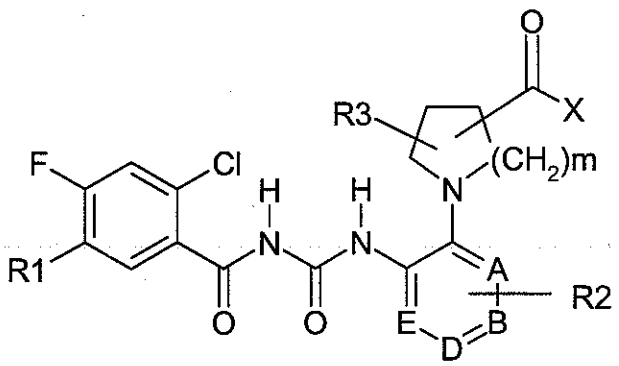
Substituted benzoylureidopyridyl-piperidine- and –pyrrolidine carboxylic acid derivatives, method for the production thereof and use thereof

The invention relates to substituted benzoylureidopyridylpiperidine- and -pyrrolidine-carboxylic acid derivatives and to their physiologically tolerated salts and physiologically functional derivatives.

It is an object of the invention to provide compounds which make it possible to prevent and treat diabetes mellitus. To this end, the compounds should in particular exhibit a therapeutically utilizable blood sugar-reducing action.

The invention relates to compounds of the formula I



I

where

R1, R2 are each independently H, F, Cl, Br, $(C_1$-$C_6)$-alkyl, CF_3, OCF_3, NO_2, CN, O-$(C_1$-$C_6)$-alkyl, COO$(C_1$-$C_6)$-alkyl, COOH, CO-$(C_1$-$C_6)$-alkyl, $(C_0$-$C_6)$-alkyl-COOH, $(C_0$-$C_6)$-alkyl -COO$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl;

R3 is OH, $(C_1$-$C_6)$-alkyl, $(C_0$-$C_6)$-alkyl-aryl, O-$(C_1$-$C_6)$-alkyl, O-$(C_2$-$C_6)$-alkenyl, O-$(C_2$-$C_6)$-alkynyl, where the alkyl, aryl, alkenyl and alkynyl radicals may be mono- or polysubstituted by F, Cl or Br;

X is OH, O-$(C_1$-$C_6)$-alkyl, NH_2, NH$(C_1$-$C_6)$-alkyl, N$((C_1$-$C_6)$-alkyl$)_2$;

A, B, D and E are each independently CH or N, and at least one of the groups A, B, D and E has the meaning N;

m is 0, 1, 2;

and their physiologically tolerated salts.

Preference is given to compounds of the formula I where one or more radicals are defined as follows:

R1, R2 are each independently H, F, Cl, Br, $(C_1$-$C_6)$-alkyl, CF_3, OCF_3, NO_2, CN, O-$(C_1$-$C_6)$-alkyl, COO$(C_1$-$C_6)$-alkyl, COOH, CO-$(C_1$-$C_6)$-alkyl, $(C_0$-$C_6)$-alkyl-COOH, $(C_0$-$C_6)$-alkyl-COO$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl;

R3 is OH, $(C_1$-$C_6)$-alkyl, $(C_0$-$C_6)$-alkyl-aryl, O-$(C_1$-$C_6)$-alkyl, O-$(C_2$-$C_6)$-alkenyl, O-$(C_2$-$C_6)$-alkynyl, where the alkyl, aryl, alkenyl and alkynyl radicals may be mono- or polysubstituted by F, Cl or Br;

X is OH, O-$(C_1$-$C_6)$-alkyl, NH_2, NH$(C_1$-$C_6)$-alkyl, N$((C_1$-$C_6)$-alkyl$)_2$;

A, B, D and E are each independently CH or N, and at least one of the groups A, B, D and E has the meaning N;

m is 1, 2;

and their physiologically tolerated salts.

Particular preference is given to compounds of the formula I where one or more radicals are defined as follows:

R1 is H, F;

R2 is each independently H, F, Cl, Br, $(C_1$-$C_6)$-alkyl, CF_3, OCF_3, O-$(C_1$-$C_6)$-

alkyl, $COO(C_1-C_6)$-alkyl, COOH, $CO-(C_1-C_6)$-alkyl, (C_0-C_6)-alkyl-COOH, (C_0-C_6)-alkyl-$COO(C_1-C_6)$-alkyl, $SO_2-(C_1-C_6)$-alkyl;

R3 is OH, (C_1-C_6)-alkyl, (C_0-C_6)-alkyl-aryl, $O-(C_1-C_6)$-alkyl, $O-(C_2-C_6)$-alkenyl, $O-(C_2-C_6)$-alkynyl, where the alkyl, aryl, alkenyl and alkynyl radicals may be mono- or polysubstituted by F, Cl or Br;

X is OH, $O-(C_1-C_6)$-alkyl, NH_2, $NH(C_1-C_6)$-alkyl, $N((C_1-C_6)-alkyl)_2$;

A is N

B, D, E are CH

m is 1, 2;

and their physiologically tolerated salts.

Very particular preference is given to compounds of the formula I where one or more radicals are defined as follows:

R1 is H, F;

R2 is H, Cl, (C_1-C_6)-alkyl, CF_3, $COO(C_1-C_6)$-alkyl, COOH,

R3 is H, phenyl;

X is OH, $O-(C_1-C_6)$-alkyl, NH_2, $NH(C_1-C_6)$-alkyl, $N((C_1-C_6)-alkyl)_2$;

A is N;

B, D, E are CH;

m is 2;

and their physiologically tolerated salts.

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

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

When radicals or substituents can occur more than once in the compounds of the formula I, they may all each independently be defined as specified, and be the same or different.

As a consequence of their higher water solubility compared to the starting or basic compounds, pharmaceutically tolerated salts are particularly suitable for medical applications. These salts have to have a pharmaceutically tolerated anion or cation. Suitable pharmaceutically tolerated acid addition salts of the compounds according to the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid and sulfuric acid, and also of organic acids, e.g. acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isethionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, p-toluenesulfonic acid and tartaric acid. Suitable pharmaceutically tolerated 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 ethylene-diamine.

Salts having a pharmaceutically unacceptable anion, for example trifluoroacetate, are likewise encompassed by the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically tolerated 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 according to the invention, e.g. an ester which is able, on administration to a mammal, e.g. a human, to (directly or indirectly) form a compound of the formula I or an active metabolite thereof.

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

The compounds according to the invention can also exist in different polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds according to the invention are encompassed by the scope of the invention and are a further aspect of the invention.

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

In this context, an aryl radical is a phenyl, naphthyl, biphenyl, tetrahydronaphthyl, alpha- or beta-tetralone, indanyl or indan-1-onyl radical.

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

The amount of a compound of formula I which is required in order to achieve the desired biological effect is dependent upon a series of factors, for example the specific compound selected, 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 per kilogram of bodyweight, for example 3-10 mg/kg/day. An intravenous dose may, for example, be in the range from 0.3 mg to 1.0 mg/kg and may advantageously be administered as an infusion of

from 10 ng to 100 ng per kilogram per minute. Suitable infusion solutions for these purposes may, for example, contain from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Individual doses may contain, for example, from 1 mg to 10 g of the active ingredient. Ampules for injections may therefore contain, for example, from 1 mg to 100 mg, and single dose formulations which can be administered orally, for example tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. The compounds of formula I may be used for therapy of the abovementioned conditions as the compounds themselves, although they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier of course has to be acceptable, in the sense that it is compatible with the other constituents of the composition and is not damaging to the health of the patient. 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. Further pharmaceutically active substances may likewise be present, including further compounds of formula I. The pharmaceutical compositions according to the invention may be produced by one of the known pharmaceutical methods which consist essentially of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions according to the invention are those which are 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 type of the compound of formula I used in each case. Coated formulations and coated slow-release formulations are also encompassed by the scope of the invention. Preference is given to acid- and gastric fluid-resistant formulations. Suitable gastric fluid-resistant coatings include 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, for example capsules, cachets, lozenges or tablets, each of which contains a certain amount of the compound of formula I; as powder 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. In general, the compositions are prepared 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. For example, a tablet can be produced by compressing or shaping a powder or granules of the compound, optionally with one or more additional ingredients. Compressed tablets can be prepared by tableting the compound in free-flowing form, for example a powder or granules, optionally mixed with a binder, lubricant, inert diluent and/or one (or more) surfactants/dispersants in a suitable machine. Shaped tablets can be prepared by shaping the pulverulent compound moistened with an inert liquid diluent in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges which contain a compound of formula I with a flavoring, customarily sucrose, and gum arabic or tragacanth, and pastilles which include the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Suitable pharmaceutical compositions for parenteral administration include 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 the administration may also be subcutaneous, intramuscular or intradermal as an injection. These preparations can preferably be produced by mixing the compound with water and making the solution obtained sterile and isotonic with the blood. The injectable compositions according to the invention generally contain from 0.1 to 5% by weight of the active compound.

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

Suitable pharmaceutical compositions for topical use on the skin are preferably in the form of an ointment, cream, lotion, paste, spray, aerosol or oil. Useful carriers include petroleum jelly, 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, preferably from 0.5 to 2%.

Transdermal administration is also possible. Suitable pharmaceutical compositions for transdermal applications may be in the form of single plasters which are suitable for long-term close contact with the epidermis of the patient. Such plasters advantageously contain the active ingredient in an optionally buffered aqueous solution, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is from approx. 1% to 35%, preferably from approx. 3 to 15%. A particular means of releasing the active ingredient is by electrotransport or iontophoresis, as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

Further useful active ingredients for combination products are as follows:
All antidiabetics mentioned in the Rote Liste 2001, chapter 12. They can be combined with the compounds of the formula I according to the invention, in particular for synergistic enhancement of the action. The active ingredient combination can be administered either by separately administering 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 hereinbelow are disclosed in USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

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

The orally active hypoglycemic active ingredients preferably include sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, potassium channel openers, for example those disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S, insulin sensitizers, inhibitors of liver enzymes which are 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 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, 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, 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, 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, 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, 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, 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), for example, HMR 1741.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, 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, 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), for example, HMR1171, HMR1586.

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with an antioxidant, 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, 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, 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, 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, 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, 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, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

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

In yet another embodiment, the compounds of the formula I are administered in combination with a meglitinide, for example, repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione, 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, 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, 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 abovementioned 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, 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-oxo-ethyl]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-yl-oxy)ethylamino]ethanol hydrochloride (WO 01/83451)), MSH (melanocyte-stimulating hormone) agonists, CCK-A agonists (e.g. {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoro-acetic acid salt (WO 99/15525)), serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed serotoninergic 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.

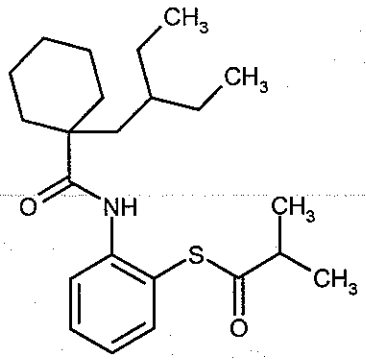
In another embodiment, the other active ingredient is sibutramine.

In one embodiment, the other active ingredient is orlistat.

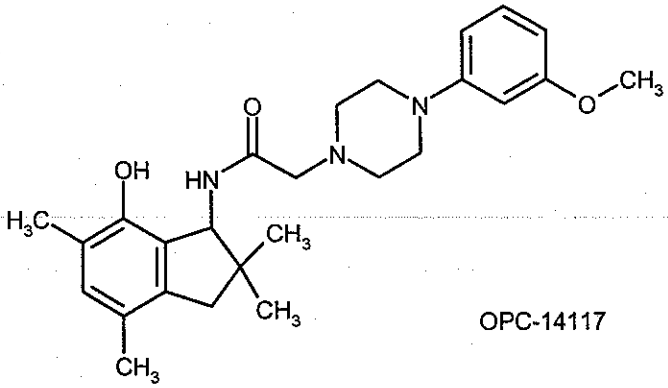
In one embodiment, the other active ingredient is mazindol or phentermine.

In one embodiment, the compounds of the formula I are administered in combination with 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 supplied by 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 also be administered in the form of foodstuffs, for example, in bakery products or muesli bars.

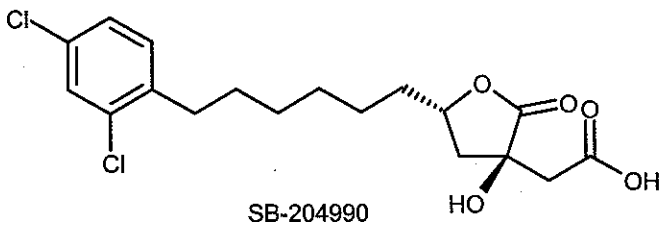
It will be appreciated that any suitable combination of the compounds according to the invention with one or more of the abovementioned compounds and optionally one or more further pharmacologically active substances is regarded as being covered by the scope of protection of the present invention.



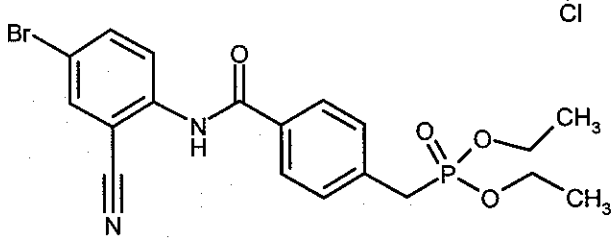
JTT-705



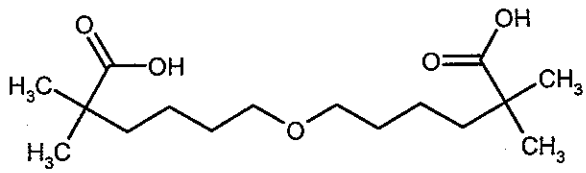
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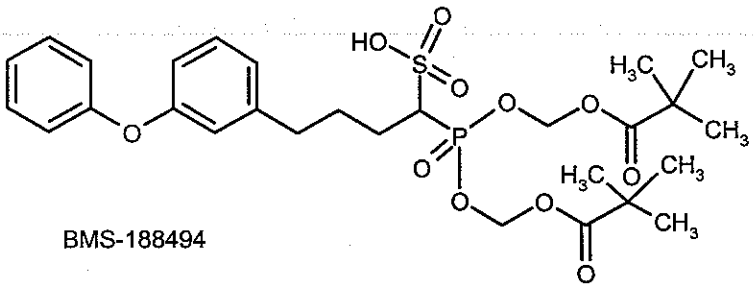
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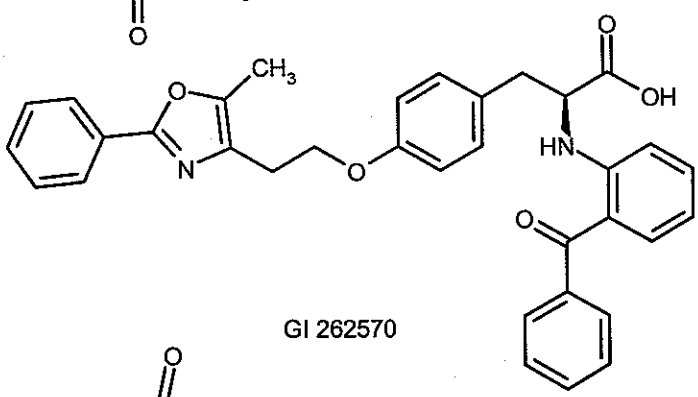
NO-1886



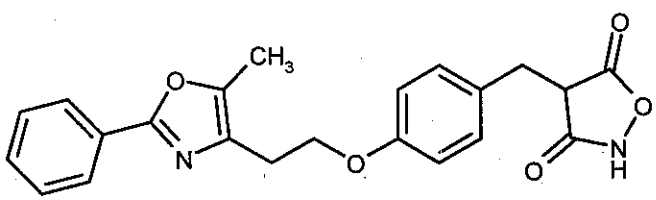
CI-1027



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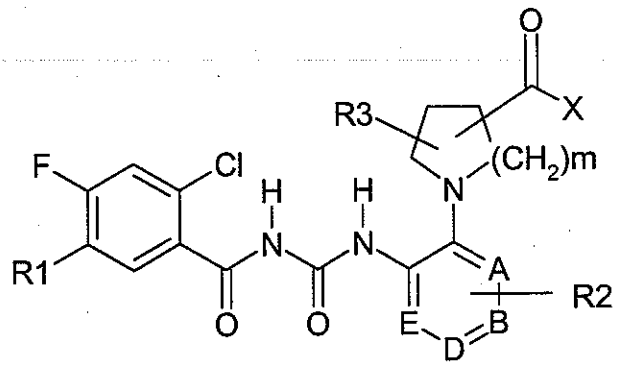


GI 262570



JTT-501

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



Ex.	R1	R2	R3	A	B	D	E	-(C=O)-X	m	m.p.
1	H	H	H	N	CH	CH	CH	4-COOH	2	220.2
2	F	H	H	N	CH	CH	CH	4-COOH	2	229.5
3	F	H	H	N	CH	CH	CH	4-COOMe	2	195.9
4	F	H	H	N	CH	CH	CH	4-CONH2	2	215.9
5	F	H	H	N	CH	CH	CH	4-CONHCH$_2$CH$_2$OH	2	202.8
6	F	H	4-Ph	N	CH	CH	CH	4-COOH	2	250.9

The effectiveness of the compounds was tested as follows:

Glycogen phosphorylase a activity test

The effect of compounds on the activity of the active form of glycogen phosphorylase (GPa) was measured in the reverse direction by monitoring the synthesis of glycogen from glucose 1-phosphate by determining the release of inorganic phosphate. All reactions were carried out as duplicate determinations in 96-well microtiter plates (half area plates, Costar No. 3696), and the change in absorption as a consequence of the formation of the reaction product was measured at the wavelength specified below in a Multiskan Ascent Elisa Reader (Lab Systems, Finland).

In order to measure the GPa enzyme activity in the reverse direction, the conversion of glucose 1-phosphate to glycogen and inorganic phosphate was measured by the

general method of Engers et al. (Engers HD, Shechosky S, Madsen NB, Can J Biochem 1970 Jul;48(7):746-754) with the following modifications: human glycogen phosphorylase a (for example containing 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 to a concentration of 10 µg of protein/ml 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 of glycogen. Test substances were prepared as a 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 of glycogen, and also 10 µl of a solution of human glycogen phosphorylase a (10 µg of protein/ml) and 20 µl of 2.5 mM glucose 1-phosphate. The base value of the activity of glycogen phosphorylase a 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 released inorganic phosphate was determined by means of 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 of ammonium molybdate, 10.9 mM of zinc acetate, 3.6% of ascorbic acid, 0.9% of SDS are added to 50 µl of the enzyme mixture. After 60 minutes of incubation at 45°C, the absorption was measured at 820 nm. To determine the background absorption, the stop solution was added immediately after the addition of the glucose 1-phosphate solution in a separate reaction.

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

Table 2: Biological activity

Ex.	IC-50 (µM)
1	0.04
2	0.01
4	0.16
5	3.65

It can be seen from the table that the compounds of the formula I inhibit the activity of glycogen phosphorylase a and are thus very suitable for reducing the blood sugar level.

The preparation of some examples is described in detail hereinbelow, and the remaining compounds of the formula I were obtained in a similar manner:

Experimental section:

Example 1:

a) 3'-Nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid

The mixture consisting of 634 mg of 2-chloro-3-nitropyridine, 620 mg of piperidine carboxylic acid, 820 mg of potash and 3 ml of NMP was stirred at 80°C for 2 hours. After allowing to cool, 30 ml of water of water were added and the crude product was extracted with 30 ml of ethyl acetate. After drying the organic phase with sodium sulfate, it was concentrated under reduced pressure.

Yield: 850 mg m.p.: oil (crude)

In a similar manner, the following were prepared:

3'-Nitro-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (m.p.: oil)

Methyl 3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylate (m.p.: oil)

b) 3'-Amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid

The solution of 850 mg of 3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid in 40 ml of ethyl acetate was admixed with 2.3 g of tin(II) chloride and stirred at room temperature for 3 hours. The mixture was then extracted with 50 ml of water, the aqueous phase was adjusted to pH = 6 using sodium dihydrogenphosphate and the product was extracted with ethyl acetate. After drying the organic phase over sodium sulfate, it was concentrated under reduced pressure.

Yield: 480 mg m.p.: resin

In a similar manner, the following were prepared:

Methyl 3'-amino-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylate (m.p.: resin)

3'-Amino-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid (m.p.: 201.4°C)

c) 3'-[3-(2-Chloro-4-fluorobenzoyl)ureido]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid

The equimolar solution of 2-chloro-4-fluorobenzoyl isocyanate in acetonitrile was added dropwise with stirring to the solution of 100 mg of 3'-amino-3,4,5,6-tetrahydro-2H-(1,2'')bipyridinyl-4-carboxylic acid in 5 ml of acetonitrile. The mixture was stirred at RT for 6 and the precipitate was filtered off with suction and dried at RT under reduced pressure.

Yield: 105 mg m.p.: 220.2°C

Example 2:

3'-[3-(2-Chloro-4,5-difluorobenzoyl)ureido]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid

Example 3:

Methyl 3'-[3-(2-chloro-4,5-difluorobenzoyl)ureido]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylate

Example 4:

3'-[3-(2-Chloro-4,5-difluorobenzoyl)ureido]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxamide

The mixture consisting of 50 mg of 3'-[3-(2-chloro-4,5-difluorobenzoyl)ureido]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid, 0.5 ml of DMF, 6.1 mg of ammonium chlorid, 40 μl of Hünig's base and 37.3 mg of Totu was stirred at room temperature for 2 hours. Afterwards, it was diluted with 5 ml of water and the mixture was stirred briefly. The precipitate was filtered of with suction and dried under reduced pressure.

Yield: 43 mg m.p.: 215.9°C

Example 5:

N-(2-hydroxyethyl)-3'-[3-(2-chloro-4,5-difluorobenzoyl)ureido]-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxamide (A003105307)

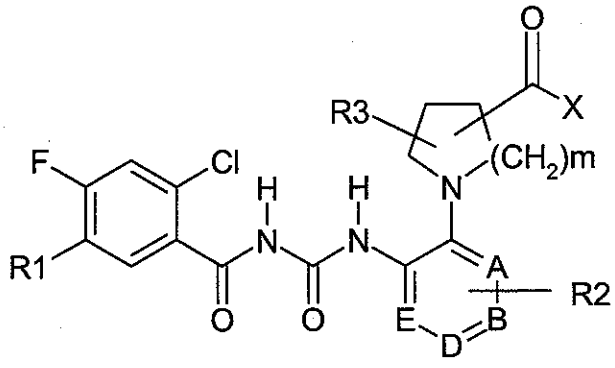
was prepared in a similar manner to example 4 by replacing ammonium chloride with 2-aminoethanol. M.p.: 202.8°C

Example 6:

3'-[3-(2-Chloro-4,5-difluorobenzoyl)ureido]-4-phenyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid

What is claimed is:

1. Compounds of the formula I



where

R1, R2 are each independently H, F, Cl, Br, $(C_1\text{-}C_6)$-alkyl, CF_3, OCF_3, NO_2, CN, O-$(C_1\text{-}C_6)$-alkyl, COO$(C_1\text{-}C_6)$-alkyl, COOH, CO-$(C_1\text{-}C_6)$-alkyl, $(C_0\text{-}C_6)$-alkyl-COOH, $(C_0\text{-}C_6)$-alkyl -COO$(C_1\text{-}C_6)$-alkyl, SO_2-$(C_1\text{-}C_6)$-alkyl;

R3 is OH, $(C_1\text{-}C_6)$-alkyl, $(C_0\text{-}C_6)$-alkyl-aryl, O-$(C_1\text{-}C_6)$-alkyl, O-$(C_2\text{-}C_6)$-alkenyl, O-$(C_2\text{-}C_6)$-alkynyl, where the alkyl, aryl, alkenyl and alkynyl radicals may be mono- or polysubstituted by F, Cl or Br;

X is OH, O-$(C_1\text{-}C_6)$-alkyl, NH_2, NH$(C_1\text{-}C_6)$-alkyl, N$((C_1\text{-}C_6)\text{-alkyl})_2$;

A, B, D and E are each independently CH or N, and at least one of the groups A, B, D and E has the meaning N;

m is 0, 1, 2;

and their physiologically tolerated salts.

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

R1, R2 are each independently H, F, Cl, Br, (C_1-C_6)-alkyl, CF_3, OCF_3, NO_2, CN, O-(C_1-C_6)-alkyl, $COO(C_1-C_6)$-alkyl, COOH, CO-(C_1-C_6)-alkyl, (C_0-C_6)-alkyl-COOH, (C_0-C_6)-alkyl-$COO(C_1-C_6)$-alkyl, SO_2-(C_1-C_6)-alkyl;

R3 is OH, (C_1-C_6)-alkyl, (C_0-C_6)-alkyl-aryl, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, where the alkyl, aryl, alkenyl and alkynyl radicals may be mono- or polysubstituted by F, Cl or Br;

X is OH, O-(C_1-C_6)-alkyl, NH_2, $NH(C_1-C_6)$-alkyl, $N((C_1-C_6)\text{-alkyl})_2$;

A, B, D and E are each independently CH or N, and at least one of the groups A, B, D and E has the meaning N;

m is 1, 2;

and their physiologically tolerated salts.

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

R1 is H, F;

R2 is each independently H, F, Cl, Br, (C_1-C_6)-alkyl, CF_3, OCF_3, O-(C_1-C_6)-alkyl, $COO(C_1-C_6)$-alkyl, COOH, CO-(C_1-C_6)-alkyl, (C_0-C_6)-alkyl-COOH, (C_0-C_6)-alkyl-$COO(C_1-C_6)$-alkyl, SO_2-(C_1-C_6)-alkyl;

R3 is OH, (C_1-C_6)-alkyl, (C_0-C_6)-alkyl-aryl, O-(C_1-C_6)-alkyl, O-(C_2-C_6)-alkenyl, O-(C_2-C_6)-alkynyl, where the alkyl, aryl, alkenyl and alkynyl radicals may be mono- or polysubstituted by F, Cl or Br;

X is OH, O-(C_1-C_6)-alkyl, NH_2, $NH(C_1-C_6)$-alkyl, $N((C_1-C_6)\text{-alkyl})_2$;

A is N

B, D, E are CH

m is 1, 2;

and their physiologically tolerated salts.

4. Compounds of the formula I as claimed in one or more of claims 1 to 3, wherein

R1 is H, F;

R2 is H, Cl, $(C_1$-$C_6)$-alkyl, CF_3, $COO(C_1$-$C_6)$-alkyl, COOH,

R3 is H, phenyl;

X is OH, O-$(C_1$-$C_6)$-alkyl, NH_2, $NH(C_1$-$C_6)$-alkyl, $N((C_1$-$C_6)$-alkyl$)_2$;

A is N;

B, D, E are CH;

m is 2;

and their physiologically tolerated salts.

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

6. A pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 4 and at least one further active ingredient.

7. A pharmaceutical as claimed in claim 6, which comprises, as a further active ingredient, one or more

antidiabetics, hypoglycemic active ingredients, HMG-CoA 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 acting 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 serotoninergic 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 one or more of claims 1 to 4 for producing a medicament for blood sugar reduction.

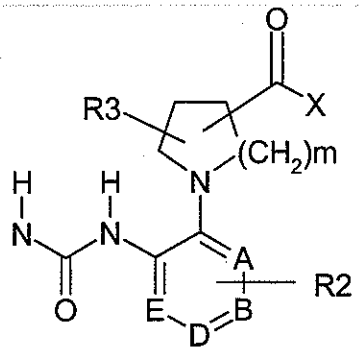
9. The use of the compounds as claimed in one or more of claims 1 to 4 for producing a medicament for treating type II diabetes.

10. The use of the compounds as claimed in one or more of claims 1 to 4 for producing a medicament for treating lipid and carbohydrate metabolism disorders.

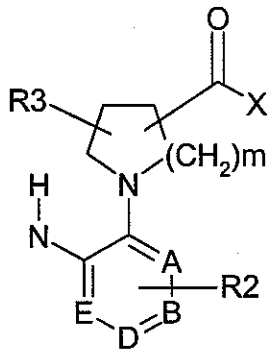
11. The use of the compounds as claimed in one or more of claims 1 to 4 for producing a medicament for treating arteriosclerotic symptoms.

12. The use of the compounds as claimed in one or more of claims 1 to 4 for producing a medicament for treating insulin resistance.

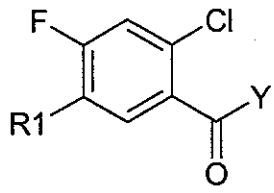
13. The preparation of the compounds of the formulal I as claimed in one or more of claims 1 to 4, which comprises reacting ureas of the formula 2 or aniline derivatives of the formula 3 with aroyl isocyanates or with reactive acid derivatives, such as acid chlorides or anhydrides, of the formula 4



2



3



4

where R1 to R3 and A, B, D and E are each as defined in claim 1.

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