell, 83:813-819, 1995). This is a further indication that the subtypes of the PPAR family differ in their pharmacological reaction to ligands.

From this, it can be concluded that compounds which activate PPARα or both PPARα and PPARγ have to be effective hypotriglyceridemic drugs which can be used for treating atherosclerosis-associated dislipidemia, non-insulin-dependent diabetes mellitus, syndrome X (Staels, B. et al., Curr. Pharm. Des., 3 (1), 1-4 (1997)) and familial combined hyperlipidemia (FCH). Syndrome X is the syndrome which is characterized by a first insulin-resistant stage which causes hyperinsulinemia, dyslipidemia and reduced glucose tolerance and which can progress to non-insulin-dependent diabetes mellitus (type II diabetes) characterized by hyperglycemia. FCH is characterized by hypercholesterolemia and hypertriglyceridemia in the same patient and in the same family.

The present invention relates to compounds of the formula I suitable for modulating PPAR receptors, and for a number of other related pharmaceutical applications.

The compounds of the formula I are suitable in particular for treating dyslipidemia, insulin resistance, type I and type II diabetes, disturbed glucose tolerance, syndrome X, obesity, eating disorders, thromboses, inflammations, cardiomyopathy and for protecting beta-cells and protection against fatty acid oxidation (see, for example, Jean-Charles Fruchart, Bart Staels and Patrick Duriez: PPARS, Metabolic Disease and Atherosclerosis, Pharmacological Research, Vol. 44, No. 5, 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000; Ines Pineda Torra, Giulia Chinetti, 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).

The activity of the compounds was tested as follows:

To analyze the effectiveness of substances which bind to human PPARα, activating it in agonistic manner, a stable transfected HEK cell line (HEK = human embryo kidney) designated here as "PPARα reporter cell line" is used.
The activity of PPARα agonists is determined in a three-day test, described below:

The PPARα reporter cell line is cultivated up to 80% confluence in DMEM medium (# 41965-039, Life Technologies) with the following additives: 10% cs-FCS (fetal calf serum, #SH-30068.03, Hyclone), antibiotics (0.5 mg/ml of zeozin [#R250-01, Invitrogen], 0.5 mg/ml of G418 [#10131-019, Life Technologies], 1% penicillin streptomycin solution [#15140-031, Life Technologies]) and 2 mM of L-glutamine (#25030-032, Life Technologies). Cultivation is carried out in standard cell culture bottles (# 33111, Becton Dickinson) in a cell culture incubator at 37°C and 5% CO_2. The 80% confluent cells are washed once with 30 ml of PBS (#14190-094, Life Technologies), treated with 2 ml of trypsin solution (#25300-054, Life Technologies) at 37°C for 2 min, taken up in 5 ml of the medium described above and counted in a cell counter. After dilution to 500 000 cells/ml, in each case 100 000 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.

The PPARα agonists to be tested are dissolved in DMSO at a concentration of 10 mM. This stock solution is diluted in Phenol-Red-free DMEM medium (#21063-029, Life Technologies) to which 5% of cs-FCS (#SH-30068.03, Hyclone), 2 mM of L-glutamine (#25030-032, Life Technologies) and the antibiotics already described under "seeding of the cells" (zeozin, G418, penicillin and streptomycin) had been added.

Test substances are usually tested at 11 different concentrations (10 μM; 3.3 μM; 1 μM; 0.33 μM; 0,1 μM; 0.033 μM; 0.01 μM; 0.0033 μM; 0.001 μM; 0.00033 μM and 0.0001 μM). More potent compounds are tested in concentration ranges of from 1 μM to 10 pM or 100 nM to 1 pM. From each well, the medium of the PPARα 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 can be carried out using a robot (Beckman Biomek 2000). The end volume of the test substances diluted in medium is 100 μl per well of a 96-well plate. The DMSO concentration in the assay is always below 0.1% v/v to prevent cytotoxic effects of the solvent.

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

The PPARα receptor cells treated with the test substances are removed from the incubator and frozen at -20°C for 1 h to improve cell lysis. After the plates have thawed (thawing at room temperature for at least 30 min), 50 μl of buffer 1 (Luc-Screen kit #LS1000, PE Biosystems Tropix) are pipetted into each well and the plates are then transferred into an apparatus for measuring luminescence, fitted with a pipetting unit (Luminoscan Ascent, LabSystems). The luciferase reaction in the measurement apparatus is started by pipetting 50 μl of buffer 2 (Luc-Screen kit #LS1000, PE Biosystems Tropix) into each well of the 96-well plate. Addition of buffer to the individual wells is carried out in defined and identical time intervals following the instructions of the manufacturer (LabSystems). All

samples are measured exactly 16 min after addition of buffer 2. Measurement time is 10 sec per sample.

The crude data of the apparatus for measuring luminescence are exported into a Microsoft Excel file. Dose-activity curves and EC_{50} values are calculated using the program XL.Fit according to the instructions of the manufacturer (IDBS).

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

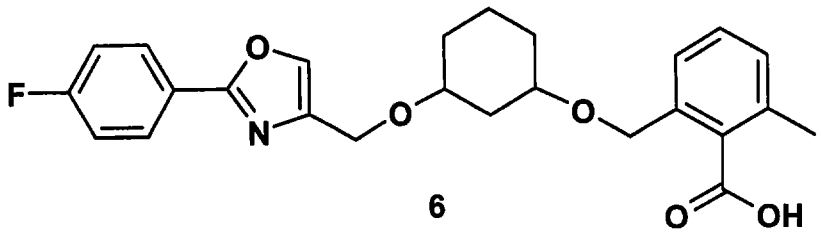
Table I

Example No.	EC50 PPARα [nM]
I	1
II	0.3
IV	0.3
VII	4
X	0.5
XIX	16
XXIV	0.9
XXV	13
XXVIII	14
XXIX	32
XXXII	0.97
XXXIV	0.82
XXXVI	0.62
XXXVIII	0.57
XLI	0.6
XLIII	0.58
XLIV	0.93
XLV	10
XLVI	0.56
XLVII	1.1

It is evident from table I that the compounds of the formula I according to the invention activate the PPARα receptor, thus effecting, 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, 2001; S. Kersten et al.: Roles of PPARs in health and disease, NATURE, VOL 405, 25 MAY 2000; I. Pineda et al.: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

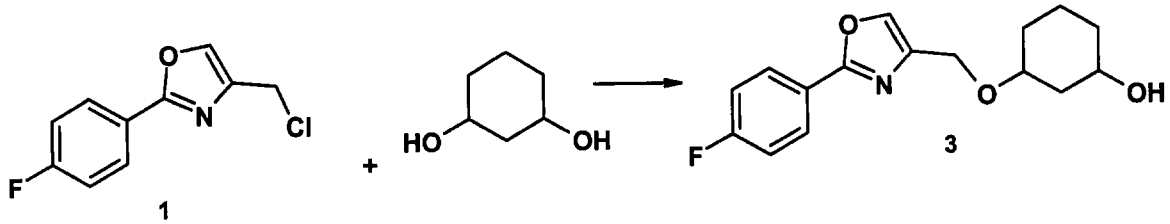
The examples given below serve to illustrate the invention, but without limiting it. The measured melting points or decomposition points (m.p.) are uncorrected and, in general, depend on the heating rate.

Example I



6

3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexanol **3**

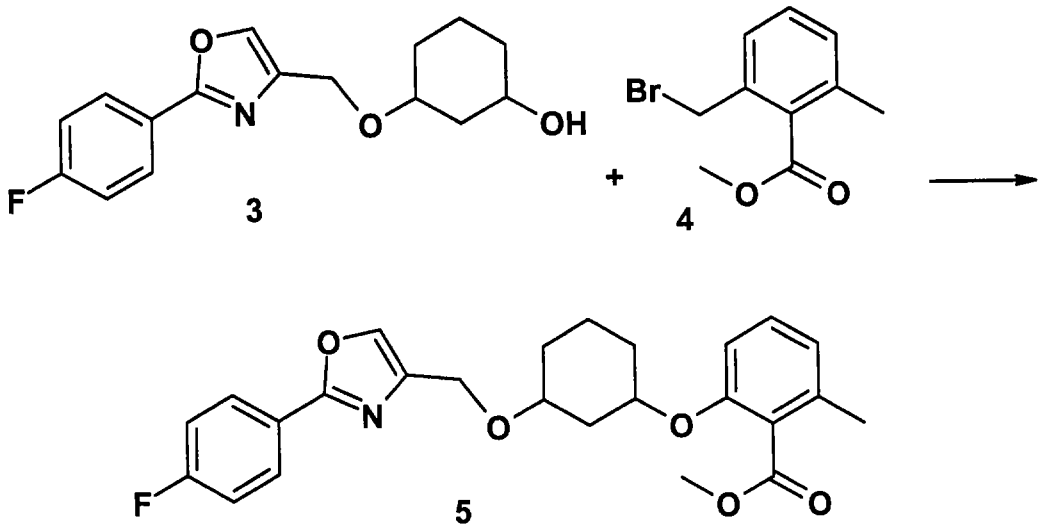


1 3

With ice-cooling, initially 2.25 g of an 80 percent suspension of sodium hydride and then 5.8 g of 1,3-cyclohexanediol are added to a mixture of 50 ml of dimethylformamide and 50 ml of tetrahydrofuran. The mixture is stirred at about 25°C for 3 hours. 10.5 g of 4-chloromethyl-2-(4-fluorophenyl)oxazole (**1**) is then added, the mixture is heated at 70°C and the reaction is monitored by thin-layer

chromatography. After the reaction has ended, the mixture is poured into ice-water and extracted with ethyl acetate. The organic phase is separated off, dried and concentrated and the residue is purified on silica gel by flash chromatography (ethyl acetate/n-heptane = 1:1). This gives the alcohol **3** as an oil. $C_{16}H_{18}FNO_3$ (291.33) MS(ESI): 292 ($M + H^+$)

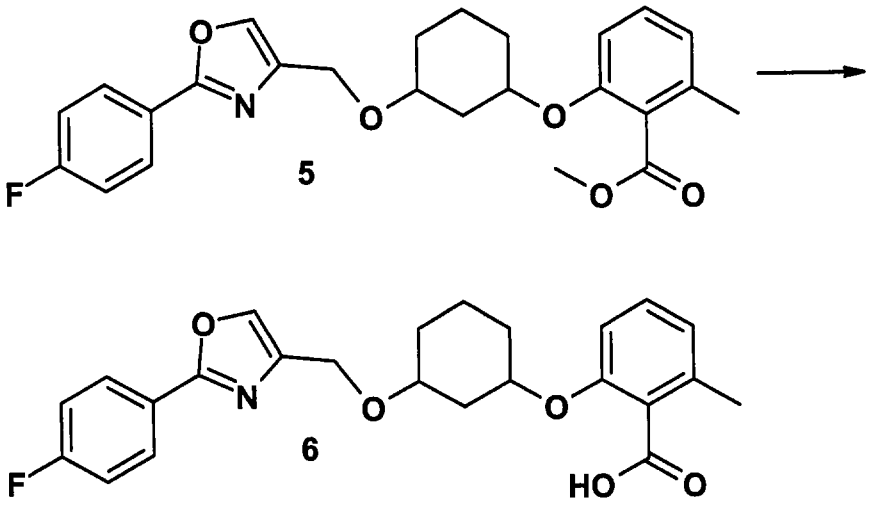
Methyl 2-{3-[2-(4-fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-6-methyl-benzoate **5**



With ice-cooling, 0.3 g of a sodium hydride suspension (80%) are introduced into a mixture of 10 ml of dimethylformamide and 20 ml of tetrahydrofuran. 1 g of alcohol **3** in 5 ml of tetrahydrofuran is then added, and the mixture is stirred at room temperature for 1 hour. 0.8 g of bromide **4** is then added, and the mixture is stirred at room temperature and with monitoring by TLC for 3-5 hours until the conversion is substantially complete. The mixture is poured into ice-water and extracted repeatedly with ethyl acetate, the organic phase is washed with a little water, dried over sodium sulfate and concentrated under reduced pressure, and the residue is purified by silica gel chromatography (ethyl acetate:n-heptane = 1:2). This gives the methyl ester **5** as an oil.

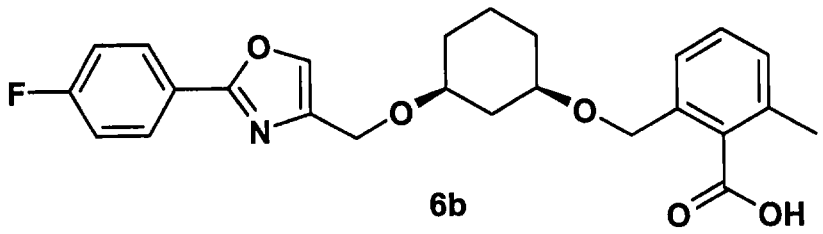
$C_{26}H_{28}FNO_5$ (453.52) MS(ESI): 454 ($M + H^+$).

2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxy}-6-methylbenzoic acid **6**

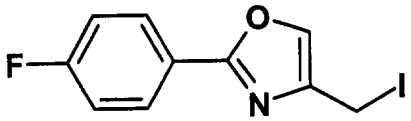


2 g of ester **5** are heated at reflux in 150 ml of tert-butanol and 24 ml of 50 percent aqueous potassium hydroxide solution for 6 hours. 4/5 of the butanol is removed under reduced pressure and the mixture is diluted with water and acidified with ice-cooling. The product is extracted with dichloromethane, dried over sodium sulfate and concentrated under reduced pressure, giving, by filtration of the residue through silica gel (CH_2Cl_2/MeOH = 20:1), the acid **6** $C_{25}H_{26}FNO_5$ (432.42) MS(ESI): 433 ($M + H^+$).

Example II

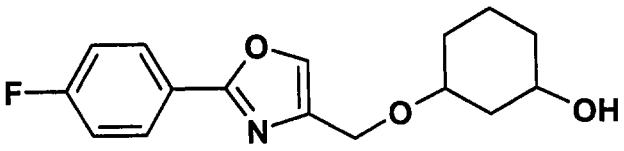


2-(4-Fluorophenyl)-4-iodomethyloxazole **2**



2

At 120°C, 31 g (123 mmol) of p-fluorobenzamide and 33 g (123 mmol) of 1,3-dichloroacetone are stirred in the absence of a solvent for 2 hours. After cooling to room temperature, the product is dissolved in 250 ml of ethyl acetate. This solution is diluted with 400 ml of n-heptane and washed 3 times with saturated NaCl solution. The organic phase is filtered through 250 ml of silica gel, and the filter pad is then washed with 200 ml of n-heptane/ethyl acetate (4:1). The solvent is distilled off, giving 4-chloromethyl-2-(4-fluorophenyl)oxazole **1** as crude product. This is dissolved in 650 ml of acetone, and 90 g of NaI are then added. The mixture is then heated at reflux for 16 hours, most of the solvent is then removed and the solid residue is suspended in 200 ml of n-heptane/ethyl acetate (1:1) and filtered through 200 ml of silica gel. The precipitate is washed with 500 ml of n-heptane/ethyl acetate (1:1), and the organic phase is concentrated. On concentration, the iodide **2** begins to crystallize as white crystals. TLC n-heptane/ethyl acetate (6:1) R_f = 0.4 for **2** and R_f = 0.35 for **1**. $C_{10}H_7FINO$ (303.08) MS(ESI): 304 ($M + H^+$).



3a (cis) and 3b (trans)

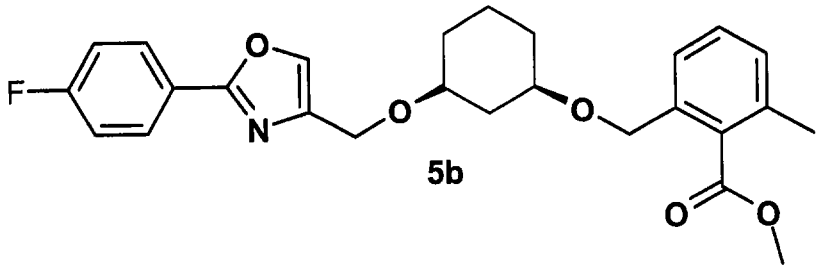
10.8 g (93.1 mmol) of cis/trans-1,3-cyclohexanediol and 15.4 g (61.8 mmol) of dibutyltin oxide are heated in 800 ml of toluene on a water separator for 5 hours. 400 ml of toluene are distilled off, and the mixture is then allowed to cool to room temperature, and 280 ml of dry DMF, 15 g (49.5 mmol)of **2** and 12.7 g (80.1 mmol) of dry CsF are then added successively. The heterogeneous mixture is stirred at room temperature for 20 hours (TLC control starting material **2**). 200 ml of ethyl acetate are added, and the mixture is washed three times with saturated NaCl solution. The organic phase is filtered through 150 ml of silica gel and

concentrated. Following addition of n-heptane/ethyl acetate (6:1), the residue crystallizes. Further recrystallization from n-heptane/ethyl acetate gives the product **3a** (mixture of cis-enantiomers). The mixture of trans-enantiomers **3b** is obtained from the mother liquor after concentration and chromatography. TLC n-heptane/ethyl acetate (1:1). R_f **3a** (cis) = 0.2, R_f **3b** (trans) = 0.3. $C_{16}H_{18}FNO_3$ (291.33) MS(ESI): 292 ($M + H^+$).

The pair of enantiomers **3a** is separated by chiral HPLC. The dextrorotatory (+)-enantiomer **(+)3a** elutes first, followed by the levorotatory (-)-enantiomer **(-)3a** (Chiralpak AD 250 x 4.6; acetonitrile/methanol (9:1)).

The absolute stereochemistry was assigned by X-ray structural analysis of the camphanic acid esters of the separated diastereomers **3.**

Methyl cis-2-(3-(2-(4-fluorophenyl)oxazol-4-ylmethoxy)cyclohexyloxymethyl)-6-methylbenzoate **5b**

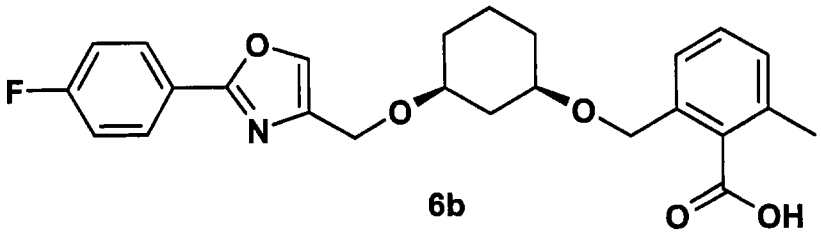


5b

1.05 g (3.6 mmol) of **(-)3a**, 1.3 g (5.4 mmol) **4** and 130 mg of KI are dissolved in 12 ml of dry DMF. 140 mg (5.7 mmol) of 95% NaH are added, and the mixture is then stirred at room temperature for 1 hour. To achieve better yields with respect to the starting material **(-)3a**, 2 more times, the same amount of **4** and NaH are added, and the mixture is in each case stirred for 1 hour. The mixture is then allowed to stand overnight. The reaction solution is diluted with 150 ml of ethyl acetate and poured into 50 ml of water. The mixture is washed 2 more times with NaCl solution and the organic phase is then filtered through silica gel and concentrated, and the residue is purified by flash chromatography (n-heptane/ethyl

acetate, 1:1). This gives **5b** as a colorless amorphous solid. TLC n-heptane-ethyl acetate (1:1). R_f = 0.5. $C_{26}H_{28}FNO_5$ (453.52) MS(ESI): 454 ($M + H^+$).

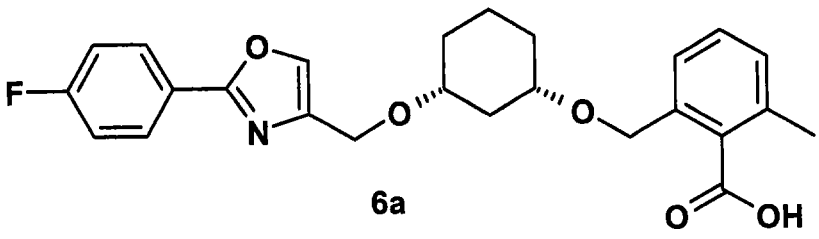
(+)-cis-2-(3-(2-(4-Fluorophenyl)oxazol-4-ylmethoxy)cyclohexyloxymethyl)-6-methylbenzoic acid **6b**



6b

4.2 g (9.2 mmol) of **5b** are dissolved in 120 ml of t-BuOH. 50 ml of 50% aq. KOH are added, and the mixture is then boiled at 100°C for 24 hours. For work-up, the mixture is allowed to cool and then diluted with 100 ml of ethyl acetate. The aqueous phase is made slightly acidic by addition of 2 N aqueous HCl and extracted 2 more times with 100 ml of ethyl acetate. The organic phase is dried over $MgSO_4$, filtered and concentrated, and the residue is purified by flash chromatography (methylene chloride/methanol/conc. ammonia, 30/5/1). This gives **6b** as a white amorphous solid. TLC (methylene chloride/methanol/conc. ammonia, 30/5/1). R_f = 0.3. Recrystallization from toluene. $C_{25}H_{26}FNO_5$ (432.42) MS(ESI): 433 ($M + H^+$).

Example III



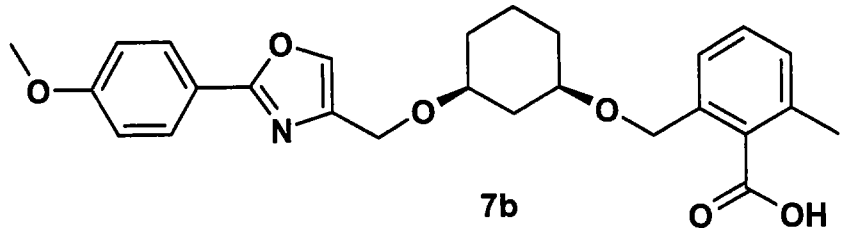
6a

(-)-cis-2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methyl-benzoic acid **6a**

(+)3a and methyl 2-bromomethyl-6-methylbenzoate **4** give, analogously to

example 1, the product **6a** of molecular weight 432.42 ($C_{25}H_{26}FNO_5$); MS(ESI): 433 ($M+H^+$).

Example IV

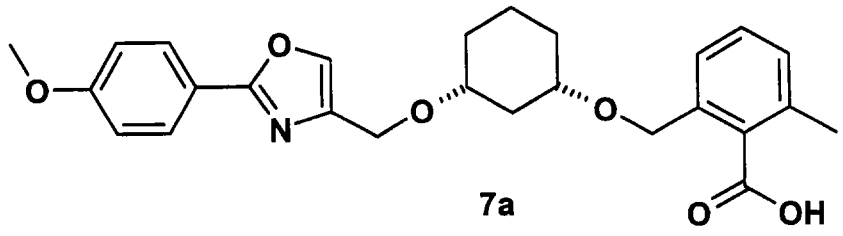


7b

cis-2-(3-(2-(4-Methoxyphenyl)oxazol-4-ylmethoxy)cyclohexyloxymethyl)-6-methyl-benzoic acid **7b**

170 mg (0.39 mmol) of **6b** are heated in 4 ml of 5.6 M NaOMe/MeOH solution at an oil bath temperature of 120 °C for 20 hours. Ethyl acetate and 2 N HCl are added, and the mixture is then worked up analogously to the synthesis of **6b**. This gives **7b** as a colorless amorphous solid. TLC: (methylene chloride/-methanol/conc. ammonia, 30/5/1). R_f ~ 0.3. $C_{26}H_{29}NO_6$ (451.52) MS(ESI): 452 ($M + H^+$).

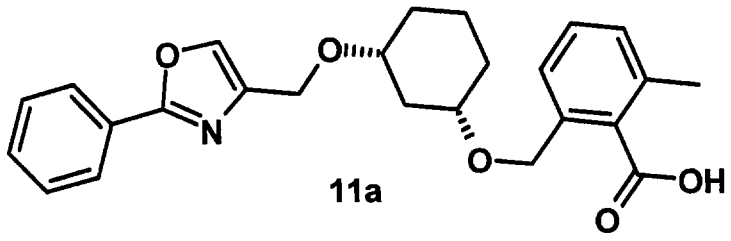
In the same manner, **6a** gives the stereoisomeric **7a**:



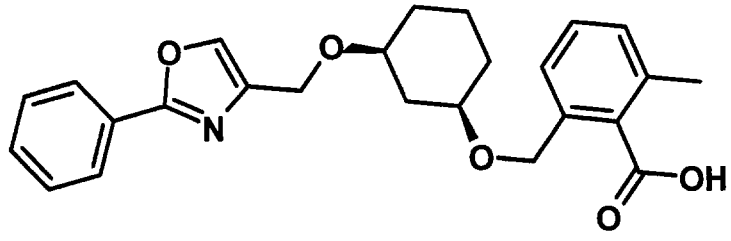
7a

TLC: (methylene chloride/methanol/conc. ammonia, 30/5/1). R_f ~ 0.3. $C_{26}H_{29}NO_6$ (451.52) MS(ESI): 452 ($M + H^+$).

Example V (**11a**) and Example VI (**11b**)

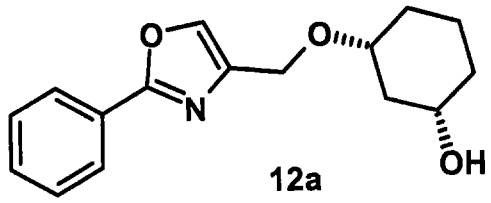


11a

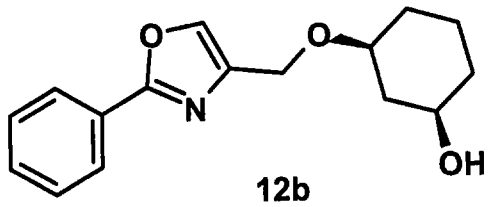


11b

cis-3-(2-Phenyloxazol-4-ylmethoxy)cyclohexanol **12a,b**



12a

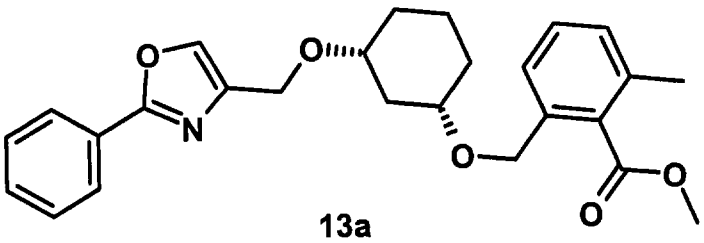


12b

1,3-Cyclohexanediol and 4-iodomethyl-2-phenyloxazole give the racemate **12** of molecular weight 273.33 ($C_{16}H_{19}NO_3$); MS(ESI): 274 ($M+H^+$).

The enantiomers are separated by HPLC on a chiral column. The (+)-enantiomer **12a** is eluted first, followed by the (-)-enantiomer **12b** (Chiralpak OD 250x4.6; n-heptane:ethanol:acetonitrile = 110:2:1 + 0.05% trifluoroacetic acid).

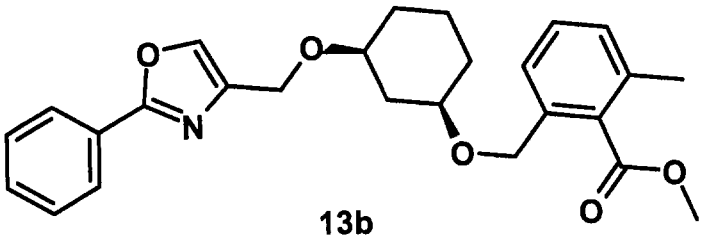
Methyl cis-2-methyl-6-[3-(2-phenyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-benzoate **13a**



13a

12a and methyl 2-bromomethyl-6-methylbenzoate give **13a** of molecular weight 435.52 ($C_{26}H_{29}NO_5$); MS(ESI): 436 ($M+H^+$).

Methyl cis-2-methyl-6-[3-(2-phenyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-benzoate **13b**



13b

12b and methyl 2-bromomethyl-6-methylbenzoate give **13b** of molecular weight 435.52 ($C_{26}H_{29}NO_5$); MS(ESI): 436 ($M+H^+$).

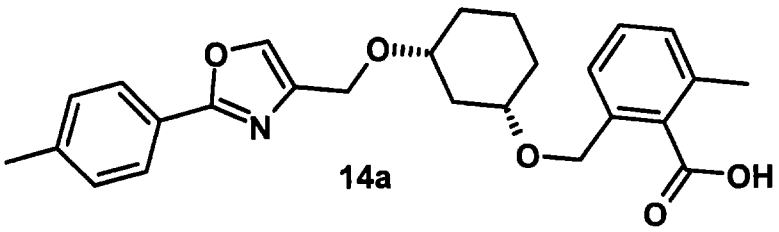
cis-2-Methyl-6-[3-(2-phenyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **11a**

Hydrolysis of **13a** gives **11a** of molecular weight 421.50 ($C_{25}H_{27}NO_5$); MS(ESI): 422 ($M+H^+$).

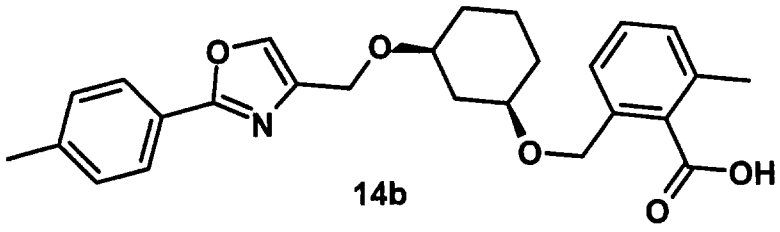
cis-2-Methyl-6-[3-(2-phenyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **11b**

Analogously, **13b** gives **11b** of molecular weight 421.50 ($C_{25}H_{27}NO_5$); MS(ESI): 422 ($M+H^+$).

Example VII (**14a**) and Example VIII (**14b**)

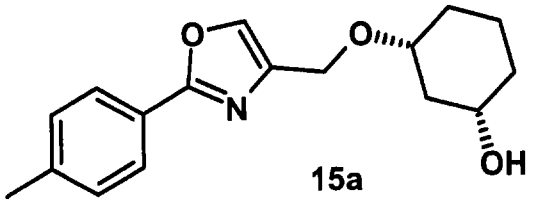


14a

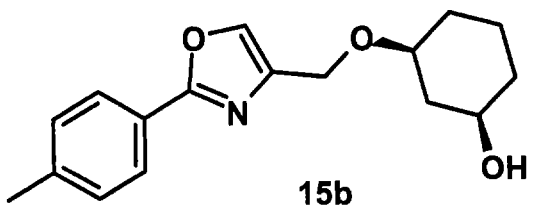


14b

cis-3-(2-p-Tolyloxazol-4-ylmethoxy)cyclohexanol **15a,b**



15a

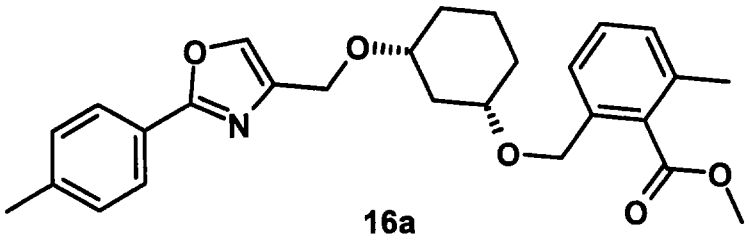


15b

Cyclohexanediol and 4-iodomethyl-2-p-tolyloxazole give the racemate **15** of molecular weight 287.36 ($C_{17}H_{21}NO_3$); MS(ESI): 288 ($M+H^+$).

Separation of the enantiomers is carried out by HPLC on a chiral column. The (+)-enantiomer **15a** elutes first, followed by the (-)-enantiomer **15b** (Chiralpak OD 250x4.6; n-heptane:ethanol:acetonitrile = 110:5:1 + 0.05% trifluoroacetic acid).

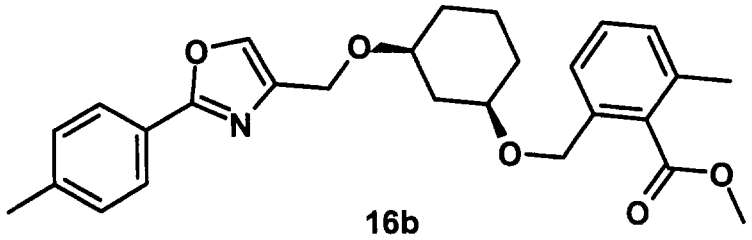
Methyl cis-2-methyl-6-[3-(2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-benzoate **16a**



16a

15a and methyl 2-bromomethyl-6-methylbenzoate give **16a** of molecular weight 449.55 ($C_{27}H_{31}NO_5$); MS(ESI): 450 ($M+H^+$).

Methyl cis-2-methyl-6-[3-(2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]-benzoate **16b**



16b

15b and methyl 2-bromomethyl-6-methylbenzoate give **16b** of molecular weight 449.55 ($C_{27}H_{31}NO_5$); MS(ESI): 450 ($M+H^+$).

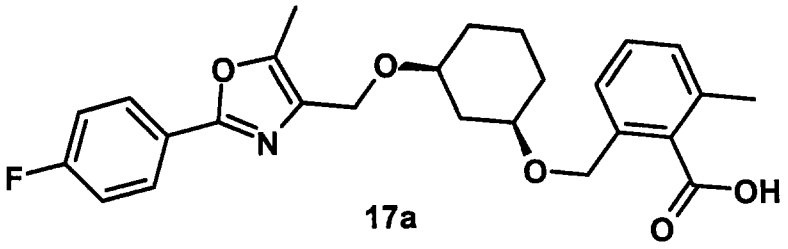
cis-2-Methyl-6-[3-(2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **14a**

16a gives **14a** of molecular weight 435.52 ($C_{26}H_{29}NO_5$); MS(ESI): 436 ($M+H^+$).

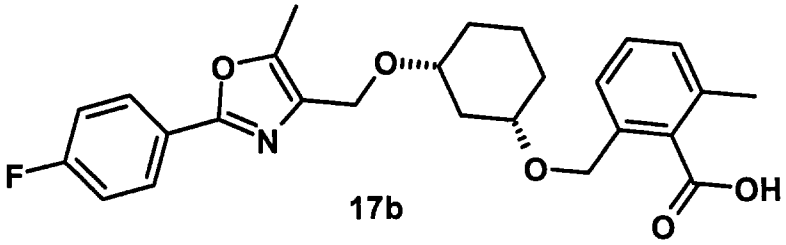
cis-2-Methyl-6-[3-(2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **14b**

16b gives the desired product of molecular weight 435.52 ($C_{26}H_{29}NO_5$); MS(ESI): 436 ($M+H^+$).

Example IX (**17a**) and Example X (**17b**)

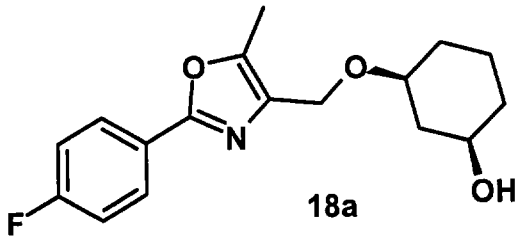


17a

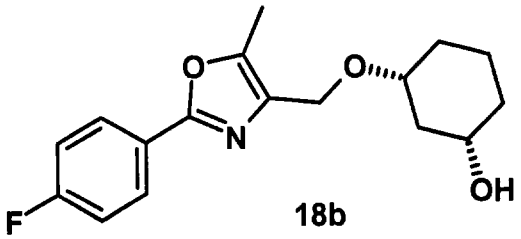


17b

cis-3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexanol **18a,b**



18a

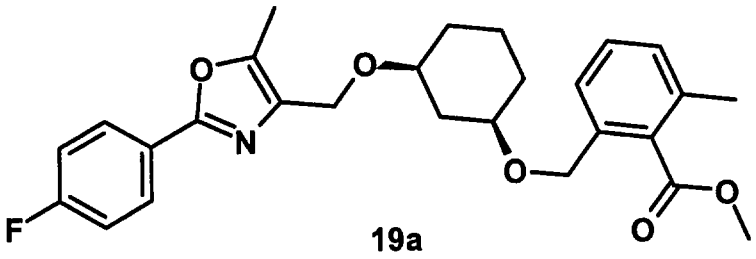


18b

Cyclohexanediol and 2-(4-fluorophenyl)-4-iodomethyl-5-methyloxazole give the

racemate **18** of molecular weight 305.35 ($C_{17}H_{20}FNO_3$); MS(ESI): 306 (M+H+). The enantiomers are separated by HPLC on a chiral column. The (+)-enantiomer **18a** elutes first, followed by the (-)-enantiomer **18b** (Chiralpak OD 250x4.6; n-heptane:ethanol:acetonitrile = 110:2:1 + 0.05% trifluoroacetic acid).

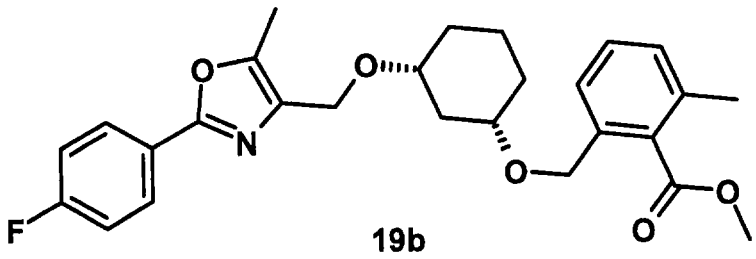
Methyl cis-2-{3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy-methyl}-6-methylbenzoate **19a**



19a

18a and methyl 2-bromomethyl-6-methylbenzoate give **19a** of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS(ESI): 468 ($M+H^+$).

Methyl cis-2-{3-[2-(4-fluorophenyl)-5-methyloxazol-4-ylmethoxy]-cyclohexyloxy-methyl}-6-methylbenzoate **19b**



19b

18b and methyl 2-bromomethyl-6-methylbenzoate give **19b** of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS(ESI): 468 ($M+H^+$).

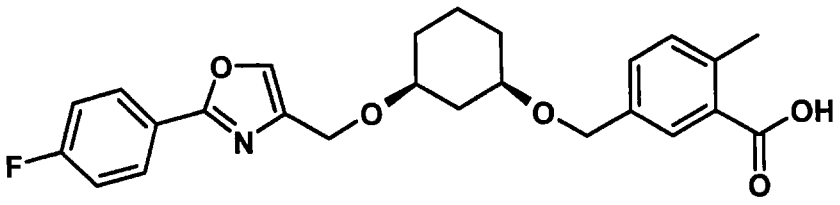
cis-2-(3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **17a**

Hydrolysis of **19a** gives **17a** of molecular weight 453.52 ($C_{26}H_{28}FNO_5$); MS(ESI): 454 ($M+H^+$).

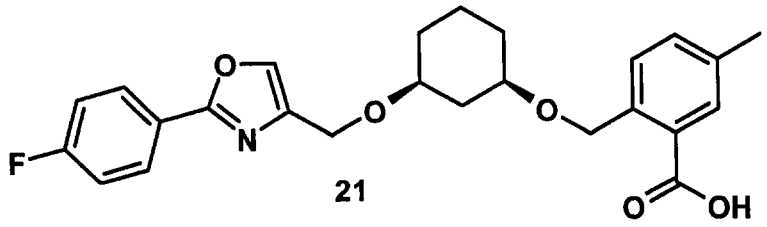
cis-2-(3-[2-(4-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **17b**

Analogously, **19b** gives **17b** of molecular weight 453.52 ($C_{26}H_{28}FNO_5$); MS(ESI): 454 ($M+H^+$).

Example XI (**20**) and Example XII (**21**)

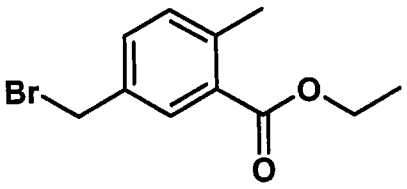


20

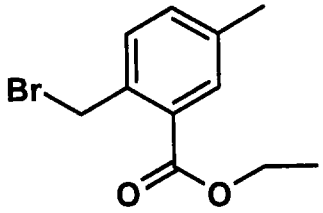


21

Ethyl 5-bromomethyl-2-methylbenzoate **22** and
ethyl 2-bromomethyl-5-methylbenzoate **23**



22

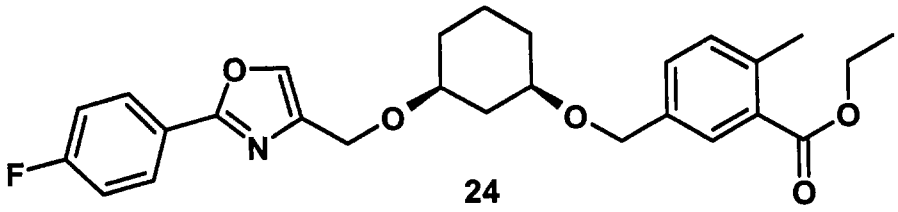


23

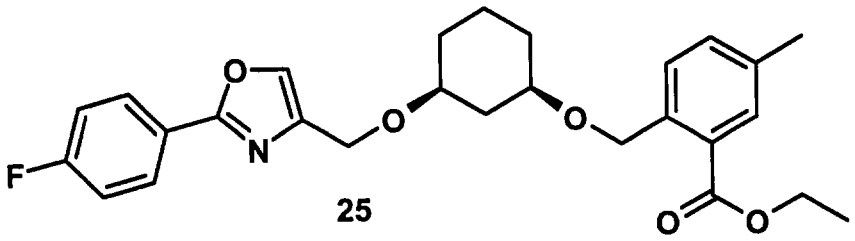
A solution of 3.5 g of ethyl 2,5-dimethylbenzoate, 3.15 g of N-bromosuccinimide and 100 ml of carbon tetrachloride is, for 3 hours, heated under reflux and

irradiated with a 300 watt photolamp. The resulting precipitate is filtered off and the concentrated filtrate is chromatographed on silica gel. This gives an approximately 2:3 (**22:23**) mixture of the regioisomeric benzyl bromides **22** and **23** of molecular weight 257.13 ($C_{11}H_{13}BrO_2$); MS (ESI+): 257 ($M+H^+$).

Ethyl rac-cis-5-{3-[2-(4-fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-2-methylbenzoate **24** and ethyl rac-cis-2-{3-[2-(4-fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-5-methylbenzoate **25**



24



25

At 0°C, a solution of 150 mg of rac-cis-3-[2-(4-fluorophenyl)oxazol-4-ylmethoxy]-cyclohexanol **3a** in 0.5 ml of dimethylformamide is added dropwise to a suspension of 40 mg of sodium hydride (55-65% in paraffin oil) in 1 ml of dimethylformamide. After the evolution of gas has ceased, 198 mg of 2:3 mixture of ethyl 5-bromomethyl-2-methylbenzoate **22** and ethyl 2-bromomethyl-5-methyl-benzoate **23** are added. After 30 minutes at 0°C, the mixture is allowed to react for a further 1 hour at room temperature. The mixture is poured into an ammonium chloride solution and extracted twice with MTBE. The extracts are dried over magnesium sulfate, filtered and concentrated using a rotary evaporator, and the product is then purified by silica gel chromatography (mobile phase: n-heptane/ethyl acetate 3:1). This gives the faster eluting product ethyl rac-cis-2-{3-[2-(4-fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-5-methylbenzoate **25** of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS (ESI+): 468 ($M+H^+$).

Also isolated is the later eluting product ethyl rac-cis-5-{3-[2-(4-fluorophenyl)-

oxazol-4-ylmethoxy]cyclohexyloxymethyl}-2-methylbenzoate **24** of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS (ESI+): 468 ($M+H^+$).

rac-cis-5-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-2-methylbenzoic acid **20**

A suspension of 47 mg of ethyl rac-cis-5-{3-[2-(4-fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-2-methylbenzoate **24**, 2 ml of 1,1-dimethylethanol and 50% (w/w) potassium hydroxide is heated at 85°C (oil bath) for 2 hours. The pH is adjusted to 3 using dilute hydrochloric acid and the mixture is extracted twice with MTBE. The extracts are dried over magnesium sulfate, filtered and concentrated on a rotary evaporator, and the product is then purified by chromatography. This gives the product **20** of molecular weight 439.49 ($C_{25}H_{26}FNO_5$); MS (ESI+): 440 ($M+H^+$).

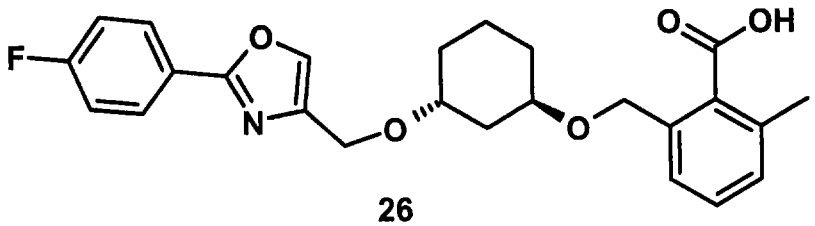
Analogously to **20**:

rac-cis-2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-5-methylbenzoic acid **21**

is prepared from ethyl rac-cis-2-{3-[2-(4-fluorophenyl)oxazol-4-ylmethoxy]-cyclohexyloxymethyl}-5-methylbenzoate **25**.

Example XIII

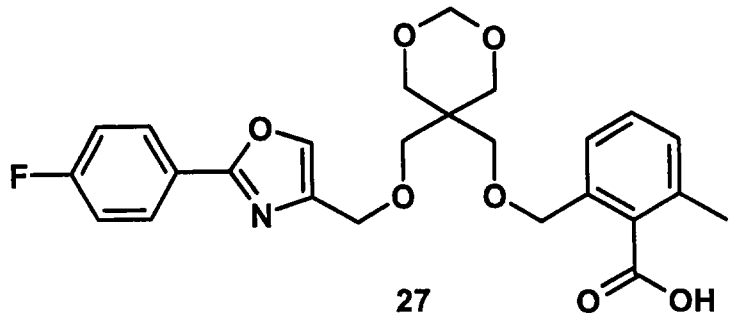
rac-trans-2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **26**



26

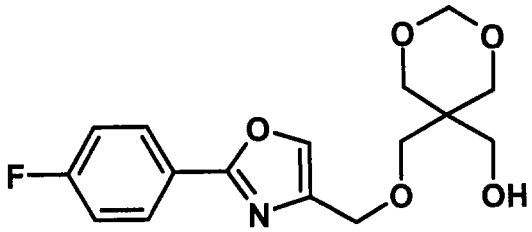
rac-trans **3b** and methyl 2-bromomethyl-6-methylbenzoate give the product **26** of molecular weight 439.49 ($C_{25}H_{26}FNO_5$); MS(ESI): 440 ($M+H^+$).

Example XIV



27

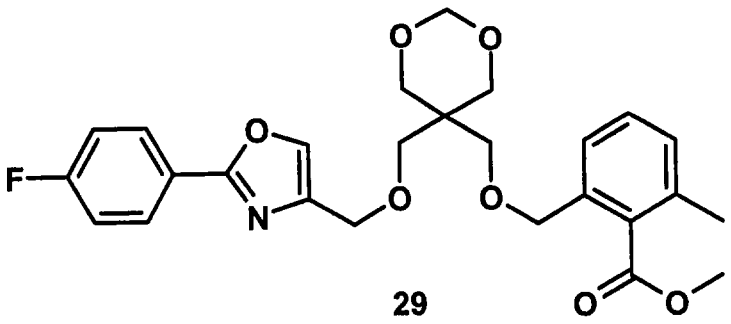
5-(2-(4-Fluorophenyl)oxazol-4-ylmethoxymethyl)-1,3-dioxan-5-ylmethanol **28**



28

1.0 g (6.7 mmol) of 5-hydroxymethyl-1,3-dioxan-5-ylmethanol and 0.5 g (16.5 mmol) of **2** are dissolved in 20 ml of dry DMF. 300 mg of 55% NaH in paraffin oil are added, and the mixture is then stirred at room temperature for 1 hour. Work-up is carried out analogously to the synthesis of compound **5b**. This gives **28** as a white amorphous solid. TLC (n-heptane/ethyl acetate 1:2). R_f = 0.4. $C_{16}H_{18}FNO_5$ (323.33) MS 324.2 $M + H^+$.

Methyl 2-{5-[2-(4-fluorophenyl)oxazol-4-ylmethoxymethyl]-1,3-dioxan-5-ylmethoxymethyl}-6-methylbenzoate **29**



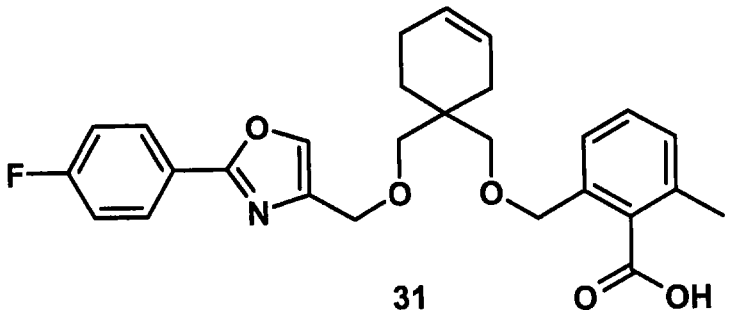
29

Compound **29** is prepared analogously to the synthesis of **5b** from **28** and **4**.

2-{5-[2-(4-Fluorophenyl)oxazol-4-ylmethoxymethyl]-1,3-dioxan-5-ylmethoxymethyl}-6-methylbenzoic acid **27**

Compound **27** is prepared analogously to the synthesis of **6b** from **29** by hydrolysis.

Example XV

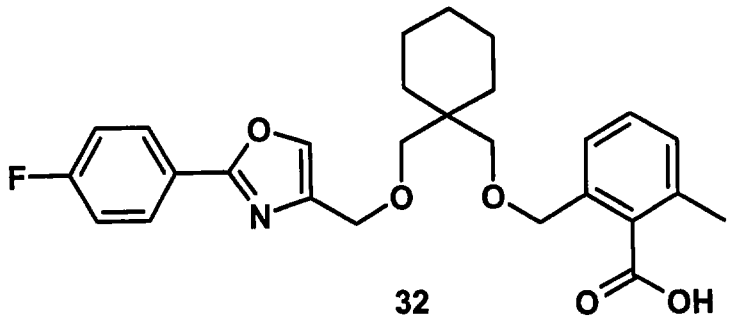


31

2-{1-[2-(4-Fluorophenyl)oxazol-4-ylmethoxymethyl]cyclohex-3-enylmethoxymethyl}-6-methylbenzoic acid **31**

Starting from (1-hydroxymethylcyclohex-3-enyl)methanol, iodide **2** and bromide **4**, a procedure as described for **27** gives the product **31** of molecular weight 465.53 ($C_{27}H_{28}FNO_5$); MS(ESI): 466 ($M+H^+$).

Example XVI

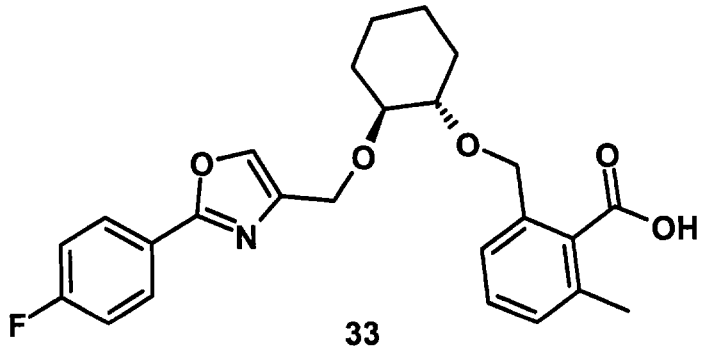


32

2-{1-[2-(4-Fluorophenyl)oxazol-4-ylmethoxymethyl]cyclohexylmethoxymethyl}-6-methylbenzoic acid **32**

Starting from (1-hydroxymethylcyclohexyl)methanol, iodide **2** and bromide **4**, a procedure as described for **27** gives the product **32** of molecular weight 467.53 ($C_{27}H_{30}FNO_5$); MS(ESI): 468 ($M+H^+$).

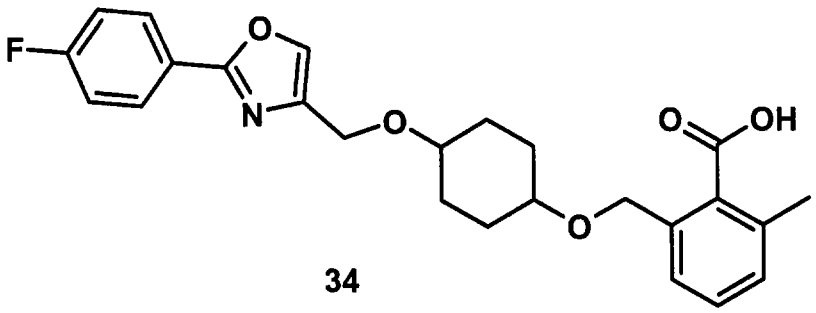
Example XVII



33

rac-trans-2-{2-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **33**

trans-1,2-Dihydroxycyclohexanol, iodide **2** and bromide **4** give, analogously to **27**, the desired product of molecular weight 439.49 ($C_{25}H_{26}FNO_5$); MS(ESI): 440 ($M+H^+$).



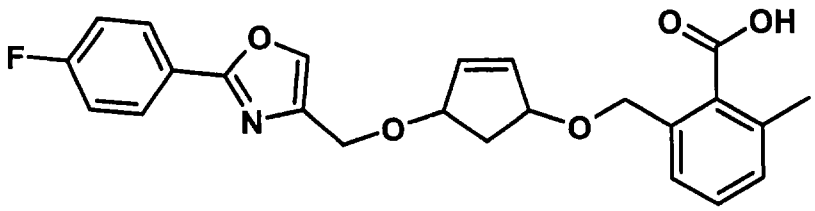
34

Example XVIII

2-{4-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **34**

1,4-Cyclohexanediol, iodide **2** and bromide **4** give **34** of molecular weight 439.49 ($C_{25}H_{26}FNO_5$); MS(ESI): 440 ($M+H^+$).

Example XIX

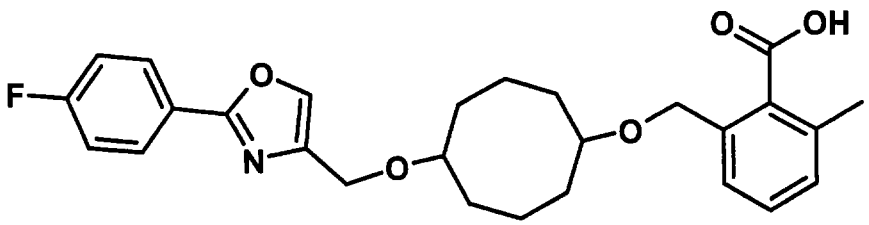


35

2-{4-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclopent-2-enyloxymethyl}-6-methylbenzoic acid **35**

Cyclopent-2-ene-1,4-diol, iodide **2** and bromide **4** give the product **35** of molecular weight 423.45 ($C_{24}H_{22}FNO_5$); MS(ESI): 424 ($M+H^+$).

Example XX

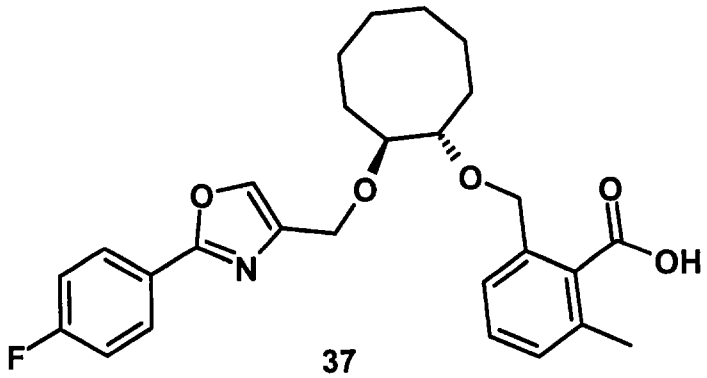


36

2-{5-[2-(4-Fluorophenyl)oxazol-4-yl]methoxy}cyclooctyloxymethyl}-
6-methylbenzoic acid **36**

1,5-Cyclooctanediol, iodide **2** and bromide **4** give **36** of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS(ESI): 468 ($M+H^+$).

Example XXI

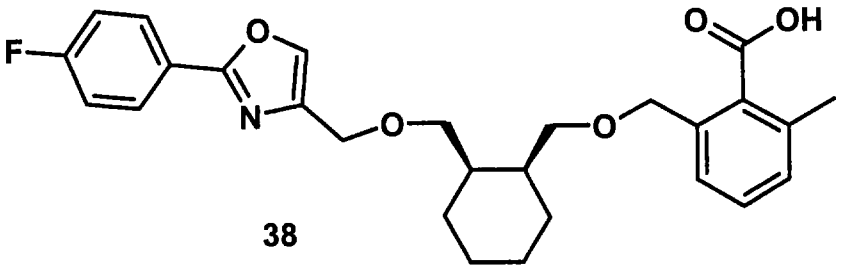


37

rac-trans-2-{2-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclooctyloxymethyl}-
6-methylbenzoic acid **37**

trans-1,2-Cyclooctanediol, iodide **2** and bromide **4** give the desired product of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS(ESI): 468 ($M+H^+$).

Example XXII

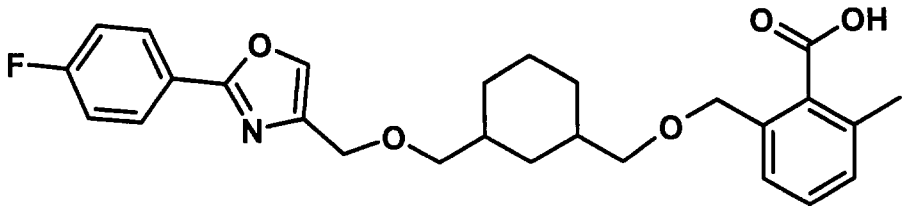


38

rac-cis-2-{2-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]methylcyclohexyl-methoxymethyl}-6-methylbenzoic acid **38**

cis-(2-Hydroxymethylcyclohexyl)methanol, iodide **2** and bromide **4** give the product **38** of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS(ESI): 468 ($M+H^+$).

Example XXIII

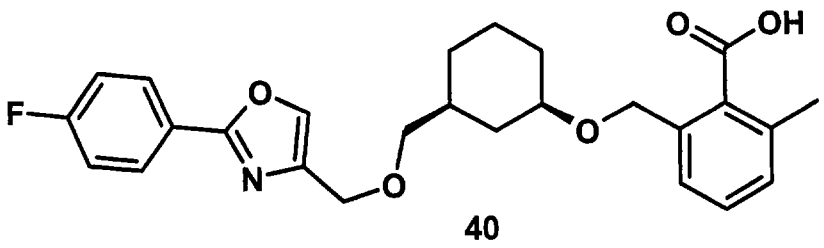


39

2-{2-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]methylcyclohexylmethoxymethyl}-6-methylbenzoic acid **39**

(3-Hydroxymethylcyclohexyl)methanol, iodide **2** and bromide **4** give the product **39** of molecular weight 467.54 ($C_{27}H_{30}FNO_5$); MS(ESI): 468 ($M+H^+$).

Example XXIV

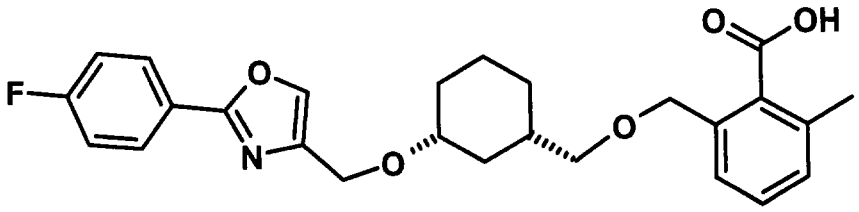


40

rac-cis-2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxymethyl]cyclohexyloxymethyl}-6-methylbenzoic acid **40**

cis-3-Hydroxymethylcyclohexanol, iodide **2** and bromide **4** give **40** of molecular weight 453.52 ($C_{26}H_{28}FNO_5$); MS(ESI): 454 ($M+H^+$).

Example XXV

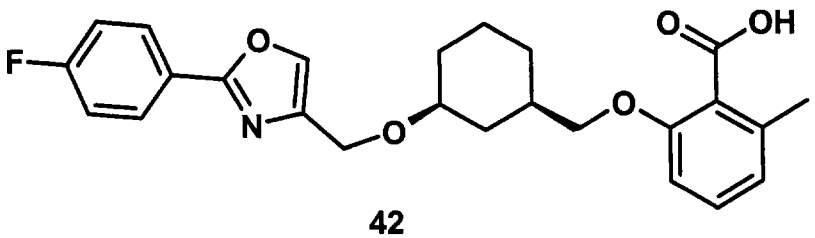


41

rac-cis-2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexylmethoxymethyl}-6-methylbenzoic acid **41**

cis-3-Hydroxymethylcyclohexanol, bromide **4** and iodide **2** (reverse reaction sequence) give the product **41** of molecular weight 453.52 ($C_{26}H_{28}FNO_5$); MS(ESI): 454 ($M+H^+$).

Example XXVI

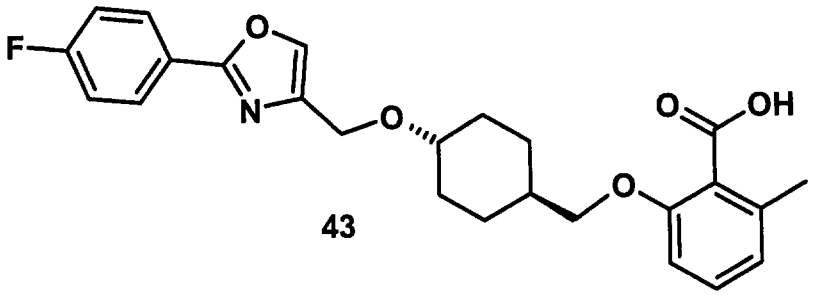


42

rac-cis-2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy}-6-methylbenzoic acid **42**

cis-3-Hydroxymethylcyclohexanol, iodide **2** and ethyl 2-hydroxy-6-methylbenzoate give the product **42** of molecular weight 439.49 ($C_{25}H_{26}FNO_5$); MS(ESI): 440 ($M+H^+$).

Example XXVII

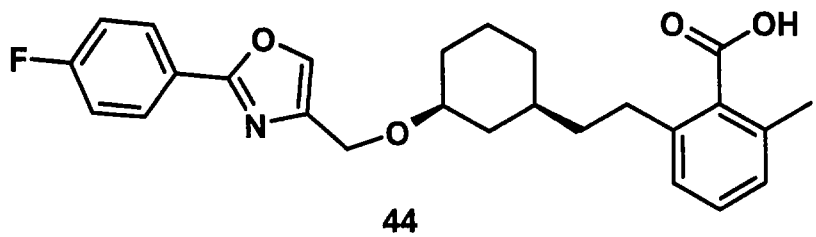


43

rac-trans-2-{4-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexylmethoxy}-6-methylbenzoic acid **43**

trans-4-Hydroxymethylcyclohexanol, iodide **2** and ethyl 2-hydroxy-6-methylbenzoate give the product **43** of molecular weight 439.49 ($C_{25}H_{26}FNO_5$); MS(ESI): 440 ($M+H^+$).

Example XXVIII

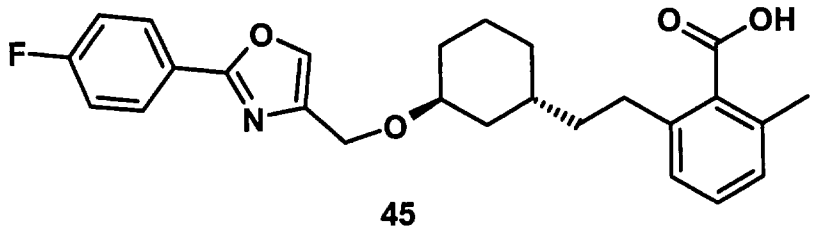


44

rac-cis-2-(2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)-6-methylbenzoic acid **44**

cis-3-Ethynylcyclohex-2-enol, ethyl 2-methyl-6-trifluoromethanesulfonyloxy-benzoate and iodide **2** give the product **44** of molecular weight 437.52 ($C_{26}H_{28}FNO_4$); MS(ESI): 438 ($M+H^+$).

Example XXIX

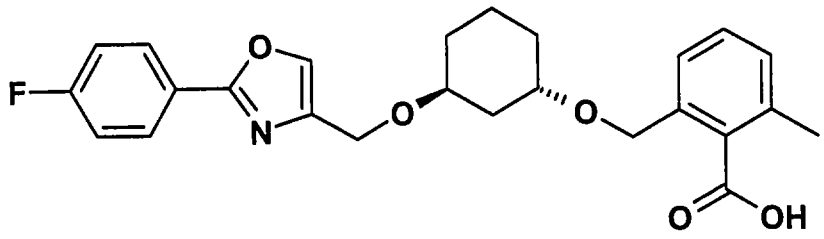


45

rac-trans-2-(2-{3-[2-(4-Fluorophenyl)oxazol-4-ylmethoxy]cyclohexyl}ethyl)-6-methylbenzoic acid **45**

trans-3-Ethynylcyclohex-2-enol, ethyl 2-methyl-6-trifluoromethanesulfonyloxy-benzoate and iodide **2** give the product **45** of molecular weight 437.52 ($C_{26}H_{28}FNO_4$); MS(ESI): 438 ($M+H^+$).

Example XXX

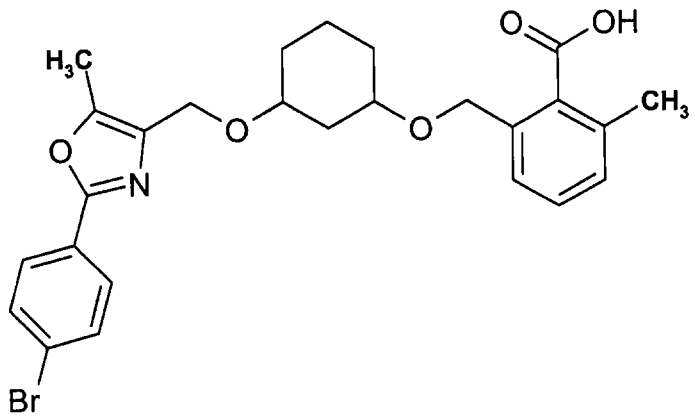


46

rac-trans-2-(3-(2-(4-Fluorophenyl)oxazol-4-ylmethoxy)cyclohexyloxymethyl)-6-methylbenzoic acid **46**

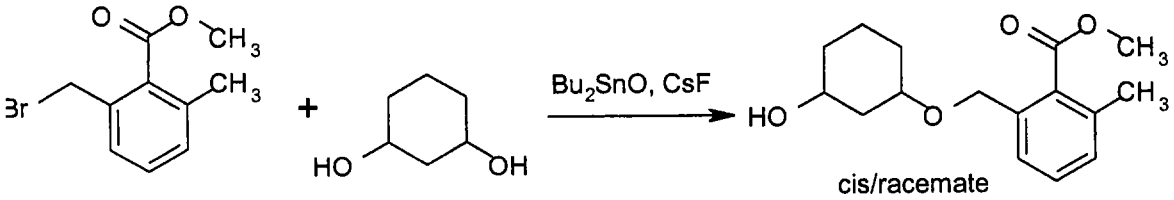
The racemic trans-enantiomer mixture **3b** (see example I) and methyl 2-bromomethyl-6-methylbenzoate **4** give the desired product of molecular weight 439.49 ($C_{25}H_{26}FNO_5$); MS(ESI): 440 (M+H+).

Example XXXI



50

Methyl 2-(cis-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate **47** and methyl 2-(trans-3-hydroxycyclohexyloxymethyl)-6-methylbenzoate **48**



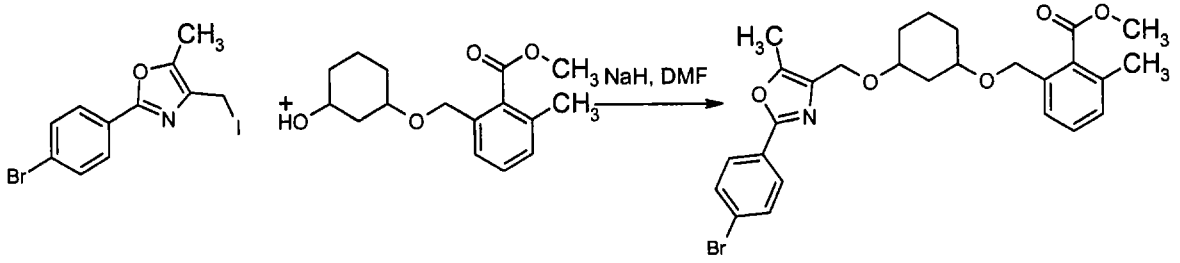
cis/racemate

8.7 g 1,3-cyclohexanediol and 12 g dibutyltin oxide are dissolved in 600 ml of toluene and, under reflux on a water separator, heated to the boil. During the reaction, the reaction volume is reduced to half of the original volume. After 4 hours, the reaction mixture is cooled to room temperature, and 300 ml of DMF, 9.0 g of methyl 2-bromomethyl-6-methylbenzoate and 9.4 g of cesium fluoride are added. The mixture is stirred at room temperature for 12 hours. The reaction mixture is diluted by addition of ethyl acetate and washed with saturated 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 = 50:1 → 1:2). This gives about 6 g of the alcohol **47** (cis-racemate) as an oil. $C_{16}H_{22}O_4$ (278.35), MS(ESI): 279 (M + H^+). The unreacted trans-1,3-cyclohexanediol is also eluted from the chromatography column. It is alkylated analogously to example I using sodium hydride and methyl 2-bromomethyl-6-methylbenzoate. After analogous work-up and chromatography as described for the cis-racemate, the trans-racemat **48** is obtained $C_{16}H_{22}O_4$ (278.35), MS(ESI): 279 (M + H^+).

Racemates **47** and **48** are separated by chromatography on a chiral phase (Chiralpak AD/2 250x4.6; n-heptane:ethanol:methanol = 25:1:0.5 + 0.1 % trifluoroacetic acid, R_t (**47a**) = 8.9 min; retention time of the enantiomer: R_t (**47b**) = 9.9 min (the absolute retention times vary with the exact chromatography conditions).

The reactions described below can be carried out both with the pure stereoisomers and with mixtures of the stereoisomers.

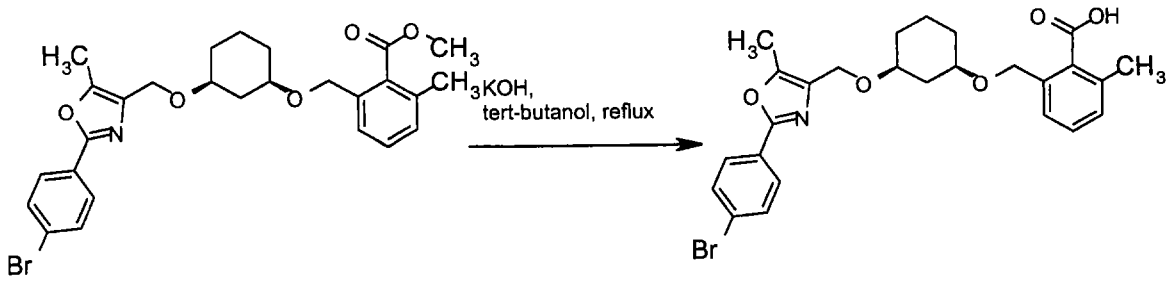
Methyl 2-{3-[2-(4-bromophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy-methyl}-6-methylbenzoate **49**



49

At room temperature, 50 mg of a 60% sodium hydride suspension and then 408 mg of 2-(4-bromophenyl)-4-iodomethyl-5-methyloxazole are added to a solution of 200 mg of methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate in 5 ml of dimethylformamide. After one hour, methyl tert-butyl ether is added, and the mixture is extracted with water. The organic phase is dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by RP-HPLC. This gives **49** as a light-yellow oil. $C_{27}H_{30}BrNO_5$ (528.45), MS(ESI): 528.2, 530.2 ($M + H^+$).

2-{3-[2-(4-Bromophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **50**

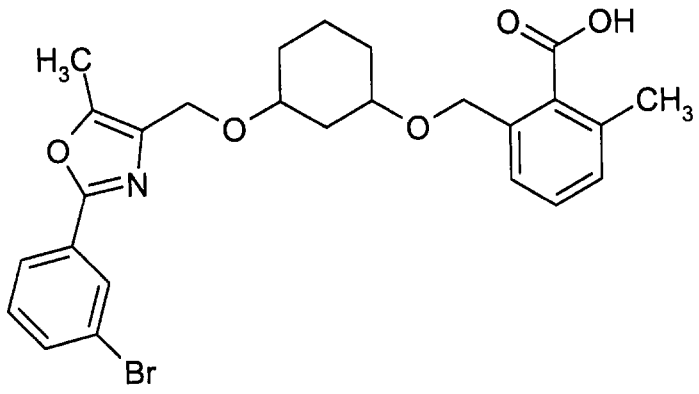


49 **50**

117 mg of **49** are stirred in a mixture of 10 ml of tert-butanol and 1 ml of 10 N aqueous potassium hydroxide solution at 90°C. After two days, the mixture is

acidified with hydrochloric acid and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by RP-HPLC. This gives **50** as an amorphous solid. $C_{26}H_{28}BrNO_5$ (514.52), MS(ESI): 514.29, 516.29 ($M + H^+$).

Example XXXII

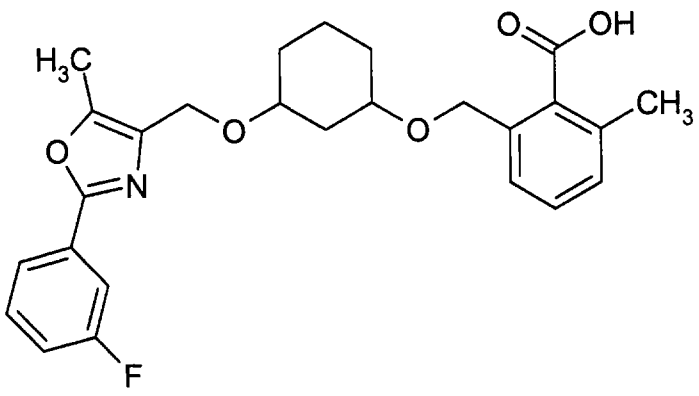


51

2-{3-[2-(3-Bromophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **51**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-bromophenyl)-4-iodomethyl-5-methyloxazole give, analogously to example **50**, the product **51** of molecular weight 514.42, ($C_{26}H_{28}BrNO_5$), MS(ESI): 514.30,516.30 ($M + H^+$).

Example XXXIII

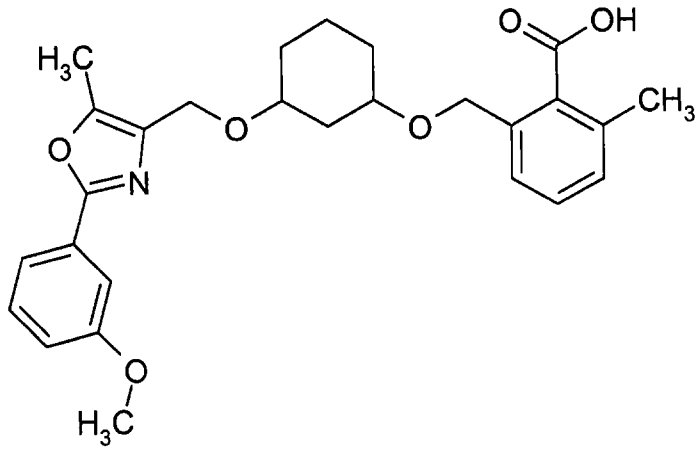


52

2-{3-[2-(3-Fluorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **52**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-fluorophenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **52** of molecular weight 453.52 ($C_{26}H_{28}FNO_5$), MS(ESI): 454.35 ($M + H^+$).

Example XXXIV

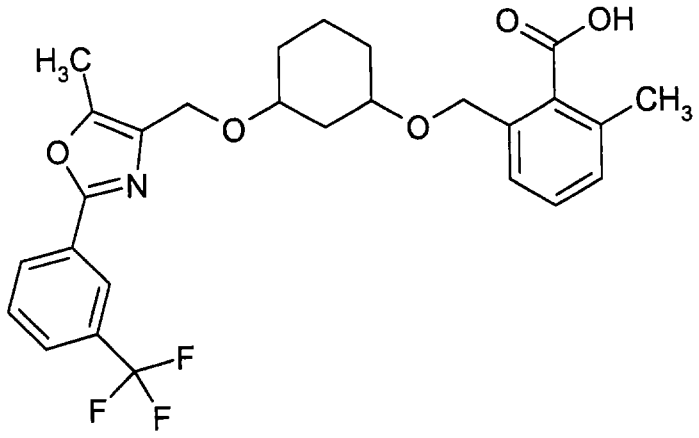


53

2-{3-[2-(3-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **53**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-methoxy-phenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **53** of molecular weight 465.55 ($C_{27}H_{31}NO_6$), MS(ESI): 466.37 ($M + H^+$).

Example XXXV

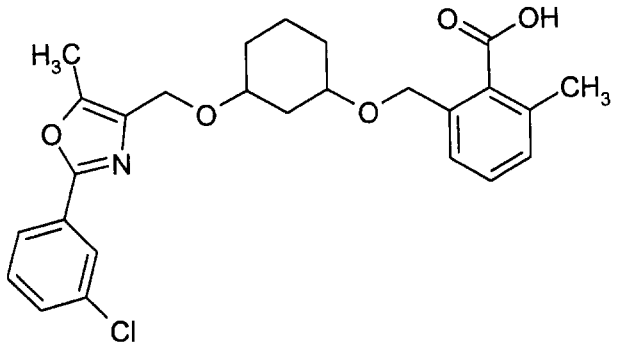


54

2-{3-[2-(3-Trifluoromethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyl-oxymethyl}-6-methylbenzoic acid **54**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-trifluoromethylphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **54** of molecular weight 503.52 ($C_{27}H_{28}F_3NO_5$), MS(ESI): 504.37 ($M + H^+$).

Example XXXVI

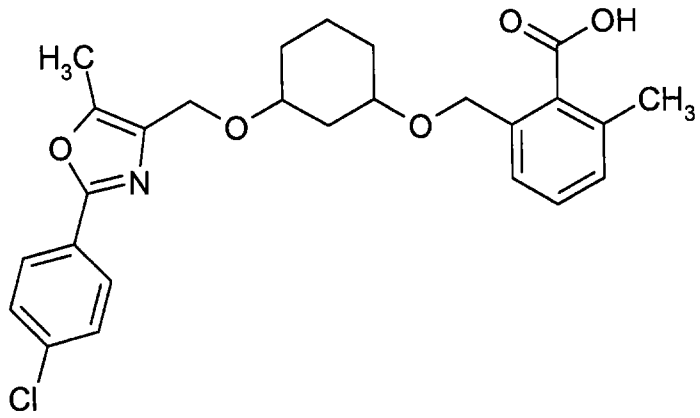


57

2-{3-[2-(3-Chlorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **57**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-chlorophenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **57** of molecular weight 469.97 ($C_{26}H_{28}ClNO_5$), MS(ESI): 470.43 ($M + H^+$).

Example XXXVII

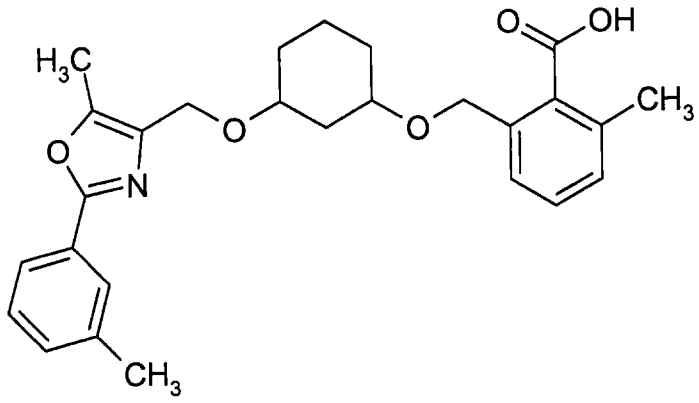


58

2-{3-[2-(4-Chlorophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **58**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-chlorophenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **58** of molecular weight 469.97 ($C_{26}H_{28}ClNO_5$), MS(ESI): 470.40 ($M + H^+$).

Example XXXVIII

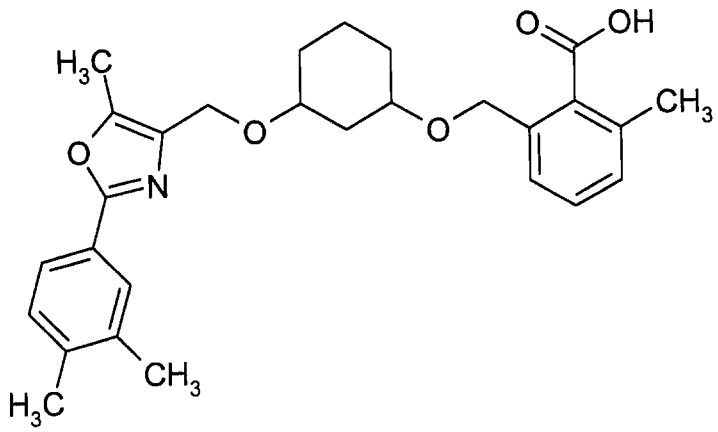


59

2-{3-[2-(3-Methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **59**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-methylphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **59** of molecular weight 449.55 ($C_{27}H_{31}NO_5$), MS(ESI): 450.53 ($M + H^+$).

Example XXXIX



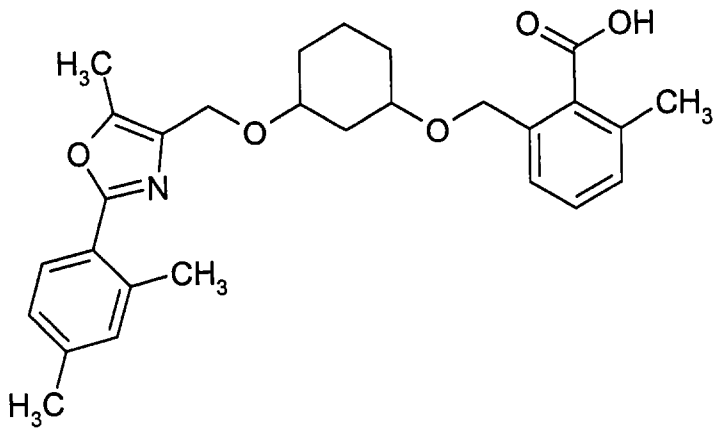
61

2-{3-[2-(3,4-Dimethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-

6-methylbenzoic acid **61**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3,4-dimethylphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **61** of molecular weight 463.58 ($C_{28}H_{33}NO_5$), MS(ESI): 464.22 ($M + H^+$).

Example XL

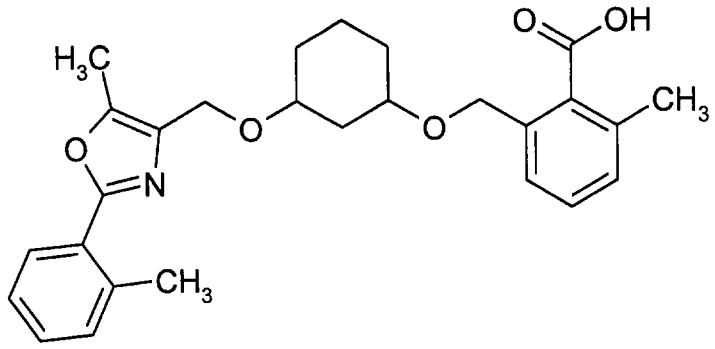


62

2-{3-[2-(2,4-Dimethylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **62**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(2,4-dimethylphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **62** of molecular weight 463.58 ($C_{28}H_{33}NO_5$), MS(ESI): 464.22 ($M + H^+$).

Example XLI

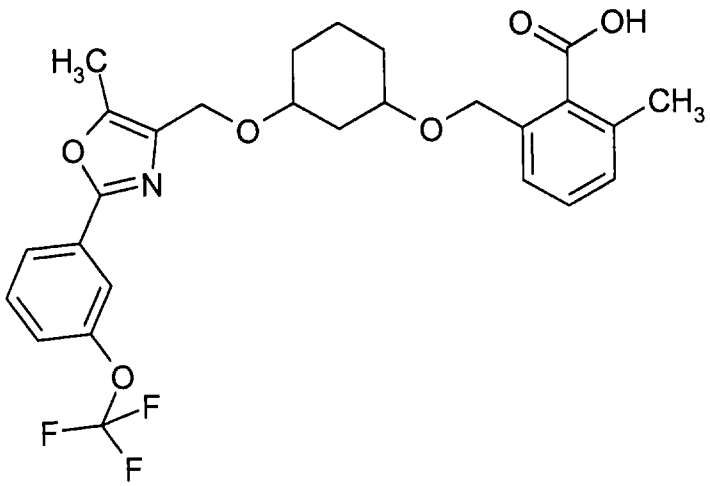


63

2-{3-[2-(2-Methylphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **63**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(2-methylphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **63** of molecular weight 449.55 ($C_{27}H_{31}NO_5$), MS(ESI): 450.20 ($M + H^+$).

Example XLII



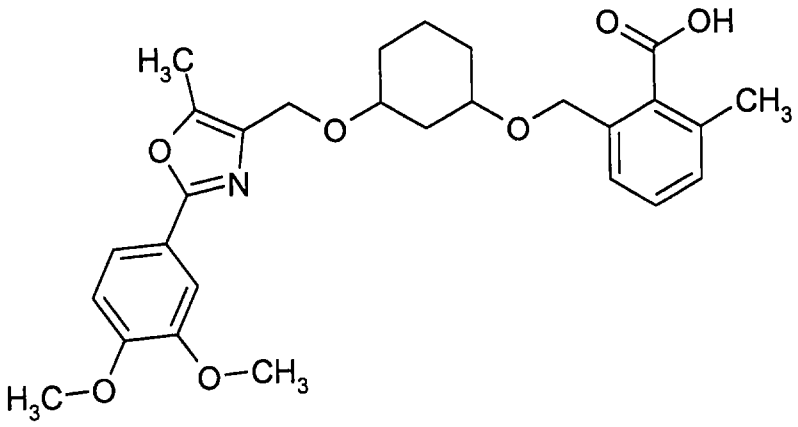
64

2-{3-[2-(3-Trifluoromethoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxy-

methyl}-6-methylbenzoic acid **64**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3-trifluoromethoxyphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **64** of molecular weight 519.52 ($C_{27}H_{28}F_3NO_6$), MS(ESI): 520.20 ($M + H^+$.

Example XLIII

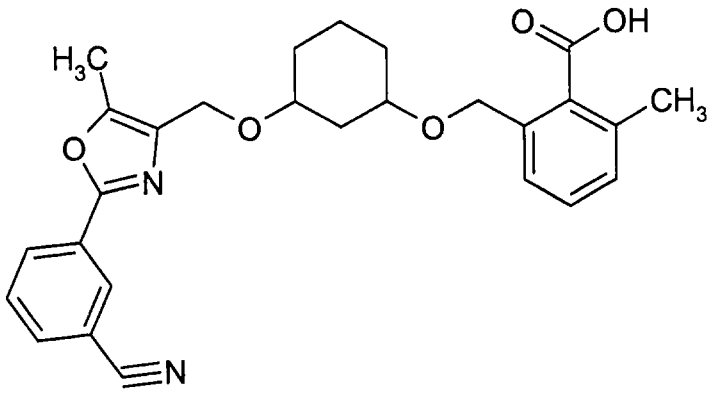


67

2-{3-[2-(3,4-Dimethoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **67**

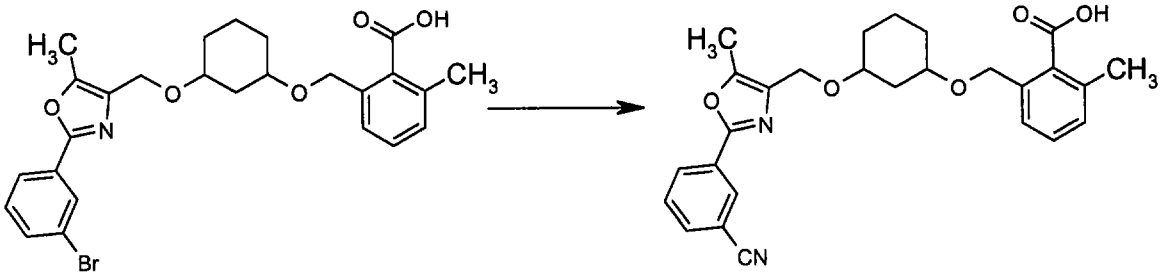
Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(3,4-dimethoxyphenyl)-4-iodomethyl-5-methyloxazol give, analogously to **50**, the product **67** of molecular weight 495.58 ($C_{28}H_{33}NO_7$), MS(ESI): 496.20 ($M + H^+$).

Example XLIV



68

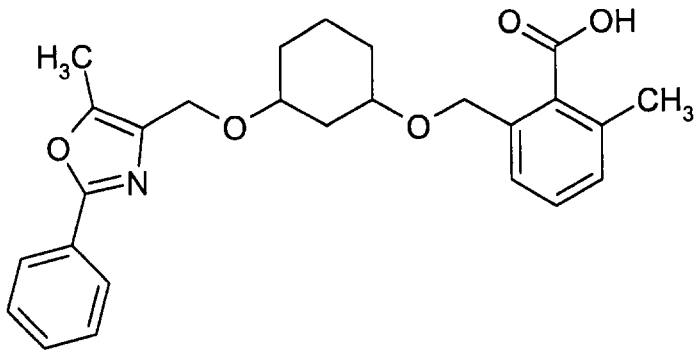
2-{3-[2-(3-Cyanophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **68**



68

13 mg of 2-{3-[2-(3-bromophenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid and 25 mg of zinc cyanide are dissolved in 5 ml of dimethylformamide. The reaction mixture is degassed and charged with argon, and 20 mg of tetrakistriphenylphosphinepalladium are added. The mixture is stirred at 100°C for 12 hours. After cooling to room temperature, water is added to the reaction mixture, which is then extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate, the solvents are removed under reduced pressure and the residue is purified by RP-HPLC. This gives **68** as an amorphous light-yellow solid. $C_{27}H_{28}N_2O_5$ (460.53), MS(ESI): 461.20 ($M + H^+$).

Example XLV

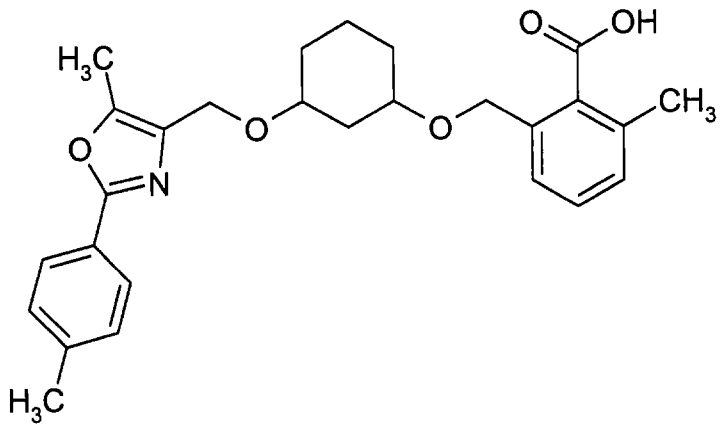


69

2-Methyl-6-[3-(5-methyl-2-phenyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **69**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-phenyl-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **69** of molecular weight 435.52 ($C_{26}H_{29}NO_5$), MS(ESI): 436.32 ($M + H^+$).

Example XLVI

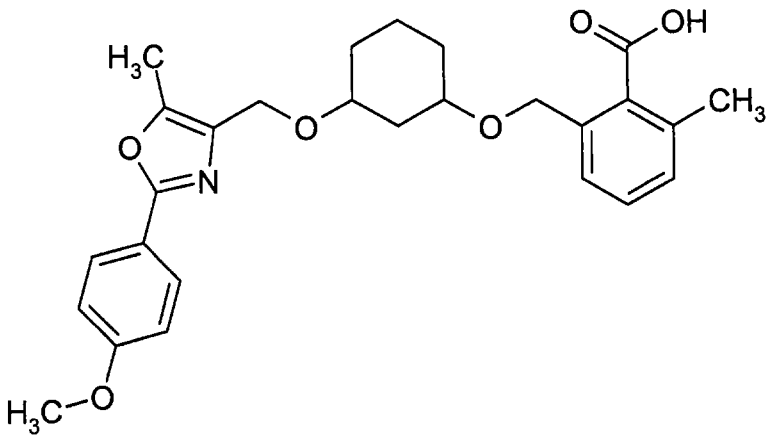


70

2-Methyl-6-[3-(5-methyl-2-p-tolyloxazol-4-ylmethoxy)cyclohexyloxymethyl]benzoic acid **70**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-methylphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **70** of molecular weight 449.55 ($C_{27}H_{31}NO_5$), MS(ESI): 450.36 ($M + H^+$).

Example XLVII



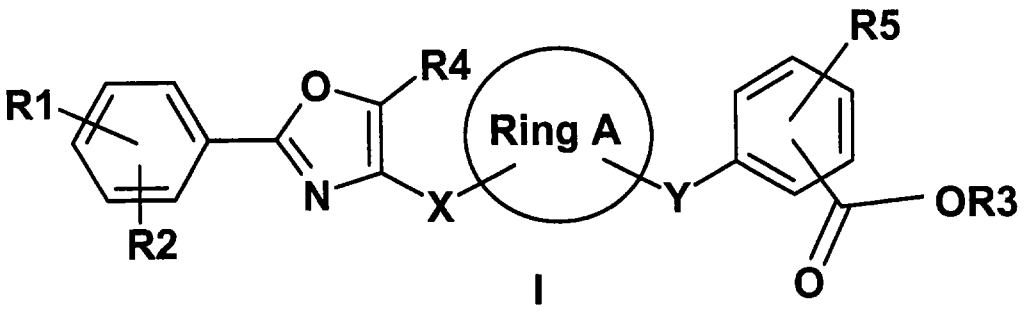
71

2-{3-[2-(4-Methoxyphenyl)-5-methyloxazol-4-ylmethoxy]cyclohexyloxymethyl}-6-methylbenzoic acid **71**

Methyl 2-(3-hydroxycyclohexyloxymethyl)-6-methylbenzoate and 2-(4-methoxyphenyl)-4-iodomethyl-5-methyloxazole give, analogously to **50**, the product **71** of molecular weight 465.55 ($C_{27}H_{31}NO_6$), MS(ESI): 466.37($M + H^+$).

We claim:

1. A compound of the formula I



I

in which

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

R1, R2, R4, R5 independently of one another are H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R3 is H or (C_1-C_6)-alkyl;

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

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

and its physiologically acceptable salts.

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

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

R1, R2, R4 independently of one another are H, F, Cl, Br, OH, NO_2, CF_3, OCF_3, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl;

R5 is (C_1-C_6)-alkyl;

R3 is H or (C_1-C_6)-alkyl;

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

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

and its physiologically acceptable salts.

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

Ring A is (C_3-C_8)-cycloalkyl or (C_3-C_8)-cycloalkenyl;

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

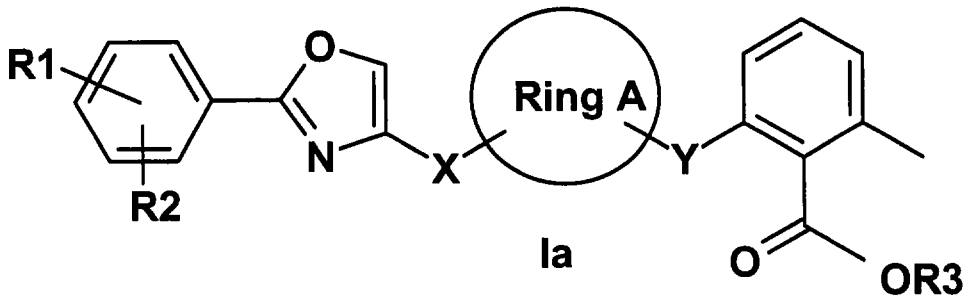
R3 is H or (C_1-C_6)-alkyl;

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

Y is (C_1-C_6)-alkyl, where in the alkyl group one or more carbon atoms are replaced by oxygen atoms;

and its physiologically acceptable salts.

4. A compound of the formula I as claimed in one or more of claims 1 to 3 having the structure Ia



Ia

Ring A is cyclohexyl;

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

R3 is H or (C_1-C_6)-alkyl;

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

Y is (C_1-C_6)-alkyl, where in the alkyl group one or more carbon atoms are replaced by oxygen atoms;

and its physiologically acceptable salts.

5. A pharmaceutical, comprising one or more compounds as claimed in one or more of claims 1 to 4.

6. A pharmaceutical comprising one or more compounds as claimed in one or more of claims 1 to 4 and one or more active compounds.

7. A pharmaceutical, comprising one or more compounds as claimed in one or more of claims 1 to 4 and one or more lipid- or triglyceride-lowering active compounds.

8. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of disorders of the lipid metabolism.

9. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of type II diabetes.

10. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of syndrome X.

11. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of disturbed glucose tolerance.

12. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of eating disorders.

13. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of obesity.

14. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of cardiomyopathy.

15. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of cardiac insufficiency.

16. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of osteoporosis.

17. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of atherosclerosis.

18. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of Alzheimer's disease.

19. The use of the compounds as claimed in one or more of claims 1 to 4 for preparing a medicament for the treatment of inflammations.

20. The use of compounds as claimed in one or more of claims 1 to 4 in combination with at least one further active compound for preparing a medicament for the treatment of disorders of the lipid metabolism.

21. The use of compounds as claimed in one or more of claims 1 to 4 in combination with at least one further active compound for preparing a medicament for the treatment of type II diabetes.

22. The use of compounds as claimed in one or more of claims 1 to 4 in combination with at least one further active compound for preparing a medicament for the treatment of syndrome X.

23. A process for preparing a pharmaceutical comprising one or more compounds as claimed in one or more of claims 1 to 4, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.