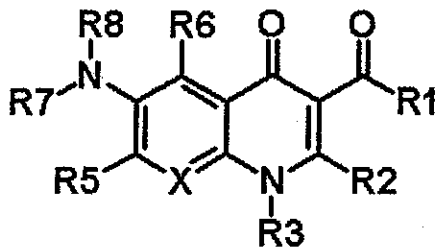
Cycloalkyl substituted 7-amino-4-quinolone-3-carboxylic acid derivatives, method for the production thereof and their use as medicaments

The invention relates to cycloalkyl-substituted 7-amino-4-quinolone-3-carboxylic acid derivatives and to the physiologically tolerated salts and physiologically functional derivatives thereof.

Compounds of similar structure have already been described in the art (Link, Helmut; Bernauer, Karl; Englert Gerhard, Helvetica Chimica Acta 65(8), 1982, 2645-2667).

The invention was based on the object of providing compounds which display a therapeutically usable blood glucose-lowering effect.

The invention therefore relates to compounds of the formula I



I

in which the meanings are

R1 OH, O-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl, N-((C_1-C_6)-alkyl)$_2$ or O-(C_1-C_6)-OCO-(C_1-C_6)-alkyl;

R2 H, (C_1-C_6)-alkyl or phenyl;

R3 H, (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, pyridyl or phenyl, where alkyl may be substituted by R9 and where pyridyl or phenyl may be substituted by R10;

R9 NH_2, NH-(C_1-C_6)-alkyl, N-((C_1-C_6)-alkyl)$_2$, -(C_3-C_7)-cycloalkyl, heteroalkyl, heteroaryl, O-phenyl or phenyl, where phenyl and heteroaryl may be substituted by R11;

R10 F, Cl, Br, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH, COO-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl or N-((C_1-C_6)-alkyl)$_2$;

R11 F, Cl, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH or COO-(C_1-C_4)-alkyl;

X N;

R5, R6, independently of one another, H, F, Cl, Br, OH, NO_2, CN, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl, where alkyl may be substituted more than once by F, Cl or Br;

R7 H or (C_1-C_6)-alkyl;

R8 (C_3-C_{12})-cycloalkyl, where cycloalkyl may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkenyl, (C_1-C_4)-alkynyl, F, Cl, CN, CF_3, COOH or COO-(C_1-C_4)-alkyl;

and the physiologically tolerated salts thereof.

Preference is given to compounds of the formula I in which one or more radicals have the following meaning:

R1 OH, O-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl, N-((C_1-C_6)-alkyl)$_2$ or O-(C_1-C_6)-OCO-(C_1-C_6)-alkyl;

R2 H;

R3 H, (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, pyridyl or phenyl, where alkyl may be substituted by R9 and where pyridyl or phenyl may be substituted by R10;

R9 NH_2, NH-(C_1-C_6)-alkyl, N-((C_1-C_6)-alkyl)$_2$, -(C_3-C_7)-cycloalkyl, heteroalkyl, heteroaryl, O-phenyl or phenyl, where phenyl and heteroaryl may be substituted by R11;

R10 F, Cl, Br, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH, COO-(C_1-C_6)-alkyl, NH_2,

NH-(C_1-C_6)-alkyl or N-((C_1-C_6)-alkyl)$_2$;

R11 F, Cl, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH or COO-(C_1-C_4)-alkyl;

X N;

R5 H, F, Cl, Br, OH, NO_2, CN, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl, where alkyl may be substituted more than once by F, Cl or Br;

R6 H;

R7 H;

R8 (C_3-C_{12})-cycloalkyl, where cycloalkyl may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkenyl, (C_1-C_4)-alkynyl, F, Cl, CN, CF_3, COOH or COO-(C_1-C_4)-alkyl;

and the physiologically tolerated salts thereof.

Particular preference is given to compounds of the formula I in which one or more radicals have the following meaning:

R1 OH, O-(C_1-C_6)-alkyl;

R2 H;

R3 (C_1-C_8)-alkyl;

R9 NH_2, NH-(C_1-C_6)-alkyl, N-((C_1-C_6)-alkyl)$_2$, -(C_3-C_7)-cycloalkyl, heteroalkyl, heteroaryl, O-phenyl or phenyl, where phenyl and heteroaryl may be substituted by R11;

R10 F, Cl, Br, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH, COO-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl or N-((C_1-C_6)-alkyl)$_2$;

R11 F, Cl, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH or COO-(C_1-C_4)-alkyl;

X N;

R5 H, F, Cl, Br, OH, NO_2, CN, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl, where alkyl may be substituted more than once by F, Cl or Br;

R6 H;

R7 H;

R8 (C_3-C_{12})-cycloalkyl, where cycloalkyl may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkenyl, (C_1-C_4)-alkynyl, F, Cl, CN, CF_3, COOH or COO-(C_1-C_4)-alkyl;

and the physiologically tolerated salts thereof.

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

The alkyl radicals in the substituents R1, R2, R3, R5, R6, R7, R8, R9, R10 and R11 may be both straight-chain and branched.

If radicals or substituents may occur more than once in the compounds of the formula I, they may all, independently of one another, have the stated meanings and be identical or different.

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

salts), alkaline earth metal salts (such as magnesium and calcium salts), trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine, or ethylenediamine.

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

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

Physiologically functional derivatives include prodrugs of the compounds of the invention. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

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

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

A heteroaryl radical means a pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzimidazolyl, thiophenyl or a furanyl radical.

The compound(s) of the formula (I) can also be administered in combination with further active ingredient.

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 and 50 mg) per day and per kilogram of bodyweight, 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 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, 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 ingredient. 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, cachets, suckable tablets or tablets, each of which contain

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

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, cream, lotion, paste, spray, aerosol or oil. Carriers which can be used are petrolatum, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

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

Further active ingredients suitable for combination products are:
all antidiabetics mentioned in the Rote Liste 2001, chapter 12. They may be combined with the compounds of the formula I of the invention in particular for a synergistic improvement of the effect. Administration of the active ingredient combination may take place either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. Most of the active ingredients listed below are disclosed in the 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 effective hypoglycemic active ingredients.

The orally effective hypoglycemic active ingredients 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 ingredients and antilipidemic active ingredients, compounds

which reduce food intake, PPAR and PXR agonists and active ingredients which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA 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, Gl 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, DE10142734.4.

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 absorption 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 one further 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 ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, with 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, e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]cyclohexylmethyl}amide; hydrochloride (CGP 71683A)), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]-amide; (WO 01/91752)), orexin antagonists (e.g.

1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea; hydrochloride (SB-334867-A)), H3 agonists (3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208)); TNF agonists, CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (e.g. urocortin), urocortin agonists, β3 agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)-ethylamino]-ethanol hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (e.g. {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexyl-ethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525)), serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed sertoninergic and noradrenergic compounds (e.g. WO 00/71549), 5HT agonists e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), bombesin agonists, galanin antagonists, growth hormone (e.g. human growth hormone), growth hormone-releasing compounds (6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (WO 01/85695)), TRH agonists (see, for example, EP 0 462 884), uncoupling protein 2 or 3 modulators, leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881), DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR modulators or TR-β agonists.

In one embodiment of the invention, the other active ingredient 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 ingredient is dexamphatamine or amphetamine.

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

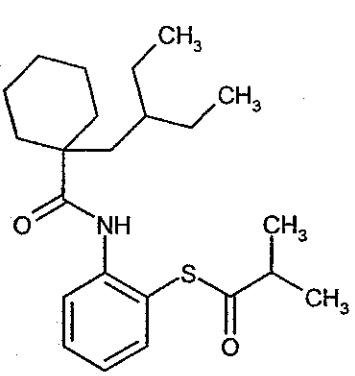
In another embodiment, the other active ingredient is sibutramine.

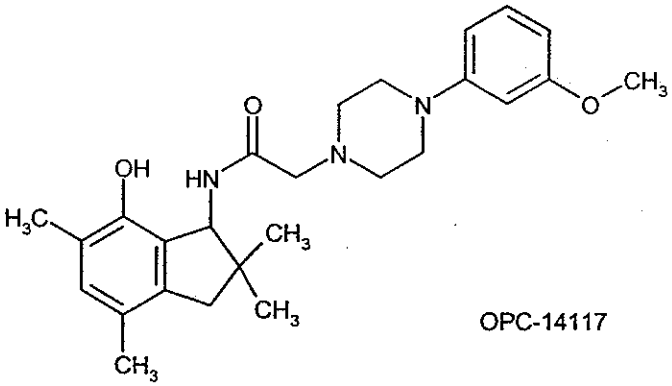
In one embodiment, the other active ingredient is orlistat.

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

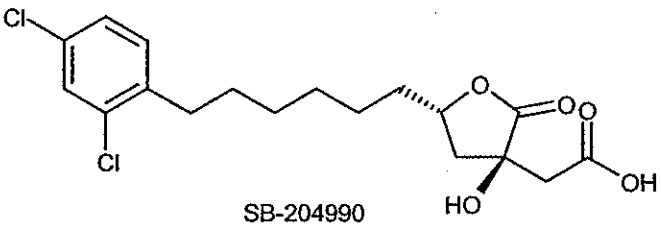
In one embodiment, the compounds of the formula I are administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6.)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

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

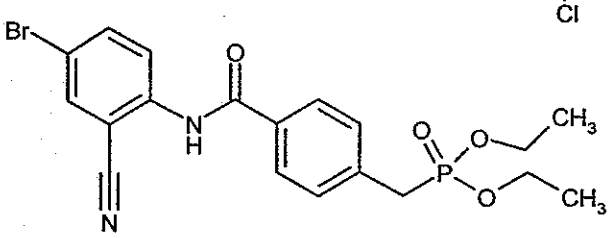




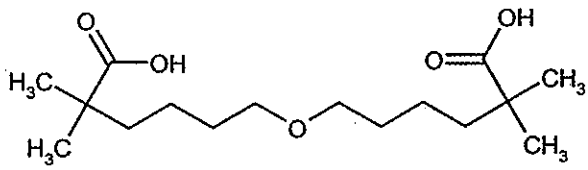
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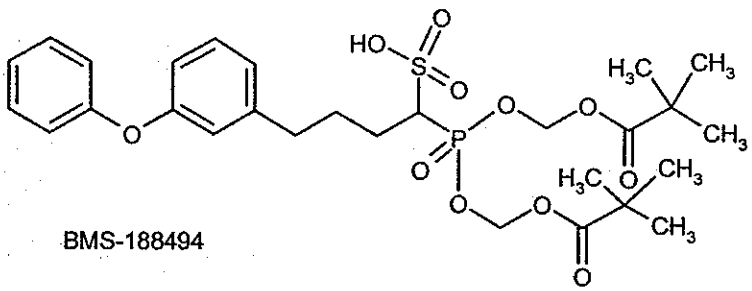
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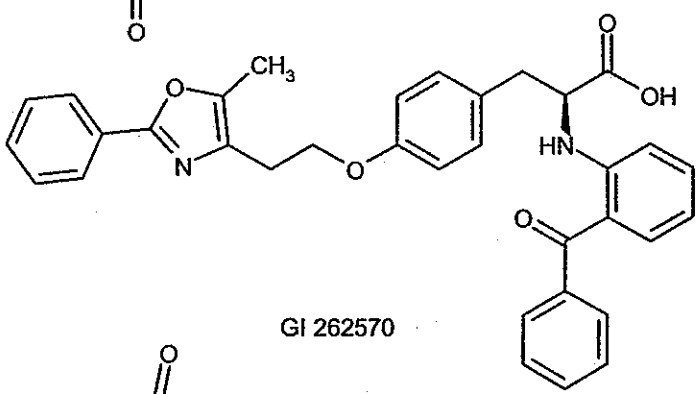
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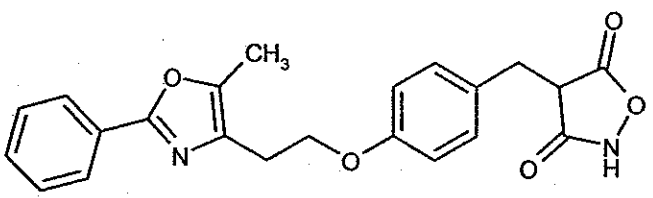
CI-1027



BMS-188494



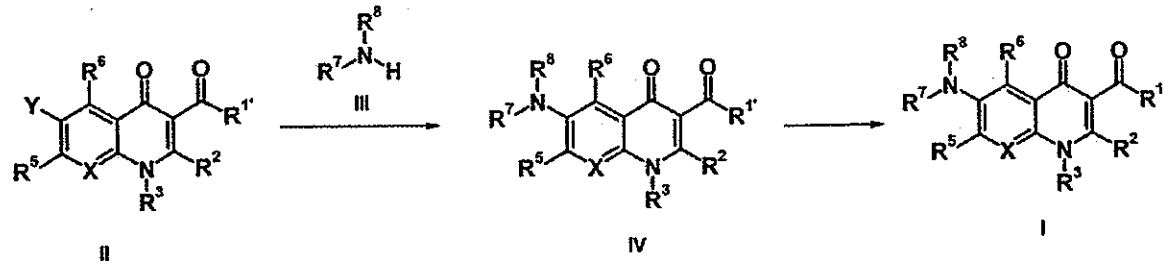
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Preparation of the compounds of the formula I is described in the following schemes: Compounds of the formula II can be reacted under Buchwald conditions with amines of the formula III to give compounds of the formula IV in which R1' has the meaning of an ester. In this case, Y is Br, I or triflate. With these Buchwald conditions it is possible to employ catalyst systems with $Pd(OAc)_2$ or $Pd_2(dba)_3$ as palladium sources, BINAP, xanthphos and DPPF as ligands and Cs_2CO_3, K_3PO_4 or NaO^tBu as bases. Solvents which can be used are, for example, toluene, DME, dioxane, THF or DMF. The reaction conditions may be chosen from conventional heating or heating and reaction in a microwave. (Literature: Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805)

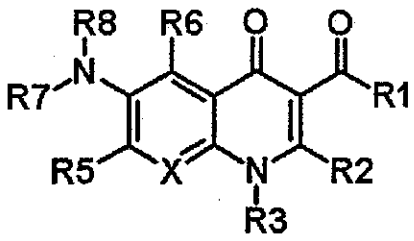
Optional subsequent hydrolysis of the compounds of the formula IV and optional conversion to different amides or esters lead to compounds of the formula I.

Scheme 1:



The examples listed below serve to illustrate the invention but without restricting it.

Table 1:



Example	R1	R2	R3	X	R5	R6	R7	R8
1	OEt	H	Et	N	Me	H	H	
2	OEt	H	Et	N	Me	H	H	
3	OH	H	Et	N	Me	H	H	
4	OH	H	Et	N	Me	H	H	

The activity of the compounds was assayed as follows:

Glycogen phosphorylase a activity assay

The effect of compounds on the activity of the active form of glycogen phosphorylase (GPa) was measured in the reverse direction by following the synthesis of glycogen from glucose 1-phosphate by determining the liberation of inorganic phosphate. All the reactions were carried out as duplicate determinations in microtiter plates with 96 wells (Half Area Plates, Costar No 3696), measuring the change in absorption owing to the formation of the reaction product at the wavelength specified hereinafter in a Multiskan Ascent Elisa Reader (Lab Systems, Finland).

In order to measure the GPa enzymic activity in the reverse direction, the general method of Engers et al. (Engers HD, Shechosky S, Madsen NB, Can J Biochem 1970 Jul;48(7):746-754) was used to measure the conversion of glucose 1-phosphate into glycogen and inorganic phosphate, with the following modifications: human glycogen phosphorylase a (for example with 0.76 mg of protein/ml (Aventis Pharma Deutschland GmbH), dissolved in buffer solution E (25 mM β-glycerophosphate, pH 7.0, 1 mM EDTA and 1 mM dithiothreitol) was diluted with buffer T (50 mM Hepes, pH 7.0, 100 mM KCl, 2.5 mM EDTA, 2.5 mM $MgCl_2 \cdot 6H_2O$) and addition of 5 mg/ml glycogen to a concentration of 10 µg of protein/ml. Test substances were prepared as 10 mM solution in DMSO and diluted to 50 µM with buffer solution T. To 10 µl of this solution were added 10 µl of 37.5 mM glucose, dissolved in buffer solution T, and 5 mg/mL glycogen, plus 10 µl of a solution of human glycogen phosphorylase a (10 µg of protein/ml) and 20 µl of glucose 1-phosphate, 2,5 mM. The baseline glycogen phosphorylase a activity in the absence of test substance was determined by adding 10 µl of buffer solution T (0.1% DMSO). The mixture was incubated at room temperature for 40 minutes, and the liberated inorganic phosphate was measured by the general method of Drueckes et al. (Drueckes P, Schinzel R, Palm D, *Anal Biochem* 1995 Sep 1;230(1):173-177) with the following modifications: 50 µl of a stop solution of 7.3 mM ammonium molybdate, 10.9 mM zinc acetate, 3.6% ascorbic acid, 0.9% SDS are added to 50 µl of the enzyme mixture. After incubation at 45°C for 60 minutes, the absorption at 820 nm was measured. To determine the background absorption, in a separate mixture the stop solution was added immediately after addition of the glucose 1-phosphate solution.

This test was carried out with a concentration of 10 µM of the test substance in order to determine the particular inhibition of glycogen phosphorylase a in vitro by the test substance.

Table 2: Biological activity

Ex.	**% inhibition at 10 µM**
1	24
2	42
3	35
4	16

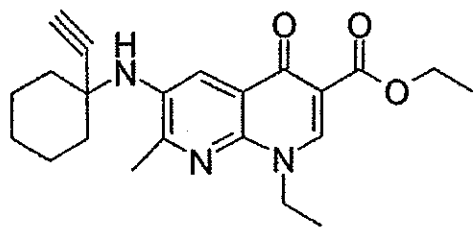
It is evident from the table that the compounds of the formula I inhibit the activity of glycogen phosphorylase a and are thus very suitable for lowering the blood glucose level.

The preparation of some examples is described in detail below, and the other compounds of the formula I were obtained analogously:

Experimental part:

Example 2

Ethyl 1-ethyl-6-(1-ethynylcyclohexylamino)-7-methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylate

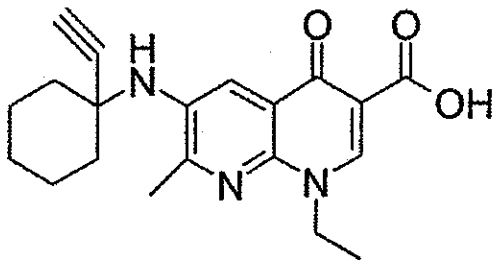


100 mg of ethyl 6-bromo-1-ethyl-8-methyl-4-oxo-1,4-dihydroquinolone-3-carboxylate were transferred together with 36 mg of 1-ethynylcyclohexylamine, 6.6 mg of $Pd(OAc)_2$, 36 mg of XANTPHOS and 200 mg of cesium carbonate into a suitable reaction vessel, a protective gas atmosphere was generated with argon, and 10 ml of dioxane were added. The mixture was then heated at 80°C for 8 hours. The pure product was isolated from the reaction solution by chromatography on an HPLC system. This entailed use of a Merck Purospher- RP18 column and an acetonitrile:water mixture as eluent; the initial acetonitrile content was 15% and rose to 95% over the course of 20 minutes.

Yield: 4%

Example 3

1-Ethyl-6-(1-ethynylcyclohexylamino)-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid

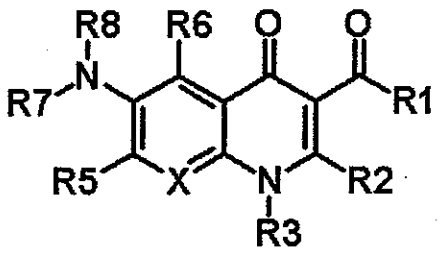


Ethyl 1-ethyl-6-(1-ethynylcyclohexylamino)-7-methyl-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylate (10 mg) was dissolved in 5 ml of dioxane, 2.5 equivalents of a 1 N NaOH solution were added, and the mixture was heated at 60°C for 4 h. Removal of the solvent in vacuo was followed by chromatography on an HPLC system to purify the product. The pure product was isolated from the reaction solution by chromatography on an HPLC system. This entailed use of a Merck Purospher-RP18 column and an acetonitrile:water mixture as eluent; the initial acetonitrile content was 15% and rose to 95% over the course of 20 minutes.

Yield: 85 %

Claims:

1. A compound of the formula I



I

in which the meanings are

R1 OH, O-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl, N-((C_1-C_6)-alkyl)$_2$ or O-(C_1-C_6)-OCO-(C_1-C_6)-alkyl;

R2 H, (C_1-C_6)-alkyl or phenyl;

R3 H, (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, pyridyl or phenyl, where alkyl may be substituted by R9 and where pyridyl or phenyl may be substituted by R10;

R9 NH_2, NH-(C_1-C_6)-alkyl, N-((C_1-C_6)-alkyl)$_2$, -(C_3-C_7)-cycloalkyl, heteroalkyl, heteroaryl, O-phenyl or phenyl, where phenyl and heteroaryl may be substituted by R11;

R10 F, Cl, Br, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH, COO-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl or N-((C_1-C_6)-alkyl)$_2$;

R11 F, Cl, (C_1-C_6-alkyl), O-(C_1-C_6)-alkyl, COOH or COO-(C_1-C_4)-alkyl;

X N;

R5, R6 independently of one another H, F, Cl, Br, OH, NO_2, CN, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl, where alkyl may be substituted more than once by F, Cl or Br;

R7 H or (C_1-C_6)-alkyl;

R8 (C_3-C_{12})-cycloalkyl, where cycloalkyl may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkenyl, (C_1-C_4)-alkynyl, F, Cl, CN, CF_3, COOH or COO-(C_1-C_4)-alkyl;

and the physiologically tolerated salts thereof.

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

R1 OH, O-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl, N-$((C_1-C_6)\text{-alkyl})_2$ or O-(C_1-C_6)-OCO-(C_1-C_6)-alkyl;

R2 H;

R3 H, (C_1-C_8)-alkyl, (C_3-C_7)-cycloalkyl, pyridyl or phenyl, where alkyl may be substituted by R9 and where pyridyl or phenyl may be substituted by R10;

R9 NH_2, NH-(C_1-C_6)-alkyl, N-$((C_1-C_6)\text{-alkyl})_2$, -$(C_3-C_7)$-cycloalkyl, heteroalkyl, heteroaryl, O-phenyl or phenyl, where phenyl and heteroaryl may be substituted by R11;

R10 F, Cl, Br, $(C_1-C_6$-alkyl), O-(C_1-C_6)-alkyl, COOH, COO-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl or N-$((C_1-C_6)\text{-alkyl})_2$;

R11 F, Cl, $(C_1-C_6$-alkyl), O-(C_1-C_6)-alkyl, COOH or COO-(C_1-C_4)-alkyl;

X N;

R5 H, F, Cl, Br, OH, NO_2, CN, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl, where alkyl may be substituted more than once by F, Cl or Br;

R6 H;

R7 H;

R8 (C_3-C_{12})-cycloalkyl, where cycloalkyl may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkenyl, (C_1-C_4)-alkynyl, F, Cl, CN, CF_3, COOH or COO-(C_1-C_4)-alkyl;

and the physiologically tolerated salts thereof.

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

R1 OH, O-(C_1-C_6)-alkyl;

R2 H;

R3 (C_1-C_8)-alkyl;

R9 NH_2, NH-(C_1-C_6)-alkyl, N-$((C_1-C_6)$-alkyl$)_2$, -(C_3-C_7)-cycloalkyl, heteroalkyl, heteroaryl, O-phenyl or phenyl, where phenyl and heteroaryl may be substituted by R11;

R10 F, Cl, Br, $(C_1-C_6$-alkyl), O-(C_1-C_6)-alkyl, COOH, COO-(C_1-C_6)-alkyl, NH_2, NH-(C_1-C_6)-alkyl or N-$((C_1-C_6)$-alkyl$)_2$;

R11 F, Cl, $(C_1-C_6$-alkyl), O-(C_1-C_6)-alkyl, COOH or COO-(C_1-C_4)-alkyl;

X N;

R5 H, F, Cl, Br, OH, NO_2, CN, (C_1-C_6)-alkyl or O-(C_1-C_6)-alkyl, where alkyl may be substituted more than once by F, Cl or Br;

R6 H;

R7 H;

R8 (C_3-C_{12})-cycloalkyl, where cycloalkyl may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkenyl, (C_1-C_4)-alkynyl, F, Cl, CN, CF_3, COOH or COO-(C_1-C_4)-alkyl;

and the physiologically tolerated salts thereof.

4. A compound as claimed in claim 1 for use as medicament.

5. A medicament comprising one or more of the compounds as claimed in claim 1.

6. A medicament comprising one or more of the compounds as claimed in claim 1 and at least one other active ingredient.

7. The medicament as claimed in claim 4, wherein the other active ingredient comprises one or more
antidiabetics, hypoglycemic active ingredients, HMGCoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, CETP inhibitors, polymeric bile acid adsorbents, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP-citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists, lipase inhibitors, insulins, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, active ingredients which act on the ATP-dependent potassium channel of the beta cells, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed sertoninergic and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormones, growth hormone-releasing compounds, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β agonists or amphetamines.

8. The use of the compounds as claimed in claim 1 for producing a medicament for reducing blood glucose.

9. The use of the compounds as claimed in claim 1 for producing a medicament for the

treatment of type II diabetes.

10. The use of the compounds as claimed in claim 1 for producing a medicament for the treatment of disturbances of lipid and carbohydrate metabolism.

11. The use of the compounds as claimed in claim 1 for producing a medicament for the treatment of arteriosclerotic manifestations.

12. The use of the compounds as claimed in claim 1 for producing a medicament for the treatment of insulin resistance.

13. A process for producing a medicament comprising one or more of the compounds as claimed in claim 1, which comprises mixing the active ingredient with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.