Description

4,5-Diphenyl-pyrimidinylamino substituted carboxylic acids, method for the production and use thereof as medicaments

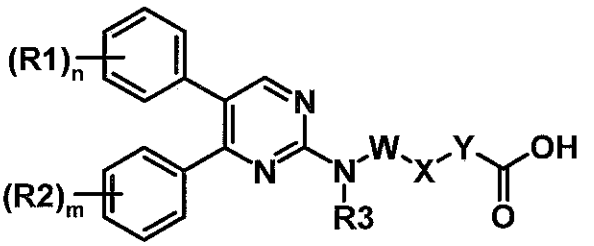
The invention relates to 4,5-diphenylpyrimidinylamino-substituted carboxylic acids and their physiologically tolerated salts.

Compounds of similar structure have been described in the prior art (see WO 2005/103022).

The invention was based on the object of providing compounds which display a therapeutically utilizable effect. The object was in particular to find novel compounds suitable for the treatment of hyperglycemia and diabetes.

Summary

According to a first aspect there is provided a compound of the formula I,



I

in which the meanings are

R1, R2 independently of one another (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, NH_2, NH(C_1-C_4)-alkyl, N[(C_1-C_4)-alkyl]$_2$, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be substituted one or more times by F, Cl, Br or CN;

n 0, 1, 2, 3, 4 or 5;

m 0, 1, 2, 3, 4 or 5;

W bond, (C_1-C_7)-alkylene, (C_2-C_7)-alkenylene or (C_2-C_7)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

X bond, mono-, bi- or tricyclic (C_3-C_{12})-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;

Y bond, (C_1-C_5)-alkylene, (C_2-C_5)-alkenylene or (C_2-C_5)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

R3 H or (C_1-C_6)-alkyl;

R4 NH_2, $NH(C_1$-$C_4)$-alkyl, $N[(C_1$-$C_4)$-alkyl$]_2$, F, Cl, Br, CN, OH, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl or (C_2-C_6)-alkynyl, where alkyl, alkenyl and alkynyl may be substituted one or more times by F, Cl, Br or CN;

R5 F, Cl, Br, CN, (C_1-C_4)-alkyl or O-(C_1-C_4)-alkyl, where alkyl may be substituted one or more times by F, Cl, Br or CN;

where W, X and Y do not simultaneously have the meaning of bond,

and the physiologically tolerated salts thereof.

According to a second aspect there is provided a compound as defined above for use as pharmaceutical.

According to a third aspect there is provided a pharmaceutical comprising one or more of the compounds as defined above.

According to a fourth aspect there is provided a pharmaceutical comprising one or more of the compounds as defined above and at least one further active ingredient.

According to a fifth aspect there is provided the use of the compounds as defined above for manufacturing a medicament for lowering blood glucose.

According to a sixth aspect there is provided the use of the compounds as defined above for manufacturing a medicament for the treatment of diabetes.

According to a seventh aspect there is provided the use of the compounds as defined above for manufacturing a medicament for increasing insulin release.

According to an eighth aspect there is provided a process for manufacturing a pharmaceutical comprising one or more of the compounds as defined above, which comprises mixing the active ingredient with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.

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

R1, R2	independently of one another $(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl, NH_2, $NH(C_1\text{-}C_4)$-alkyl, $N[(C_1\text{-}C_4)\text{-alkyl}]_2$, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be substituted one or more times by F, Cl, Br or CN;
n	0, 1, 2, 3, 4 or 5;
m	0, 1, 2, 3, 4 or 5;
W	bond, $(C_1\text{-}C_7)$-alkylene, $(C_2\text{-}C_7)$-alkenylene or $(C_2\text{-}C_7)$-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by

R4;

X bond, mono-, bi- or tricyclic (C_3-C_{12})-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;

Y bond, (C_1-C_5)-alkylene, (C_2-C_5)-alkenylene or (C_2-C_5)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

R3 H or (C_1-C_6)-alkyl;

R4 NH_2, $NH(C_1$-$C_4)$-alkyl, $N[(C_1$-$C_4)$-alkyl$]_2$;

R5 F, Cl, Br, CN, (C_1-C_4)-alkyl or O-(C_1-C_4)-alkyl, where alkyl may be substituted one or more times by F, Cl, Br or CN;

where W and X do not simultaneously have the meaning of bond;

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 meanings:

R1, R2 independently of one another (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, OH, NH_2, $NH(C_1$-$C_4)$-alkyl, $N[(C_1$-$C_4)$-alkyl$]_2$, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be subsituted one or more times by F, Cl, Br or CN;

n 0, 1, 2;

m 0, 1, 2;

W bond, (C_1-C_7)-alkylene; (C_2-C_7)-alkenylene or (C_2-C_7)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by

R4;

X bond, mono-, bi- or tricyclic (C_3-C_{12})-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;

Y bond, (C_1-C_5)-alkylene; (C_2-C_5)-alkenylene or (C_2-C_5)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

R3 H or (C_1-C_6)-alkyl;

R4 NH_2, $NH(C_1$-$C_4)$-alkyl, $N[(C_1$-$C_4)$-alkyl$]_2$;

R5 F, Cl, Br, (C_1-C_4)-alkyl or O-(C_1-C_4)-alkyl;

where W and X do not simultaneously have the meaning of bond;

and the physiologically tolerated salts thereof.

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

R1, R2 independently of one another (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be substituted one or more times by F, Cl, Br or CN;

n 0;

m 0;

W bond, (C_1-C_7)-alkylene; or if X is a bond W has the meaning of (C_4-C_7)-alkylene;

X	bond, mono- or bicyclic (C_3-C_{12})-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;
Y	bond, (C_1-C_5)-alkylene; (C_2-C_5)-alkenylene or (C_2-C_5)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;
R3	H or (C_1-C_6)-alkyl;
R4	NH_2, $NH(C_1$-$C_4)$-alkyl, $N[(C_1$-$C_4)$-alkyl$]_2$;
R5	F, Cl, Br, CN, (C_1-C_4)-alkyl or O-(C_1-C_4)-alkyl;

where W and X do not simultaneously have the meaning of bond;

and the physiologically tolerated salts thereof.

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

The alkyl, alkenyl, alkynyl, alkylene, alkenylene and alkynylene radicals in the radicals W, Y R1, R2, R3, R4 and R5 may be either straight-chain or branched.

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

Physiologically tolerated 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 physiologically tolerated anion or cation. Suitable physiologically tolerated acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic and sulfuric acids, and 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. The chlorine salt is particularly preferably used for medical purposes.
Suitable physiologically 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), zinc salts, and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine, arginine, choline, meglumine or ethylenediamine salts.

Salts with a physiologically untolerated anion or cation likewise belong within the framework of the invention as useful intermediates for preparing or purifying physiologically tolerated salts and/or for use in nontherapeutic, for example in vitro applications.

A further embodiment of this disclosure are prodrugs of the compounds of the invention. Such prodrugs can be metabolized in vivo to a compound of the disclosure. These prodrugs may themselves be active or not.

The compounds of the disclosure may also exist in various polymorphous forms, e.g. as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds according to the disclosure belong within the framework of the disclosure and are a further aspect of the disclosure.

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

The compounds of the formula (I) and the physiologically tolerated salts thereof represent ideal pharmaceuticals for the treatment of elevated lipid concentrations in the blood, the metabolic syndrome, diabetes, insulin resistance, dysregulation of LDL, HLD and VLDL or cardiovascular disorders and lipid metabolism disorders, especially hyperlipidemia.
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) 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 0.1 mg to 100 mg (typically from 0.1 mg to 50 mg) per day and

per kilogram of body weight, for example 0.1-10 mg/kg/day. Tablets or capsules may contain, for example, from 0.01 to 100 mg, typically from 0.02 to 50 mg. For the prophylaxis or 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 disclosure are those suitable for oral and peroral (for example sublingual) 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 contains 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.

Combinations with other medicaments

The compounds of the disclosure can be administered alone or in combination with one or more further pharmacologically active substances which have, for example, beneficial effects on metabolic disturbances or disorders frequently associated therewith. Examples of such medicaments are

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

They can be combined with the compounds of the disclosure of the formula I in particular for a synergistic improvement in the effect. Administration of the active ingredient combination can 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.

Further examples of active ingredients suitable for combination products are in particular: All antidiabetics which are mentioned in the Rote Liste 2006, chapter 12; all weight-reducing agents/appetite suppressants which are mentioned in the Rote Liste 2006, chapter 1; all lipid-lowering agents which are mentioned in the Rote Liste 2006, chapter 58. They may be combined with the compound of the invention of the formula I in particular for a synergistic improvement in the effect. The active ingredient combination can be administered 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 is present in a pharmaceutical preparation. Most of the active ingredients mentioned hereinafter 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 or those described in WO2005005477 (Novo Nordisk), fast-acting insulins (see US 6,221,633), inhalable insulins such as, for example, Exubera ® or oral insulins such as, for example, IN-105 (Nobex) or Oral-lyn™ (Generex Biotechnology), GLP-1 derivatives such as, for example, exenatide, liraglutide or those which have been disclosed in WO98/08871 or WO2005027978 of Novo Nordisk A/S, in WO01/04156 of Zealand or in WO00/34331 of Beaufour-Ipsen, pramlintide acetate (Symlin; Amylin Pharmaceuticals), and orally effective hypoglycemic active ingredients.

The orally effective hypoglycemic active ingredients include preferably
sulfonylureas,
biguanidines,
meglitinides,
oxadiazolidinediones,
thiazolidinediones,
glucosidase inhibitors,
inhibitors of glycogen phosphorylase,
glucagon antagonists,
glucokinase activators,
inhibitors of fructose-1,6-bisphosphatase,
modulators of glucose transporter 4 (GLUT4),
inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT),

GLP-1 agonists,
potassium channel openers such as, for example, those which have been disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S,
inhibitors of dipeptidylpeptidase IV (DPP-IV),
insulin sensitizers,
inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or glycogenolysis,
modulators of glucose uptake, of glucose transport and of glucose reabsorption,
inhibitors of 11ß-HSD1,
inhibitors of protein tyrosine phosphatase 1B (PTP1B),
modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2),
compounds which alter lipid metabolism such as antihyperlipidemic active ingredients and antilipidemic active ingredients,
compounds which reduce food intake,
compounds which increase thermogenesis,
PPAR and RXR modulators and
active ingredients which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an HMGCoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin or L-659699.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a cholesterol absorption inhibitor such as, for example, ezetimibe, tiqueside, pamaqueside, FM-VP4 (sitostanol/campesterol ascorbyl phosphate; Forbes Medi-Tech, WO2005042692), MD-0727 (Microbia Inc., WO2005021497) or with compounds as described in WO2002066464 (Kotobuki Pharmaceutical Co. Ltd.), WO2005062824 (Merck & Co.) or WO2005061451 and WO2005061452 (AstraZeneca AB).

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a PPAR gamma agonist such as, for example, rosiglitazone, pioglitazone, JTT-501, Gl 262570, R-483 or CS-011 (rivoglitazone).

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a PPAR alpha agonist such as, for example, GW9578, GW-590735, K-111,

LY-674, KRP-101 or DRF-10945.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a mixed PPAR alpha/gamma agonist such as, for example, muraglitazar, tesaglitazar, naveglitazar, LY-510929, ONO-5129, E-3030, AVE 8042, AVE 8134, AVE 0847, or as described in PCT/US 00/11833, PCT/US 00/11490, DE10142734.4 or in J.P. Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a PPAR delta agonist such as, for example, GW-501516.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with metaglidasen or with MBX-2044 or other partial PPAR gamma agonists/antagonists.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a fibrate such as, for example, fenofibrate, clofibrate or bezafibrate.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an MTP inhibitor such as, for example, implitapide, BMS-201038, R-103757 or those described in WO2005085226.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a CETP inhibitor such as, for example, torcetrapib or JTT-705.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a bile acid absorption inhibitor (see, for example, US 6,245,744, US 6,221,897 or WO00/61568), such as, for example, HMR 1741 or those as described in DE 10 2005 033099.1 and DE 10 2005 033100.9.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine or colesevelam.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an LDL receptor inducer (see US 6,342,512), such as, for example, HMR1171, HMR1586 or those as described in WO2005097738.

In one embodiment, the compound of the formula I is administered in combination with Omacor® (omega-3 fatty acids; highly concentrated ethyl esters of eicosapentaenoic acid and of docosahexaenoic acid).

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an ACAT inhibitor such as, for example, avasimibe.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an antioxidant such as, for example, OPC-14117, probucol, tocopherol, ascorbic acid, β-carotene or selenium.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a vitamin such as, for example, vitamin B6 or vitamin B12.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a lipoprotein lipase modulator such as, for example, ibrolipim (NO-1886).

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

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a squalene synthetase inhibitor such as, for example, BMS-188494 or as described in WO2005077907.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a lipoprotein(a) antagonist such as, for example, gemcabene (CI-1027).

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an HM74A receptor agonist such as, for example, nicotinic acid.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a lipase inhibitor such as, for example, orlistat or cetilistat (ATL-962).

In one embodiment of the disclosure, the compound of the formula I is administered in combination with insulin.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with a biguanide such as, for example, metformin.

In another embodiment of the disclosure, the compound of the formula I is administered in combination with a meglitinide such as, for example, repaglinide or nateglinide.

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

In one embodiment of the disclosure, the compound of the formula I is 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 of the disclosure, the compound of the formula I is administered in combination with more than one of the aforementioned compounds, e.g. 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 one embodiment of the disclosure, the compound of the formula I is administered in combination with an inhibitor of glycogen phosphorylase, such as, for example, PSN-357 or FR-258900 or those as described in WO2003084922, WO2004007455, WO2005073229-31 or WO2005067932.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with glucagon receptor antagonists such as, for example, A-770077, NNC-25-2504 or as described in WO2004100875 or WO2005065680.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with activators of glucokinase, such as, for example, RO-4389620, LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50 or those as are described for example by Prosidion in WO2004072031, WO2004072066, WO 05103021 or WO 06016178, by Roche in WO 00058293, WO 00183465, WO 00183478, WO 00185706, WO 00185707, WO 01044216, GB 02385328, WO 02008209, WO 02014312, WO 0246173, WO 0248106, DE 10259786, WO 03095438, US 04067939 or WO 04052869, by Novo Nordisk in EP 1532980, WO 03055482, WO 04002481, WO 05049019, WO 05066145 or WO 05123132, by Merck/Banyu in WO 03080585, WO03097824, WO 04081001, WO 05063738 or WO 05090332, by Eli Lilly in WO 04063194, or by Astra Zeneca in WO 01020327, WO 03000262, WO 03000267, WO 03015774, WO 04045614, WO 04046139, WO 05044801, WO 05054200, WO 05054233, WO 05056530, WO 05080359, WO 05080360 or WO 05121110.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an inhibitor of gluconeogenesis, such as, for example, FR-225654.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of fructose-1,6-bisphosphatase (FBPase), such as, for example, CS-917.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with modulators of glucose transporter 4 (GLUT4), such as, for example, KST-48 (D.-O. Lee et al.: Arzneim.-Forsch. Drug Res. 54 (12), 835 (2004)).

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), as are described for example in WO2004101528.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of dipeptidylpeptidase IV (DPP-IV), such as, for example, vildagliptin (LAF-237), sitagliptin (MK-0431), saxagliptin (BMS-477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200, GW-825964X or as are described in WO2003074500, WO2003106456, WO200450658, WO2005058901, WO2005012312, WO2005012308, PCT/EP2005/007821, PCT/EP2005/008005, PCT/EP2005/008002, PCT/EP2005/008004, PCT/EP2005/008283, DE 10 2005 012874.2 or DE 10 2005 012873.4.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11ß-HSD1), such as, for example, BVT-2733 or those as are described for example in WO200190090-94, WO200343999, WO2004112782, WO200344000, WO200344009, WO2004112779, WO2004113310, WO2004103980, WO2004112784, WO2003065983, WO2003104207, WO2003104208, WO2004106294, WO2004011410, WO2004033427, WO2004041264, WO2004037251, WO2004056744, WO2004065351, WO2004089367, WO2004089380, WO2004089470-71, WO2004089896, WO2005016877 or WO2005097759.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of protein tyrosine phosphatase 1B (PTP1B), as are described for example in WO200119830-31, WO200117516, WO2004506446, WO2005012295, PCT/EP2005/005311, PCT/EP2005/005321, PCT/EP2005/007151, PCT/EP2005/ or DE 10 2004 060542.4.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2), such as, for example, KGA-2727, T-1095, SGL-0010, AVE 2268 and SAR-7226 or as are described for example in WO2004007517, WO200452903, WO200452902, PCT/EP2005/005959, WO2005085237, JP2004359630 or by A. L. Handlon in Expert Opin.

Ther. Patents (2005) 15(11), 1531-1540.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of hormone-sensitive lipase (HSL) as described for example in WO2005073199.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC), such as, for example, those as described in WO199946262, WO200372197, WO2003072197 or WO2005044814.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an inhibitor of phosphoenolpyruvate carboxykinase (PEPCK), such as, for example, those as described in WO2004074288.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an inhibitor of glycogen synthase kinase 3 beta (GSK-3 beta), as described for example in US2005222220, WO2005085230, PCT/EP2005/005346, WO2003078403, WO2004022544, WO2003106410, WO2005058908, US2005038023, WO2005009997, US2005026984, WO2005000836, WO2004106343, EP1460075, WO2004014910, WO2003076442, WO2005087727 or WO2004046117.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an inhibitor of protein kinase C beta (PKC beta), such as, for example, ruboxistaurin.

In one embodiment of the disclosure, the compound of the formula I is administered in combination with an endothelin A receptor antagonist such as, for example, avosentan (SPP-301).

In one embodiment of the disclosure, the compound of the formula I is administered in combination with inhibitors of "I-kappaB kinase" (IKK inhibitors), as are described for example in WO2001000610, WO2001030774, WO2004022553 or WO2005097129.

In one embodiment of the disclosure, the compound of the formula I is administered in

combination with modulators of the glucocorticoid receptor, like those described for example in WO2005090336.

In a further embodiment of the disclosure, the compound of the formula I is administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone and Metabolic Research (2001), 33(9), 554-558);

NPY antagonists such as, for example, naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]cyclohexylmethyl}amide hydrochloride (CGP 71683A);

peptide YY 3-36 (PYY3-36) or analogous compounds, such as, for example, CJC-1682 (PYY3-36 conjugated with human serum albumin via Cys34), CJC-1643 (derivative of PYY3-36 which conjugates in vivo to serum albumin) or those as are described in WO2005080424;

cannabinoid receptor 1 antagonists such as, for example, rimonabant, SR147778 or those as are described for example in EP 0656354, WO 00/15609, WO02/076949, WO2005080345, WO2005080328, WO2005080343, WO2005075450, WO2005080357, WO200170700, WO2003026647-48, WO200302776, WO2003040107, WO2003007887, WO2003027069, US6,509,367, WO200132663, WO2003086288, WO2003087037, WO2004048317, WO2004058145, WO2003084930, WO2003084943, WO2004058744, WO2004013120, WO2004029204, WO2004035566, WO2004058249, WO2004058255, WO2004058727, WO2004069838, US20040214837, US20040214855, US20040214856, WO2004096209, WO2004096763, WO2004096794, WO2005000809, WO2004099157, US20040266845, WO2004110453, WO2004108728, WO2004000817, WO2005000820, US20050009870, WO200500974, WO2004111033-34, WO200411038-39, WO2005016286, WO2005007111, WO2005007628, US20050054679, WO2005027837, WO2005028456, WO2005063761-62, WO2005061509 or WO2005077897;

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)) or LB53280, LB53279, LB53278 or THIQ, MB243, RY764, CHIR-785, PT-141 or those that are described in WO2005060985, WO2005009950, WO2004087159, WO2004078717, WO2004078716, WO2004024720, US20050124652, WO2005051391, WO2004112793, WOUS20050222014, US20050176728, US20050164914, US20050124636, US20050130988, US20040167201, WO2004005324, WO2004037797, WO2005042516, WO2005040109, WO2005030797, US20040224901, WO200501921,

WO200509184, WO2005000339, EP1460069, WO2005047253, WO2005047251, EP1538159, WO2004072076 or WO2004072077;

orexin receptor antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A) or those as are described for example in WO200196302, WO200185693, WO2004085403 or WO2005075458);

histamine H3 receptor agonists (e.g. 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) or those as are described in WO200064884, WO2005082893);

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 (such as, 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;

MCH (melanin-concentrating hormone) receptor antagonists (such as, for example, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 or compounds such as are described in WO2003/15769, WO2005085200, WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2004039780, WO2003033476, WO2002006245, WO2002002744, WO2003004027 or FR2868780);

CCK-A agonists (such as, 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), SR-146131 (WO 0244150) or SSR-125180);

serotonin reuptake inhibitors (e.g. dexfenfluramine);

mixed serotoninergic and noradrenergic compounds (e.g. WO 00/71549);

5-HT receptor agonists, e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111);

5-HT2C receptor agonists (such as, for example, APD-356, BVT-933 or those as are described in WO200077010, WO20077001-02, WO2005019180, WO2003064423, WO200242304 or WO2005082859);

5-HT6 receptor antagonists as are described for example in WO2005058858;

bombesin receptor agonists (BRS-3 agonists);

galanin receptor antagonists;

growth hormone (e.g. human growth hormone or AOD-9604);
growth hormone-releasing compounds (tertiary butyl 6-benzyloxy-1-(2-diisopropyl-aminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695));
growth hormone secretagogue receptor antagonists (ghrelin antagonists) such as, for example, A-778193 or those as are described in WO2005030734;
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 or Doprexin);
lipase/amylase inhibitors (like those described for example in WO 00/40569);
inhibitors of diacylglycerol O-acyltransferases (DGATs) as described for example in US2004/0224997, WO2004094618, WO200058491, WO2005044250, WO2005072740, JP2005206492 or WO2005013907;
inhibitors of fatty acid synthase (FAS) such as, for example, C75 or those as described in WO2004005277;
oxyntomodulin;
oleoyl-estrone
or thyroid hormone receptor agonists such as, for example: KB-2115 or those as described in WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421 or WO2005092316.

In one embodiment of the disclosure, the further 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 of the disclosure, the further active ingredient is dexamphetamine or amphetamine.

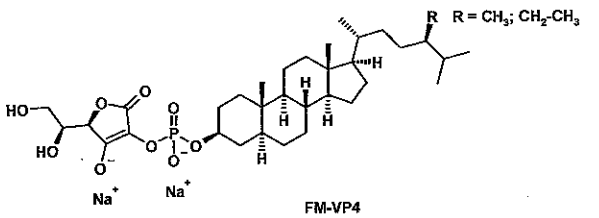
In one embodiment of the disclosure, the further active ingredient is fenfluramine or dexfenfluramine.

In another embodiment of the disclosure, the further active ingredient is sibutramine.

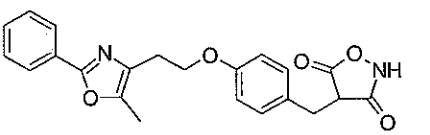
In one embodiment of the disclosure, the further active ingredient is mazindole or phentermine.

In one embodiment of the disclosure, the compound of the formula I is 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.

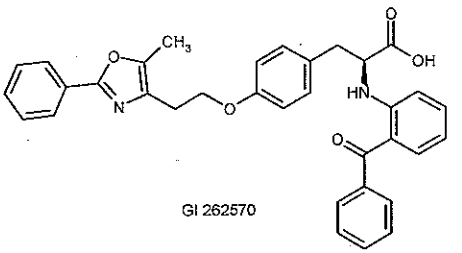
It will be understood that every suitable combination of the compounds of the disclosure with one or more of the aforementioned compounds and optionally one or more further pharmacologically active substances will be regarded as falling within the protection conferred by the present disclosure.



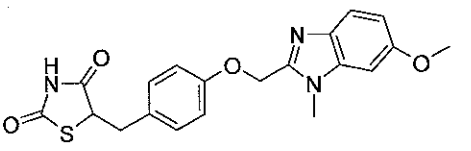
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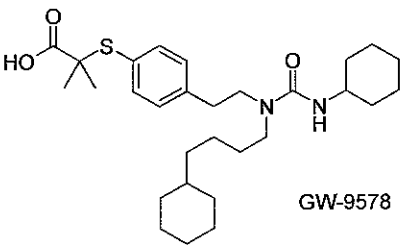
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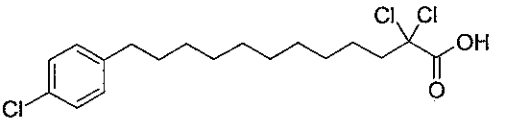
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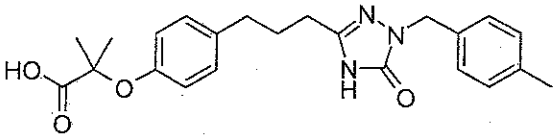
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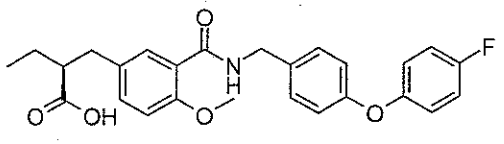
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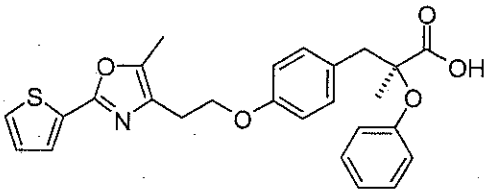
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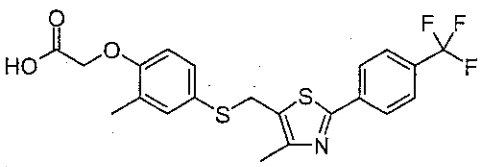
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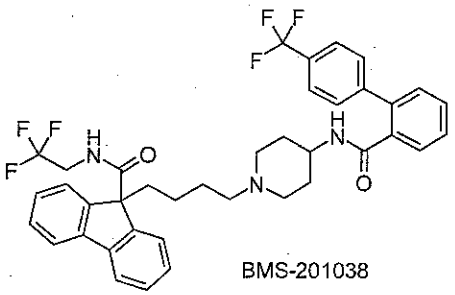
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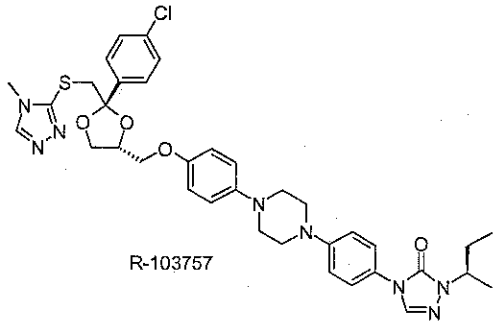
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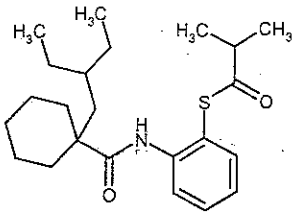
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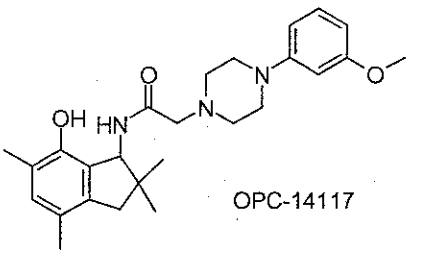
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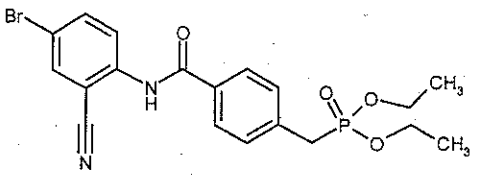
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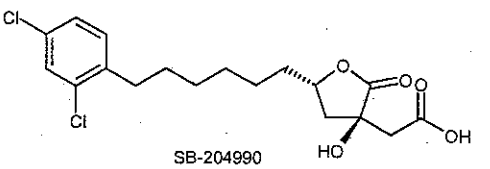
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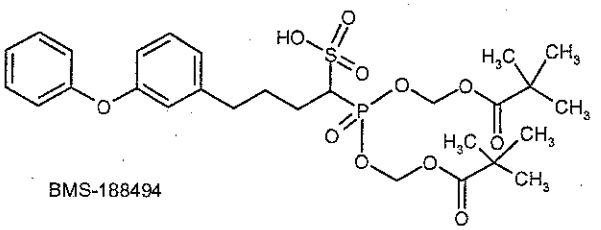
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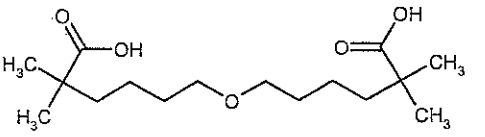
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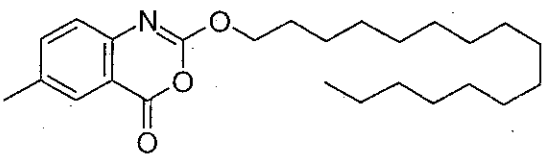
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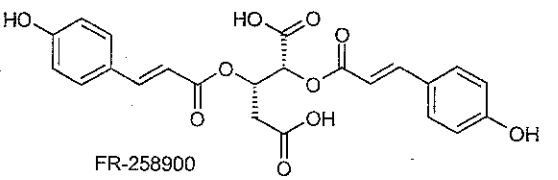
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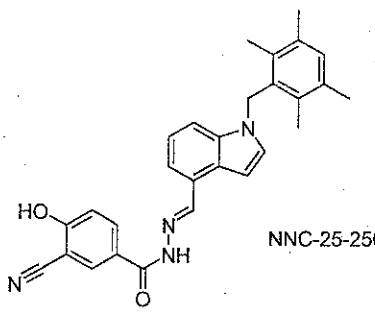
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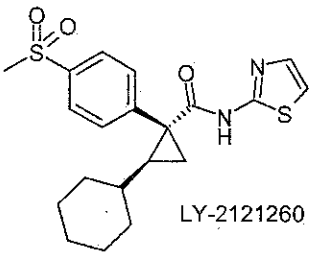
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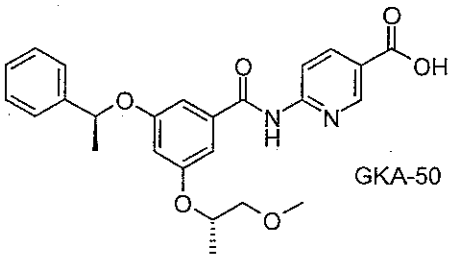
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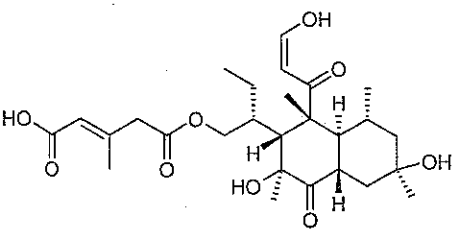
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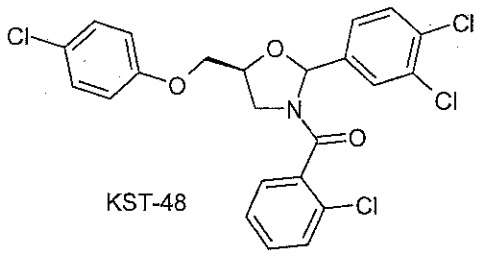
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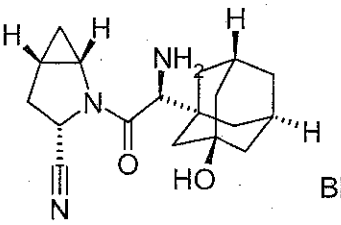
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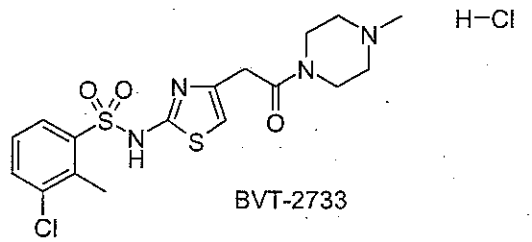
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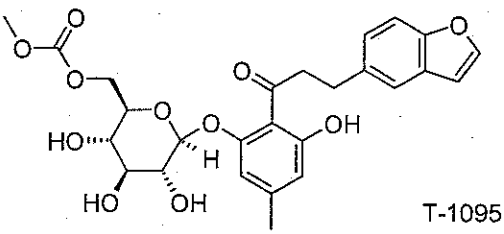
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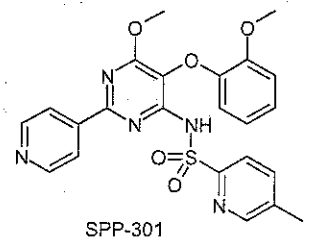
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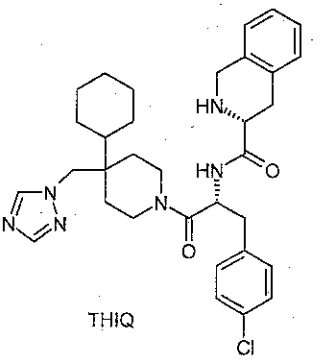
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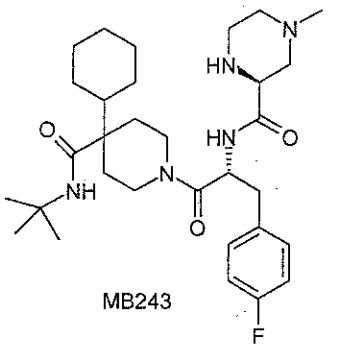
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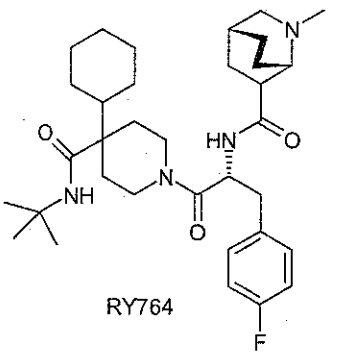
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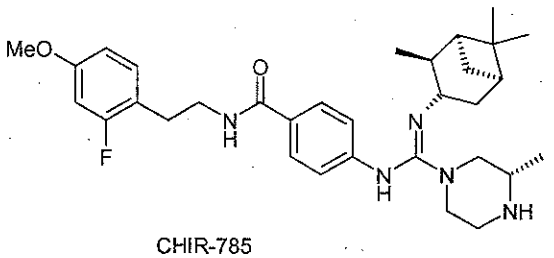
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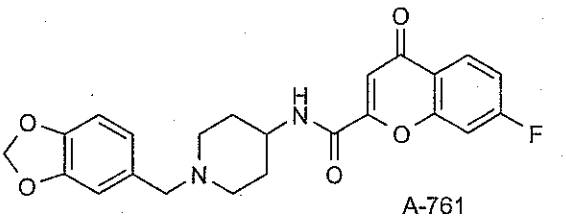
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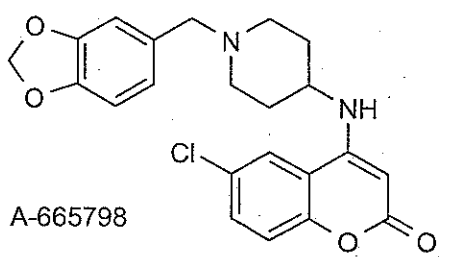
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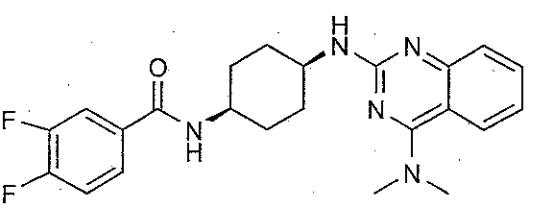
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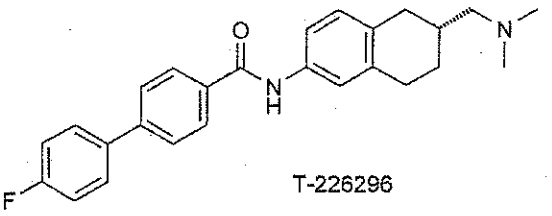
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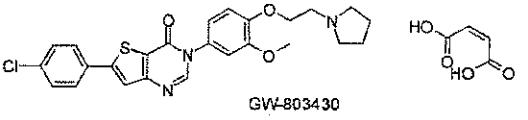
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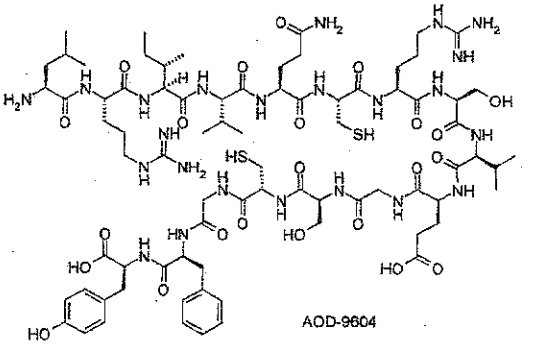
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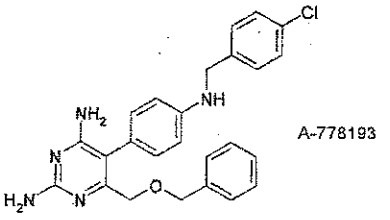
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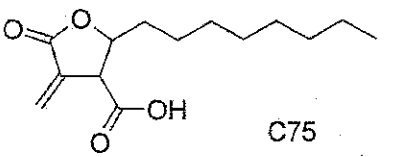
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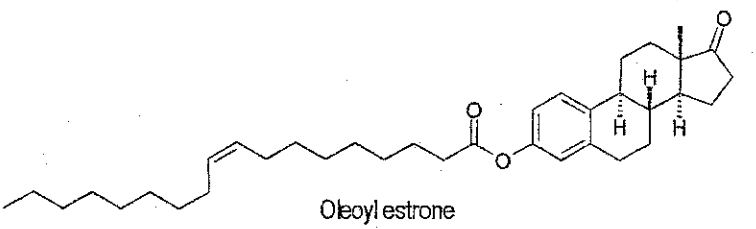
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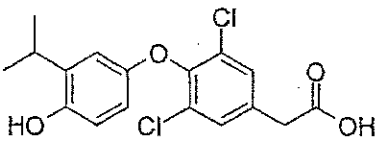


C75



Oleoyl estrone

5

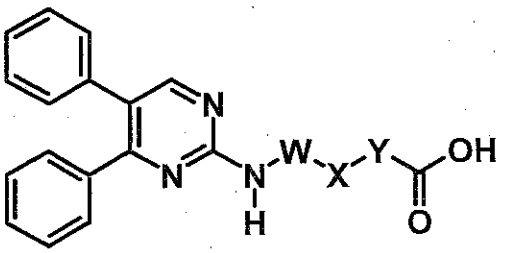


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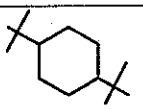
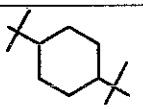
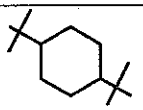
The invention further relates both to mixtures of stereoisomers of the formula I and to the pure stereoisomers of the formula I, and mixtures of diastereomers of the formula I and the pure diastereomers. Separation of the mixtures takes place chromatographically.

The examples detailed below serve to illustrate the invention without, however, restricting it.

Table 1:



I

Ex.	W	X	Y	Salt
1	$-CH_2-$	 cis/trans	-	
2	-	 trans	-	
3	$-(CH_2)_7-$	-	-	TFA
4	$-(CH_2)_6-$	-	-	TFA
5	$-(CH_2)_5-$	-	-	TFA
6	$-(CH_2)_4-$	-	$-CH(NH_2)-CH_2-$, R	TFA
7	-		$-CH_2-CH(NH_2)-$, S	TFA

The activity of the compounds was tested as follows:

In vitro FLIPR assay with recombinant cells which express the GPCR GPR40

Function-testing assays were carried out by means of the FLIPR technique ("Fluorescence Imaging Plate Reader", Molecular Devices Corp.). For this purpose, agonist-induced changes in the intracellular concentration of Ca^{2+} in recombinant HEK293 cells which expressed the

GPCR GPR40 were determined.

For the investigations, cells were seeded in 96-well microtiter plates (60 000 cells/well) and allowed to grow overnight. The medium was removed and the cells were incubated in buffer which contained the fluorescent dye fluo-4. After this loading with dye, the cells were washed, test substance was added, and changes in the intracellular Ca^{2+} concentration were measured in the FLIPR instrument. Results have been presented as percentage change relative to the control (0%: no test substance added; 100%: 10 µM reference agonist linoleic acid added).

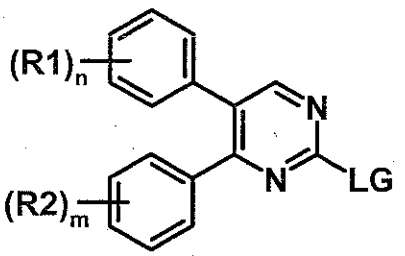
Table 2: Biological activity

Ex.	% activation @ 100 µM
1	79
3	104
4	94
5	73

It is evident from the table that the compounds of the formula I activate the GPR40 receptor and thus are very suitable for the treatment of hyperglycemia and of diabetes. Insulin release is increased by the compounds of the formula I (see Itoh et al., Nature 2003, 422, 173-176).

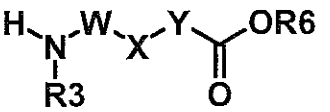
The compounds of the formula I may also show a corresponding effect on the GPR120 receptor.

The compounds of the formula I can be prepared by reacting suitable starting materials of the formula II



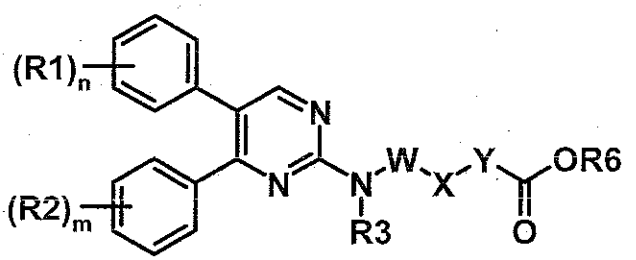
II

where LG may be a leaving group such as, for example, halogen, O-mesylate, O-tosylate, O-triflate or SO_2Me, and R1 and R2 have the abovementioned meanings, with compounds of the formula III,



III

where OR6 is a suitable protective group for ester and R3, W, X and Y have the abovementioned meanings, under the influence of suitable inorganic and organic bases such as, for example, Na_2CO_3, Cs_2CO_3, K_2CO_3, NaH, DBU, DBN or potassium tert-butoxide in a suitable solvent such as, for example, dimethylformamide, dimethyl sulfoxide, toluene or tetrahydrofuran to give compounds of the formula IV.



IV

If the ester protective group has not been eliminated under the reaction conditions, the ester protective group is subsequently eliminated by methods known from the literature to result in the compounds of the formula I.

The preparation of the examples is described in detail below:

Experimental section:

Example 1

4-[(4,5-Diphenylpyrimidin-2-ylamino)methyl]cyclohexanecarboxylic acid

550 mg (1.69 mmol) of cesium carbonate were added to a suspension of 133 mg (0.84 mmol)

of 4-aminomethylcyclohexanecarboxylic acid in 5 ml of toluene, and the mixture was stirred at room temperature. After 30 minutes, 150 mg (0.56 mmol) of 2-chloro-4,5-diphenyl-pyrimidine were added, and the mixture was stirred at 120°C for 31 hours. The solvent was removed in vacuo and the residue was mixed with dichloromethane and water. The resulting precipitate was filtered off with suction. 135 mg (62%) of the desired product were obtained.
MS: *m/z* = 388.5 (M+H).

Example 2

trans-4-(4,5-Diphenylpyrimidin-2-ylamino)cyclohexanecarboxylic acid

Ethyl trans-4-(4,5-diphenylpyrimidin-2-ylamino)cyclohexanecarboxylate

550 mg (1.69 mmol) of cesium carbonate were added to a suspension of 175 mg (0.84 mmol) of ethyl trans-4-aminocyclohexanecarboxylate in 5 ml of toluene, and the mixture was stirred at room temperature. After 30 minutes, 150 mg (0.56 mmol) of 2-chloro-4,5-diphenyl-pyrimidine were added, and the mixture was stirred at 120°C for 4 days. The solvent was removed in vacuo and the residue was partitioned between dichloromethane and water. The organic phase was dried and concentrated under high vacuum. An attempt was made to purify the residue on a silica gel column (heptane/isopropanol, gradient 100% to 5% in 15 minutes). A mixed fraction was obtained, and the product crystallized therefrom. The precipitate was filtered off with suction. 78 mg (34%) of the desired product were obtained in this way.
MS: *m/z* = 402.5 (M+H).

trans-4-(4,5-Diphenylpyrimidin-2-ylamino)cyclohexanecarboxylic acid
70 mg (0.17 mmol) of ethyl trans-4-(4,5-diphenylpyrimidin-2-ylamino)-cyclohexanecarboxylate were mixed with 872 µl of tetrahydrofuran and 872 µl of 1N aqueous lithium hydroxide solution and stirred at room temperature for 48 hours. The reaction mixture was diluted with water and acidified with sulfuric acid, and the resulting precipitate was filtered off with suction. 64 mg (98%) of the desired product were obtained.
MS: *m/z* = 374.5 (M+H).

Example 3

8-(4,5-Diphenylpyrimidin-2-ylamino)octanoic acid trifluoroacetate

Ethyl 8-(4,5-diphenylpyrimidin-2-ylamino)octanoate trifluoroacetate
1.83 g (5.63 mmol) of cesium carbonate were added to a solution of 439 mg (1.69 mmol) of ethyl 8-aminooctanoate in 10 ml of dimethylformamide, and the mixture was stirred at room temperature. After 30 minutes, a solution of 300 mg (1.13 mmol) of 2-chloro-4,5-diphenyl-pyrimidine in 5 ml dimethylformamide was added, and the mixture was stirred at 90°C for 4 hours. The solvent was concentrated and the residue was partitioned between dichloromethane and water. The organic phase was dried and concentrated under high vacuum. The residue was purified by a preparative HPLC (Waters Atlantis™ MS C_{18} 5 µm, 30×100 mm, acetonitrile/(water + 0.1% TFA), gradient 40% to 100% acetonitrile in 25 minutes). 382 mg (64%) of the desired product were obtained.
MS: *m/z* = 418.1 (M+H).

8-(4,5-Diphenylpyrimidin-2-ylamino)octanoic acid trifluoroacetate
106 mg (0.20 mmol) of ethyl 8-(4,5-diphenylpyrimidin-2-ylamino)octanoate trifluoroacetate and 0.5 ml (1.00 mmol) of 2N sodium hydroxide solution were stirred at room temperature for 5 hours. Then 1 ml (1.00 mmol) of 1N sodium hydroxide solution was added, and the mixture was again stirred at room temperature for 24 hours. This was followed by adjustment to pH 1 with sulfuric acid and extraction with ethyl acetate. The organic phase was dried and concentrated in vacuo. The residue was separated by preparative HPLC (Waters Atlantis™ MS C_{18} 5 µm, 30×100 mm, acetonitrile/(water + 0.1 % TFA), 10% acetonitrile to 95% in 10 minutes). 12 mg (12%) of the desired product were obtained.
MS: *m/z* = 390.5 (M+H).

Example 4

7-(4,5-Diphenylpyrimidin-2-ylamino)heptanoic acid trifluoroacetate

7-(4,5-Diphenylpyrimidin-2-ylamino)heptanoic acid trifluoroacetate was obtained from ethyl 7-aminoheptanoate and 2-chloro-4,5-diphenylpyrimidine in analogy to example 3.
MS: m/z = 374.7 (M-H).

Example 5

6-(4,5-Diphenylpyrimidin-2-ylamino)hexanoic acid trifluoroacetate

6-(4,5-Diphenylpyrimidin-2-ylamino)hexanoic acid trifluoroacetate was obtained from ethyl 6-aminohexanoate and 2-chloro-4,5-diphenylpyrimidine in analogy to example 3.
MS: m/z = 362.2 (M+H).

Example 6

(R)-4-Amino-8-(4,5-diphenylpyrimidin-2-ylamino)octanoic acid trifluoroacetate

481 mg (1.48 mmol) of cesium carbonate were added to a solution of 135 mg (0.49 mmol) of ethyl (R)-8-amino-4-tert-butoxycarbonylaminooctanoate in 3.5 ml of dimethylformamide, and the mixture was stirred at room temperature. After 60 minutes, a solution of 87 mg (0.33 mmol) of 2-chloro-4,5-diphenylpyrimidine in 2.5 ml of dimethylformamide was added, and the mixture was stirred at 90°C for 6 hours. The solvent was concentrated and the residue was partitioned between ethyl acetate and water. The organic phase was dried and concentrated under high vacuum. The residue was purified by a preparative HPLC (Purosphere, gradient acetonitrile/(water + 0.5% TFA), gradient 20% acetonitrile to 100% in 30 minutes). 10 mg of ethyl (R)-4-tert-butoxycarbonylamino-8-(4,5-diphenylpyrimidin-2-ylamino)octanoate were obtained. The product obtained in this way was stirred with 50% trifluoroacetic acid for 2 hours, mixed with water and freeze dried. 12 mg (4%) of the desired product were obtained.
MS: *m/z* = 405.6 (M+H).

Example 7

(S)-2-Amino-3-[4-(4,5-diphenylpyrimidin-2-ylamino)cyclohexyl]propionic acid trifluoroacetate

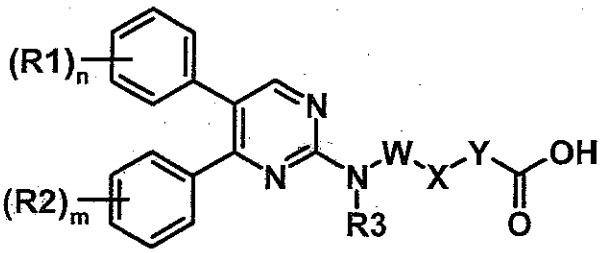
550 mg (1.69 mmol) of cesium carbonate were added to a solution of 161 mg (0.56 mmol) of (S)-3-(4-aminocyclohexyl)-2-tert-butoxycarbonylaminopropionic acid in 3 ml of dimethylformamide, and the mixture was stirred at room temperature. After 30 minutes, a solution of 100 mg (0.38 mmol) of 2-chloro-4,5-diphenylpyrimidine in 2 ml of

dimethylformamide was added, and the mixture was stirred at 90°C for 6 hours. The solvent was concentrated and the residue was partitioned between ethyl acetate and water. The organic phase was dried and concentrated under high vacuum. The residue was separated by a preparative HPLC (Purosphere, gradient acetonitrile/(water + 0.5 % TFA), gradient 20% acetonitrile to 100% in 30 minutes). 22 mg of (S)-2-tert-butoxycarbonylamino-3-[4-(4,5-diphenylpyrimidin-2-ylamino)cyclohexyl]propionic acid were obtained. The product obtained in this way was stirred with 50% trifluoroacetic acid in acetonitrile for 16 hours, mixed with water and freeze dried. 17 mg (11%) of the desired product were obtained.

MS: *m/z* = 417.2 (M+H).

Claims:

1. A compound of the formula I,



I

in which the meanings are

R1, R2		independently of one another (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, NH_2, NH(C_1-C_4)-alkyl, N[(C_1-C_4)-alkyl]$_2$, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be substituted one or more times by F, Cl, Br or CN;
n		0, 1, 2, 3, 4 or 5;
m		0, 1, 2, 3, 4 or 5;
W		bond, (C_1-C_7)-alkylene, (C_2-C_7)-alkenylene or (C_2-C_7)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;
X		bond, mono-, bi- or tricyclic (C_3-C_{12})-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;
Y		bond, (C_1-C_5)-alkylene, (C_2-C_5)-alkenylene or (C_2-C_5)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;
R3		H or (C_1-C_6)-alkyl;
R4		NH_2, NH(C_1-C_4)-alkyl, N[(C_1-C_4)-alkyl]$_2$, F, Cl, Br, CN, OH, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl or (C_2-C_6)-alkynyl, where alkyl, alkenyl and

alkynyl may be substituted one or more times by F, Cl, Br or CN;

R5 F, Cl, Br, CN, (C_1-C_4)-alkyl or O-(C_1-C_4)-alkyl, where alkyl may be substituted one or more times by F, Cl, Br or CN;

where W, X and Y do not simultaneously have the meaning of bond,

and the physiologically tolerated salts thereof.

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

R1, R2 independently of one another (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, NH_2, NH(C_1-C_4)-alkyl, N$[(C_1-C_4)$-alkyl$]_2$, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be substituted one or more times by F, Cl, Br or CN;

n 0, 1, 2, 3, 4 or 5;

m 0, 1, 2, 3, 4 or 5;

W bond, (C_1-C_7)-alkylene, (C_2-C_7)-alkenylene or (C_2-C_7)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

X bond, mono-, bi- or tricyclic (C_3-C_{12})-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;

Y bond, (C_1-C_5)-alkylene, (C_2-C_5)-alkenylene or (C_2-C_5)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

R3 H or (C_1-C_6)-alkyl;

R4 NH_2, NH(C_1-C_4)-alkyl, N$[(C_1-C_4)$-alkyl$]_2$;

R5 F, Cl, Br, CN, (C_1-C_4)-alkyl or O-(C_1-C_4)-alkyl, where alkyl may be substituted one or more times by F, Cl, Br or CN;

where W and X do not simultaneously have the meaning of bond;

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, R2 independently of one another (C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, OH, NH_2, $NH(C_1-C_4)$-alkyl, $N[(C_1-C_4)\text{-alkyl}]_2$, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be subsituted one or more times by F, Cl, Br or CN;

n 0, 1, 2;

m 0, 1, 2;

W bond, (C_1-C_7)-alkylene; (C_2-C_7)-alkenylene or (C_2-C_7)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

X bond, mono-, bi- or tricyclic (C_3-C_{12})-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;

Y bond, (C_1-C_5)-alkylene; (C_2-C_5)-alkenylene or (C_2-C_5)-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;

R3 H or (C_1-C_6)-alkyl;

R4 NH_2, $NH(C_1-C_4)$-alkyl, $N[(C_1-C_4)\text{-alkyl}]_2$;

R5 F, Cl, Br, (C_1-C_4)-alkyl or O-(C_1-C_4)-alkyl;

where W and X do not simultaneously have the meaning of bond;

and the physiologically tolerated salts thereof.

4. A compound of the formula I as claimed in one or more of claims 1 to 3, in which the meanings are

R1, R2	independently of one another $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, OH, CN, F, Cl, Br, O-phenyl, CF_3, OCF_3 or OCH_3, where alkyl may be substituted one or more times by F, Cl, Br or CN
n	0;
m	0;
W	bond, $(C_1$-$C_7)$-alkylene; or if X is a bond W has the meaning of $(C_4$-$C_7)$-alkylene;
X	bond, mono- or bicyclic $(C_3$-$C_{12})$-cycloalkyl ring, where the cycloalkyl ring may be substituted one or more times by R5;
Y	bond, $(C_1$-$C_5)$-alkylene; $(C_2$-$C_5)$-alkenylene or $(C_2$-$C_5)$-alkynylene, where alkylene, alkenylene and alkynylene may be substituted one or more times by R4;
R3	H or $(C_1$-$C_6)$-alkyl;
R4	NH_2, $NH(C_1$-$C_4)$-alkyl, $N[(C_1$-$C_4)$-alkyl$]_2$;
R5	F, Cl, Br, CN, $(C_1$-$C_4)$-alkyl or O-$(C_1$-$C_4)$-alkyl;

where W and X do not simultaneously have the meaning of bond;

and the physiologically tolerated salts thereof.

5. A compound as claimed in one or more of claims 1 to 4 for use as pharmaceutical.

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

7. 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.

8. A pharmaceutical as claimed in claim 7, which comprises as further active ingredient one or more antidiabetics, hypoglycemic active ingredients, HMGCoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, PPAR delta 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, HM74A receptor agonists, lipase inhibitors, insulins, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, active ingredients which act on the ATP-dependent potassium channel of the beta cells, glycogen phosphorylase inhibitors, glucagon receptor antagonists, activators of glucokinase, inhibitors of gluconeogenesis, inhibitors of fructose-1,6-bisphosphatase, modulators of glucose transporter 4 (GLUT4), inhibitors of glutamine-fructose-6-phosphate amidotransferase, inhibitors of dipeptidylpeptidase IV (DPP-IV), inhibitors of 11-beta-hydroxysteroid dehydrogenase 1, inhibitors of protein tyrosine phosphatase 1B, modulators of the sodium-dependent glucose transporter 1 or 2, inhibitors of hormone-sensitive lipase, inhibitors of acetyl-CoA carboxylase, inhibitors of phosphoenolpyruvate carboxykinase, inhibitors of glycoge synthase kinase-3 beta, inhibitors of protein kinase C beta, endothelin-A receptor antagonists, inhibitors of I kappaB kinase, modulators of the glucocorticoid receptor, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, CB1 receptor antagonists, 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, lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR-β agonists or amphetamines.

9. The use of the compounds as claimed in one or more of claims 1 to 4 for manufacturing a medicament for lowering blood glucose.

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

11. The use of the compounds as claimed in one or more of claims 1 to 4 for manufacturing a medicament for increasing insulin release.

12. A process for manufacturing 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.