

Description

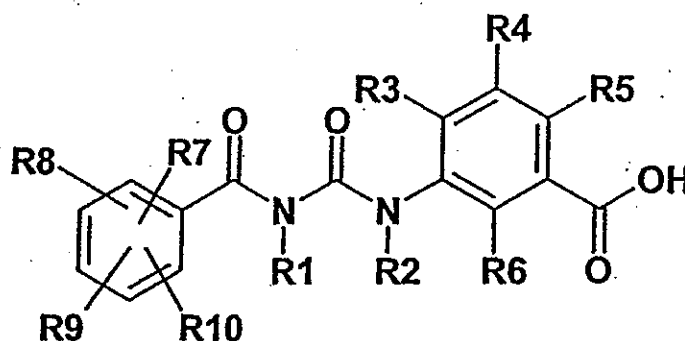
Acyl-4-carboxyphenylurea derivatives, processes for preparing them and
 5 their use

The invention relates to acyl-4-carboxyphenylurea derivatives and to their
 physiologically tolerated salts and physiologically functional derivatives.

10 EP 0 193 249 (Duphar) describes acylcarboxyphenylurea derivatives which
 possess antitumor activity.

Compounds which can be used for preventing and treating diabetes type 2 may
 usefully be provided, and in particular, compounds which can have an effect
 which is markedly superior to that of the compounds disclosed in EP 0 193 249.

In a first aspect, there is provided compounds of the formula I,



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in which

25 R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br, OH,
 NO₂, CN, O-(C₁-C₆)-alkyl, O-(C₂-C₆)-alkenyl, O-(C₂-C₆)-
 alkynyl, O-SO₂-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl or
 (C₂-C₆)-alkynyl, where alkyl, alkenyl and alkynyl can be
 substituted, once or more than once, by F, Cl or Br;

30 R1 and R2 are, independently of each other, H, (C₁-C₆)-alkyl, where alkyl
 can be substituted by OH, O-(C₁-C₄)-alkyl, NH₂, NH(C₁-C₄)-
 alkyl or N[(C₁-C₆)-alkyl]₂, O-(C₁-C₆)-alkyl, CO-(C₁-C₆)-alkyl,

COO-(C₁-C₆)-alkyl, (C₁-C₆)-alkylene-COOH or (C₁-C₆)-alkylene-COO-(C₁-C₆)-alkyl;

- 5 R3 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);
- 10 R4 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);
- 15 R5 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);
- 20 R6 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);
- 25 R11 is H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl or (C₂-C₈)-alkynyl, where alkyl, alkenyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OH or O-(C₁-C₄)-alkyl;
- 30 R12 and R13 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl, phenyl or SO₂-phenyl, where the phenyl ring can be
- 35

substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

5 or R12 and R13 form, together with the nitrogen atom to which they are bonded, a 3-7-membered, saturated heterocyclic ring which can contain up to 2 further heteroatoms from the group N, O or S and where the heterocyclic ring can be substituted, up to four times, by F, Cl, Br, OH, Oxo, (C₁-C₄)-alkyl or N(R14)(R15);

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R14 and R15 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl, phenyl or SO₂-phenyl, where the phenyl ring can be substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

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R16 and R17 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl, phenyl or SO₂-phenyl, where the phenyl ring can be substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

25

or R16 and R17 form, together with the nitrogen atom to which they are bonded, a 3-7-membered, saturated heterocyclic ring which can contain up to 2 further heteroatoms from the group N, O or S and where the heterocyclic ring can be substituted, up to four times, by F, Cl, Br, OH, Oxo, (C₁-C₄)-alkyl or N(R14)(R15);

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it always being the case that at least one of the radicals R3, R7, R8, R9 and R10 is not hydrogen,

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and the physiologically tolerated salts thereof.

In a second aspect, there is provided a pharmaceutical which comprises one or more compounds of the formula I.

In a third aspect, there is provided a pharmaceutical which comprises one or more compounds of the formula I and one or more blood sugar-lowering active compounds.

In a fourth aspect, there is provided a pharmaceutical which comprises one or more compounds of the formula I and one or more statins.

In a fifth aspect, there is provided the use of the compounds of formula I for producing a medicament for treating type 2 diabetes.

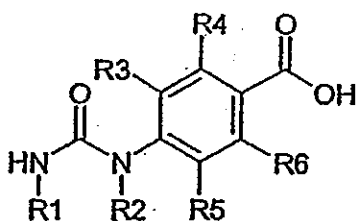
In a sixth aspect, there is provided the use of the compounds of formula I for producing a medicament for lowering blood sugar.

In a seventh aspect, there is provided the use of the compounds of formula I in combination with at least one further blood sugar-lowering active compound for producing a medicament for treating type 2 diabetes.

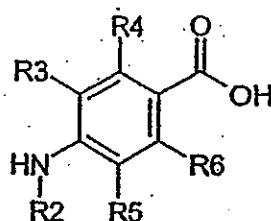
In an eighth aspect, there is provided the use of the compounds of formula I in combination with at least one further blood sugar-lowering active compound for producing a medicament for lowering blood sugar.

In a ninth aspect, there is provided a process for producing a pharmaceutical which comprises one or more compounds of formula I, which comprises mixing the active compound with a pharmaceutically suitable excipient and bringing the mixture into a form which is suitable for administration.

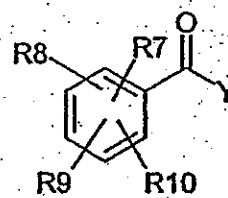
In a tenth aspect, there is provided a process for preparing the compounds of formula I, which comprises reacting ureas of the formula 2 or aniline derivatives of the formula 3 with aaryl isocyanates, with reactive acid derivatives, with acid chlorides or with anhydrides, of the formula 4,



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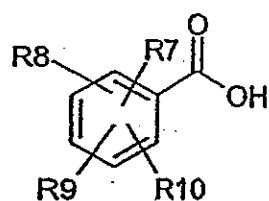
in which R1 to R10 have the meanings as defined above.

In an eleventh aspect, there is provided a process for preparing the physiologically tolerated salts of the compounds of the formula I which comprises reacting the free acids of the compounds of the formula I with a corresponding base.

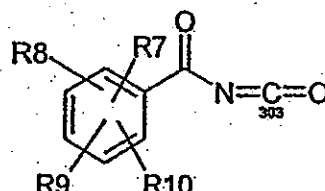
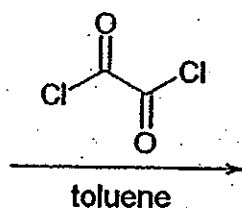
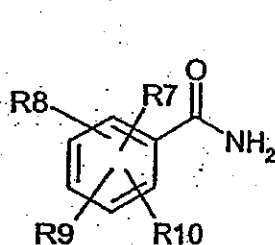
In a twelfth aspect, there is provided a process for preparing the compounds of the formula I, which comprises, in accordance with the following reaction scheme in which R1 to R10 have the meanings as defined above,

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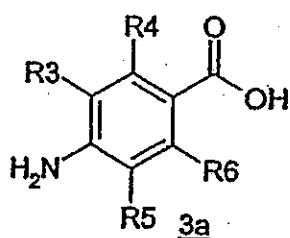
for example:



1. SOCl_2 , toluene
2. $\text{NH}_3(\text{g})$
3. THF, H_2O
4. $\text{NaHCO}_3(\text{aq})$



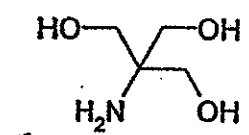
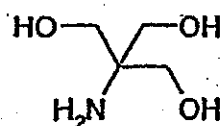
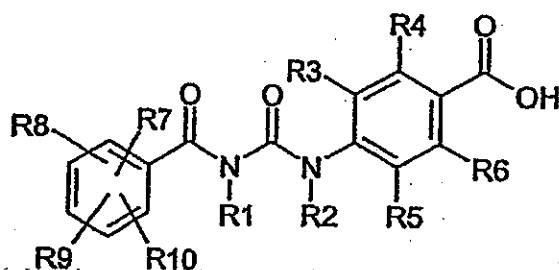
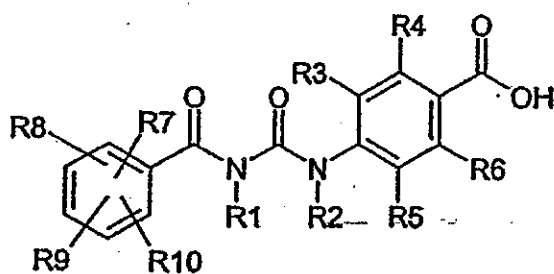
not isolated



for example:

1. Toluene/THF
2. H_2O

for example:

for example:
2-Propanol

- in a first step, using a suitable reagent to convert the compound 4b, in a solvent which is suitable for the purpose, into the acid chloride, and
- 5 in a second step, using a suitable reagent to convert the resulting acid chloride, in a solvent which is suitable for the purpose, into the acid amide 4b, and
- 10 in a third step, converting the acid amide 4b, by reacting it with oxalyl chloride, into the aroyl isocyanate 4a, and
- in a fourth step, reacting the aroyl isocyanate 4a with the aniline 3a, in a suitable solvent, to give the free acid of the compound of the formula I, and
- 15 in a fifth step, reacting the free acid of the compound of the formula I with a base to give a physiologically tolerated salt of the compound of the formula 1.

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

R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br, OH, NO₂, CN, (C₁-C₆)-alkyl or O-(C₁-C₆)-alkyl, where alkyl can be substituted, once or more than once, by F;

R1 and R2 are H;

R3 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11 or COOR11;

R4 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl, can be substituted, once or more than once, by F;

R5 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted, once or more than once, by F;

R6 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl where alkyl can be substituted, once or more than once, by F;

R11 is H, (C₁-C₈)-alkyl, (C₁-C₈)-alkylene-O-(C₁-C₈)-alkyl or (C₁-C₈)-alkyl-OH, where alkyl can be substituted, once or more than once, by F;

R12 and R13 are, independently of each other, H or (C₁-C₈)-alkyl; or R12 and R13 form, together with the nitrogen atom to which they are bonded, a 3-7-membered, saturated heterocyclic ring which can contain up to 2 further heteroatoms from the group N, O or S and where the heterocyclic ring can be substituted, up to four times, by F, Cl, Br, OH, Oxo, (C₁-C₄)-alkyl or N(R14)(R15);

R14 and R15 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl, phenyl or SO₂-phenyl, where the phenyl ring can be

substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO(C₁-C₆)-alkyl or CONH₂;

5 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 meaning:

10 R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br, CH₃ or CF₃;

R1, R2, R5 are H;

15 R3 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted once or more than once by F;

R4 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted once or more than once by F;

20 R6 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted once or more than once by F;

25 R11 is H or (C₁-C₈)-alkyl, where alkyl can be substituted once or more than once by F,

R12 and R13 are H or (C₁-C₈)-alkyl;

30 or the two radicals R12 and R13 form, together with the nitrogen atom to which they are bonded, a 5-6-membered, saturated heterocyclic ring which can contain a further oxygen atom;

and the physiologically tolerated salts thereof.

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

R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br, CH₃ or CF₃;

R1, R2, R4, R5 and R6 are H;

5 R3 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted once or more than once by F;

R11 is H or (C₁-C₈)-alkyl, where alkyl can be substituted once or more than once by F;

10 R12 and R13 are H or (C₁-C₈)-alkyl;
or the two radicals R12 and R13 form, together with the nitrogen atom to which they are bonded, a 5-6-membered, saturated heterocyclic ring which can contain a further oxygen atom;

15 and the physiologically tolerated salts thereof.

Preference is furthermore given to compounds of formula I in which R3 is not H.

R3 is particularly preferably -OCF₃.

20 Preference is given to compounds of formula I in which at least one of the radicals R7, R8, R9 and R10 is not hydrogen.

Particular preference is given to compounds of formula I in which at least one of the radicals R7, R8, R9 and R10 has the meaning F or Cl.

25 Very particular preference is given to compounds of formula I in which at least two of the radicals R7, R8, R9 and R10 have the meaning F or Cl.

Very particular preference is given to compounds of formula I in which the radicals R7, R8, R9 and R10 have the meanings 2-Cl, 4-F, 5-F and H.

30 If radicals or substituents can occur more than once in the compounds of the formula I, such as -O-R11, they can then all, independently of each other, have the given meanings and be identical or different.

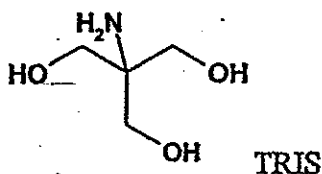
35 The invention relates to compounds of the formula I, in the form of their racemates, racemic mixtures and pure enantiomers, and to their diastereomers and mixtures thereof.

The alkyl radicals in the substituents R1, R2, R3, R4, R5, R6, R7, R8, R9,

R10, R11, R12, R13, R14, R15, R16 and R17 can be either straight-chain or branched.

5 Because of their higher solubility in water as compared with the starting compounds or basal compounds, pharmaceutically tolerated salts are particularly suitable for medical applications. These salts must possess 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, 10 phosphoric acid, metaphosphoric acid, nitric acid and sulfuric acid, and also of organic acids, such as 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. 15 Suitable pharmaceutically tolerated basic salts are ammonium salts, alkali metal salts (such as sodium salts and potassium salts), alkaline earth metal salts (such as magnesium salts and calcium salts), trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

20 Particular preference is given to the trometamol salts (also termed TRIS, tris(hydroxymethyl)methylamine) of the compounds of formula I. They exhibit a higher bioavailability than do the corresponding free acids.



25 Salts which contain an anion which is not pharmaceutically tolerated, such as trifluoroacetate, also belong within the scope of the invention as useful intermediates for preparing or purifying pharmaceutically tolerated salts and/or for use in nontherapeutic, for example in-vitro, applications.

30 The term "physiologically functional derivative" which is used here denotes any physiologically tolerated derivative of a compound according to the invention of the formula I, e.g. an ester which is able, on being administered to a mammal, such as a human, to form (directly or indirectly) 35 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, as described, for example, in H. Okada et al., Chem. Pharm. Bull, 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to give a compound according to the invention. These prodrugs may or may not themselves be active.

The compounds according to the invention can also be present in different polymorphic forms, e.g. as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds according to the invention belong within the scope of the invention and are another aspect of the invention.

In that which follows, all references to "compound(s) according to formula I" refer to compound(s) of the formula I as described above and to their salts, solvates and physiologically functional derivatives as described herein.

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

The quantity of a compound according to Formula I which is required in order to achieve the desired biological effect depends on a number of factors, e.g. the specific compound which is selected, the intended use, the nature of administration and the clinical condition of the patient. In general, the daily dose is in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day per kilogram of bodyweight, e.g. 3-10 mg/kg/day. An intravenous dose can, for example, be in the range from 0.3 mg to 1.0 mg/kg, which dose can expediently be administered as an infusion of from 10 ng to 100 ng per kilogram per minute. Infusion solutions which are suitable for these purposes can, for example, contain from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Individual doses can, for example, contain from 1 mg to 10 g of the active compound. Thus, ampoules for injections can, for example, contain from 1 mg to 100 mg, and orally administrable individual dose formulations, such as tablets or capsules, can, for example, contain from 1.0 to 1000 mg, typically from 10 to 600 mg. While, for the therapy of the abovementioned conditions, the compounds according to formula I can be used themselves as compounds, they are preferably present, together with a tolerated excipient, in the form of a pharmaceutical composition. The excipient naturally has to be tolerated in the sense that it is compatible with the other components of the

composition and is not harmful to the health of the patient. The excipient can be a solid or a liquid or both and is preferably formulated together with the compound as an individual dose, for example as a tablet, which can contain from 0.05% to 95% by weight of the active compound. Other
5 pharmaceutically active substances can also be present, including other compounds according to formula I. The pharmaceutical compositions according to the invention can be prepared using one of the known pharmaceutical methods, which essentially consist in the constituents being mixed with pharmacologically tolerated excipients and/or auxiliary
10 substances.

Pharmaceutical compositions according to the invention are those which are suitable for oral, rectal, topical, peroral (e.g. sublingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous)
15 administration, even though 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 according to formula I which is employed in each case. Coated formulations and coated delayed-release formulations also belong within the scope of the invention.
20 Preference is given to formulations which are acid-resistant and gastric juice-resistant. Suitable gastric juice-resistant coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

25 Suitable pharmaceutical compounds for oral administration can be present in separate units, such as capsules, cachets, sucking tablets or tablets which in each case contain a defined quantity of the compound according to formula I; as powders or granules; as a solution or suspension in an
30 aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. As already mentioned, these compositions can be prepared using any suitable pharmaceutical method which comprises a step in which the active compound and the excipient (which can be composed of one or more additional constituents) are brought into contact. In general, the
35 compositions are prepared by uniformly and homogeneously mixing the active compound with a liquid and/or finely divided solid excipient, after which the product is molded, if required. Thus, a tablet, for example, can be prepared by pressing or molding a powder or granulate of the compound, where appropriate together with one or more additional constituents.

Pressed tablets can be prepared by tableting the compound in freely flowing form, such as a powder or granulate, where appropriate mixed with a binding agent, lubricant, inert diluent and/or a (several) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be prepared by molding the pulverulent compound, which is moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration include sucking tablets, which contain a compound according to formula I together with a flavoring agent, usually sucrose and gum arabic or tragacanth, and lozenges, which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Suitable pharmaceutical compositions for parenteral administration preferably include sterile aqueous preparations of a compound according to formula I which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, even though the administration can also take place as an injection subcutaneously, intramuscularly or intradermally. These preparations can preferably be prepared by mixing the compound with water and making the resulting solution sterile and isotonic with the blood. In general, injectable compositions according to the invention comprise from 0.1 to 5% by weight of the active compound.

Suitable pharmaceutical compositions for rectal administration are preferably present as individual dose suppositories. These can be prepared by mixing a compound according to formula I with one or more conventional solid excipients, for example cocoa butter, and molding the resulting mixture.

Suitable pharmaceutical compositions for topical use on the skin are preferably present as an ointment, cream, lotion, paste, spray, aerosol or oil. Excipients which can be used are vaseline, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances.

The active compound is generally present at a concentration of from 0.1 to 15% by weight of the composition, for example from 0.5 to 2%.

Transdermal administration is also possible. Suitable pharmaceutical compositions for transdermal uses can be present as individual plasters

which are suitable for long-term intimate contact with the epidermis of the patient. Such plasters expediently contain the active compound in an aqueous solution, which is, where appropriate, buffered, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active compound concentration is from approx. 1% to 35%, preferably from approx. 3% to 15%. As a particular possibility, the active compound can, as described, for example, in Pharmaceutical Research, 2(6): 318 (1986), be released by means of electrotransport or iontophoresis.

10 The following are suitable for use as additional active compounds for the combination preparations:

All antidiabetics which are named in the Roten Liste [Red List] 2001, Chapter 12. They can be combined with the compounds according to the invention of the formula I, particularly for improving the effect synergistically. The active compound combination can be administered either by administering the active compounds separately to the patient or in the form of combination preparations in which several active compounds are present in one pharmaceutical preparation. Most of the active compounds which are listed below are disclosed in USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001. Antidiabetics include insulin and insulin derivatives, such as Lantus® (see www.lantus.com) or HMR 1964, rapidly acting insulins (see US 6,221,633), GLP-1 derivatives, such as those which were disclosed in WO 98/08871 by Novo Nordisk A/S, and hypoglycemic active compounds which are effective orally.

The hypoglycemic active compounds which are effective orally preferably include sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists, GLP-1 agonists, calcium channel openers, such as those which were disclosed by Novo Nordisk A/S in WO 97/26265 and WO 99/03861, insulin sensitizers, inhibitors of liver enzymes which are involved in stimulating gluconeogenesis and/or glycogenolysis, modulators of glucose uptake, compounds, such as antihyperlipidemic active compounds and antilipidemic active compounds, which alter fat metabolism, compounds which decrease the intake of foodstuffs, agonists of PPAR and PXR, and active compounds which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMGCoA reductase inhibitor, such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin or rosuvastatin.

5

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

10 In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist, such as rosiglitazone, pioglitazone, JTT-501 or GI 262570.

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

20 In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, such as GW 1536, AVE 8042, AVE 8134 or AVE 0847, or as described in PCT/US 11833, PCT/US 11490 or DE10142734.4.

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

30 In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor, such as implitapide, BMS-201038 or R-103757.

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorber, such as

cholestyramine or colestevlam.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer (see US
5 6,342,512), such as HMR1171 or HMR1586.

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipoprotein lipase inhibitor, such as NO-
15 1886.

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

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

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

In one embodiment of the invention, the compounds of the formula I are
30 administered in combination with a lipase inhibitor, such as 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
35 combination with a sulfonylurea, such as tolbutamide, glibenclamide, glipizide or glimepiride.

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

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

In one embodiment, the compounds of the formula I are administered in combination with a thiazolidinedione, such as troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds which are disclosed by Dr. Reddy's Research Foundation in WO 97/41097, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy)phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment, the compounds of the formula I are administered in combination with an α -glucosidase inhibitor, such as miglitol or acarbose.

In one embodiment, the compounds of the formula I are administered in combination with an active compound which acts on the ATP-dependent potassium channel of the beta cells, such as 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 another embodiment, the compounds of the formula I are administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A, et al., M.:Hormone and Metabolic Research (2001), 33(9), 554-558), NPY antagonists, e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]cyclohexylmethyl}amide; hydrochloride (CGP 71683A)), MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]amide; (WO 01/91752)), orexin antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea]; hydrochlorides (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-triazafuoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (e.g. urocortin), urocortin agonists, β 3-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 trifluoroacetic acid salt (WO 99/15525)); serotonin reuptake inhibitors (e.g. dexfenfluramines), mixed serotonin
 5 compounds 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 (tert-butyl 6-benzyloxy-1-(2-diisopropylaminoethylcarbamoyl)-3,4-dihydro-1H-
 10 isoquinoline-2-carboxylate (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),
 15 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 additional active compound is
 20 leptin; see, e.g., "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 additional active compound is dexamphetamine or
 25 amphetamine.

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

In yet another embodiment, the additional active compound is sibutramine.

In one embodiment, the additional active compound is orlistat.

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

In one embodiment, the compounds of the formula I are administered in
 35 combination with bulk materials, preferably insoluble bulk materials (see, e.g., 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)). The combination with Caromax® can be effected in

one preparation or by administering compounds of the formula I and Caromax® separately. In this connection, Caromax® can also be administered in the form of foodstuffs, such as in bakery products or muesli bars.

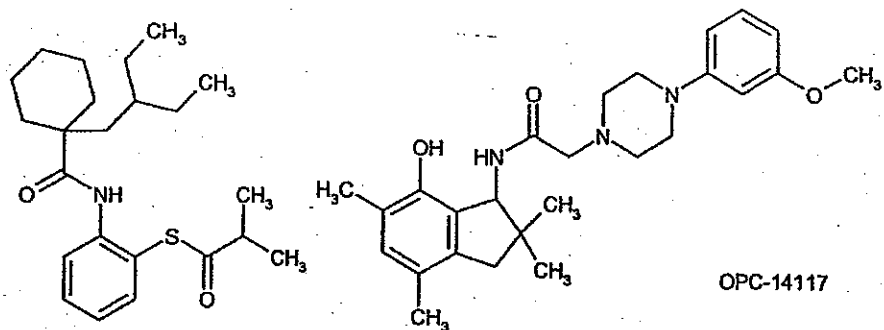
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It will be understood that each suitable combination of the compounds according to the invention with one or more of the abovementioned compounds and, as desired, one or more further pharmacologically active substances, is regarded as coming within the protective scope of the

10

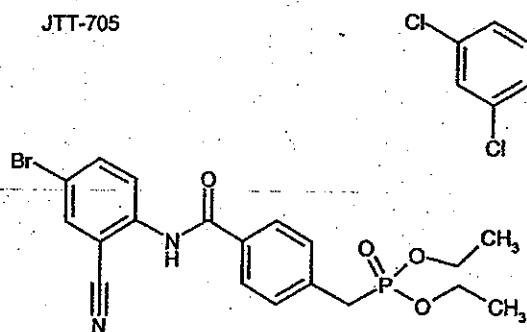
present invention.

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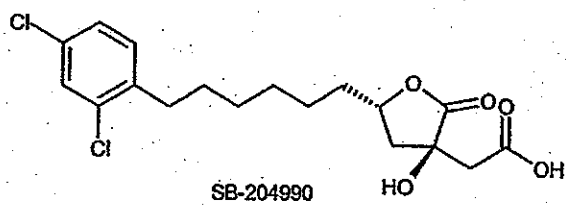


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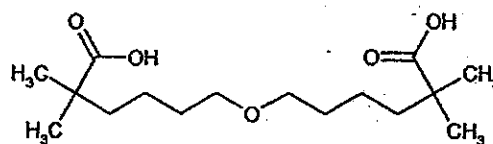
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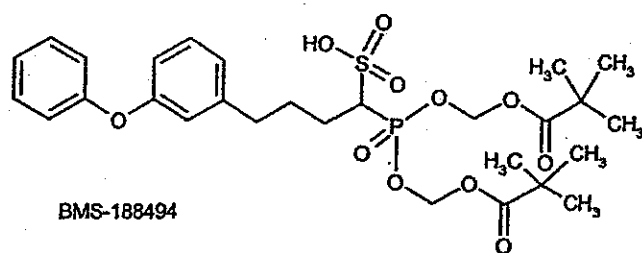
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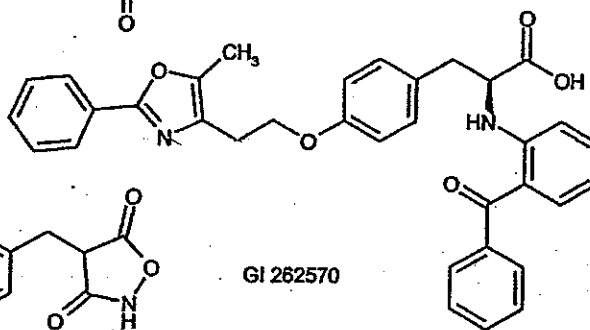
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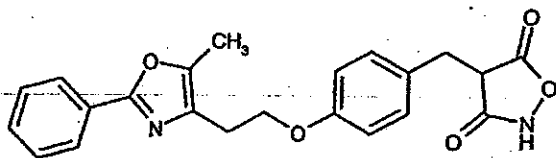
Cl-1027



BMS-188494



GI 262570



JTT-501

The examples which are adduced below serve to explain the invention without, however, limiting it.

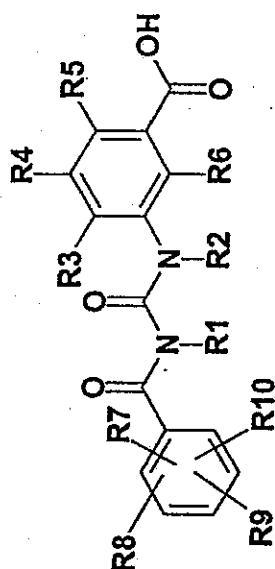


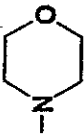
Table 1: Examples of the formula I

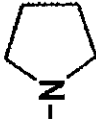
Ex.	R7, R8, R9, R10	R1	R2	R3	R4	R5	R6	Salt	MS**	M.p.
1	2-Cl, H, H, H	H	H	NO ₂	H	H	H	-	ok	240*
2	2-Cl, 4-Cl, H, H	H	H	NO ₂	H	H	H	-	ok	
3	2-Cl, 4-Cl, H, H	H	H	NO ₂	H	H	H	TRIS	ok	
4	2-Cl, H, H, H	H	H	OH	H	H	H	-	ok	
5	2-Cl, 4-Cl, H, H	H	H	OH	H	H	H	-	ok	
6	2-Cl, H, H, H	H	H	Cl	H	H	H	-	ok	
7	2-Cl, H, H, H	H	H	OCH ₃	H	H	H	-	ok	
8	2-Cl, 4-Cl, H, H	H	H	OCH ₃	H	H	H	-	ok	
9	2-Cl, 4-Cl, H, H	H	H	Cl	H	H	H	-	ok	
10	2-Cl, 5-Cl, H, H	H	H	Cl	H	H	H	-	ok	
11	2-Cl, 5-Cl, H, H	H	H	OCH ₃	H	H	H	-	ok	
12	2-F, H, H, H	H	H	OCH ₃	H	H	H	-	ok	

Ex.	R7, R8, R9, R10	R1	R2	R3	R4	R5	R6	Salt	MS**	M.p.
13	3-F, H, H, H	H	H	OCH ₃	H	H	H	-	ok	
14	3-Cl, H, H, H	H	H	OCH ₃	H	H	H	-	ok	
15	2-Cl, 5-CH ₃ , H, H	H	H	Cl	H	H	H	-	ok	
16	2-Cl, 5-CH ₃ , H, H	H	H	OCH ₃	H	H	H	-	ok	
17	4-F, H, H, H	H	H	OCH ₃	H	H	H	-	ok	
18	3-Cl, 4-Cl, H, H	H	H	OCH ₃	H	H	H	-	ok	
19	2-CH ₃ , H, H, H	H	H	Cl	H	H	H	-	ok	
20	2-F, H, H, H	H	H	Cl	H	H	H	-	ok	
21	3-F, H, H, H	H	H	Cl	H	H	H	-	ok	
22	3-Cl, H, H, H	H	H	Cl	H	H	H	-	ok	
23	3-Cl, 4-Cl, H, H	H	H	Cl	H	H	H	-	ok	
24	2-CH ₃ , H, H, H	H	H	OCH ₃	H	H	H	-	ok	
25	2-CH ₃ , 4-CH ₃ , H, H	H	H	Cl	H	H	H	-	ok	
26	2-CH ₃ , 4-CH ₃ , H, H	H	H	OCH ₃	H	H	H	-	ok	
27	2-F, 4-Cl, H, H	H	H	OCH ₃	H	H	H	-	ok	
28	2-F, 4-Cl, H, H	H	H	Cl	H	H	H	-	ok	
29	2-F, 4-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
30	2-F, 4-F, H, H	H	H	Cl	H	H	H	-	ok	
31	2-Cl, 4-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
32	2-Cl, 4-F, H, H	H	H	Cl	H	H	H	-	ok	

Ex.	R7, R8, R9, R10	R1	R2	R3	R4	R5	R6	Salt	MS**	M.p.
33	2-Cl, 4-F, H, H	H	H	Cl	H	H	H	TRIS	ok	
34	2-F, H, H, H	H	H	H	H	H	H	-	ok	
35	2-Cl, H, H, H	H	H	H	H	H	OH	-	ok	
36	2-Cl, 4-Cl, H, H	H	H	H	H	H	OH	-	ok	
37	2-Cl, 4-F, H, H	H	H	H	H	H	OH	-	ok	
38	2-Cl, 4-Cl, H, H	H	H	Cl	H	H	OH	-	ok	
39	2-Cl, 4-F, H, H	H	H	Cl	H	H	OH	-	ok	
40	2-Cl, 5-Br, H, H	H	H	OCH ₃	H	H	H	-	ok	251
41	2-Cl, 4-F, 5-F, H	H	H	OCH ₃	H	H	H	-	ok	268
42	2-Cl, 4-F, 5-F, H	H	H	OCH ₃	H	H	H	TRIS	ok	
43	2-Cl, 4-Cl, H, H	H	H	OCF ₃	H	H	H	-	ok	
44	2-Cl, 4-F, H, H	H	H	OCF ₃	H	H	H	-	ok	
45	2-F, 6-Cl, H, H	H	H	OCH ₃	H	H	H	-	ok	
46	2-CH ₃ , 6-CH ₃ , H, H	H	H	OCH ₃	H	H	H	-	ok	
47	2-Cl, 4-F, 5-F, H	H	H	Cl	H	H	H	-	ok	262
48	2-Cl, 4-F, 5-F, H	H	H	OCF ₃	H	H	H	-	ok	236
49	2-Cl, 4-F, 5-F, H	H	H	OCF ₃	H	H	H	TRIS	ok	176
50	2-Cl, 4-Cl, 5-F, H	H	H	OCH ₃	H	H	H	-	ok	261
51	2-Cl, 5-F, H, H	H	H	OCH ₃	H	H	H	-	ok	273
52	2-Cl, 4-F, H, H	H	H	H	H	H	NH ₂	-	ok	222

Ex.	R7, R8, R9, R10	R1	R2	R3	R4	R5	R6	Salt	MS**	M.p.
53	2-Cl, 4-F, H, H	H	H	CH ₃	H	H	H	-	ok	
54	2-Cl, 4-Cl, H, H	H	H	CH ₃	H	H	H	-	ok	
55	2-Cl, 4-F, 5-F, H	H	H	CF ₃	H	H	H	-	ok	
56	2-Cl, 4-F, H, H	H	H	OCH ₃	H	H	OH	-	ok	256
57	2-Cl, 4-F, 5-F, H	H	H	OCH ₃	H	H	OH	-	ok	250
58	2-Br, H, H, H	H	H	OCH ₃	H	H	H	-	ok	286
59	2-Cl, 4-F, 5-F, H	H	H	Cl	H	H	OH	-	ok	253*
60	2-Cl, 4-F, H, H	H	H	H	F	H	H	-	ok	
61	2-Cl, 4-F, 5-F, H	H	H	H	F	H	H	-	ok	
62	2-Cl, 4-F, H, H	H	H	H	Cl	H	H	-	ok	
63	2-Cl, 4-F, 5-F, H	H	H	H	Cl	H	H	-	ok	
64	2-Cl, 4-F, 5-F, H	H	H	H	OCH ₃	H	H	-	ok	
65	2-Cl, 4-F, 5-F, H	H	H	H	NO ₂	H	H	-	ok	
66	2-Cl, 4-F, 5-F, H	H	H	OCH ₂ CF ₃	H	H	H	-	ok	
67	2-Cl, 4-F, 5-F, H	H	H	OCH ₃	H	H	NO ₂	-	ok	
68	2-Cl, 4-F, H, H	H	H	Cl	H	H	OCH ₃	-	ok	
69	2-Cl, 4-F, H, H	H	H	O(CH ₂) ₂ CH ₃	H	H	H	-	ok	>300
70	2-Cl, 4-F, H, H	H	H	OCH(CH ₃) ₂	H	H	H	-	ok	269.5
71	2-Cl, 4-F, H, H	H	H	O(CH ₂) ₃ CH ₃	H	H	H	-	ok	285

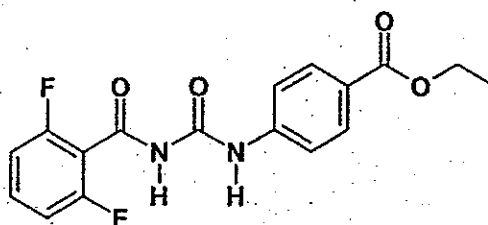
Ex.	R7, R8, R9, R10	R1	R2	R3	R4	R5	R6	Salt	MS**	M.p.
72	2-Cl, 4-F, H, H				H	H	H	-	ok	258
73	2-Cl, 4-F, H, H	H	H		H	H	H	-	ok	274
74	2-Cl, 4-Cl, 6-Cl, H	H	H	OCH ₃	H	H	H	-	ok	
75	2-Br, 4-CH ₃ , H, H	H	H	OCH ₃	H	H	H	-	ok	
76	2-Br, 4-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
77	2-Br, 5-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
78	2-F, 4-Cl, 5-F, H	H	H	OCH ₃	H	H	H	-	ok	
79	4-Cl, 5-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
80	2-Cl, 4-Cl, 6-CH ₃ , H	H	H	OCH ₃	H	H	H	-	ok	
81	2-CF ₃ , 4-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
82	2-CF ₃ , 6-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
83	2-Cl, 3-CH ₃ , H, H	H	H	OCH ₃	H	H	H	-	ok	
84	2-Cl, 6-F, 5-CH ₃ , H	H	H	OCH ₃	H	H	H	-	ok	
85	2-Cl, 6-F, 3-CH ₃ , H	H	H	OCH ₃	H	H	H	-	ok	
86	2-Cl, 4-F, H, H	H	H	N(CH ₃) ₂	H	H	H	-	ok	247
87	2-Cl, 4-F, 5-F, H	H	H	O(CH ₂) ₂ CH ₃	H	H	H	-	ok	289
88	2-Cl, 4-F, 5-F, H	H	H	O(CH ₂) ₃ CH ₃	H	H	H	-	ok	275.5

Ex.	R7, R8, R9, R10	R1	R2	R3	R4	R5	R6	Salt	MS**	M.p.
89	2-Cl, 4-F, 5-F, H	H	H		H	H	H	-	ok	209.5
90	2-Cl, 4-F, 5-F, H	H	H		H	H	H	-	ok	303
91	2-CH ₃ , 4-Br, H, H	H	H	OCH ₃	H	H	H	-	ok	
92	2-Cl, 4-Br, H, H	H	H	OCH ₃	H	H	H	-	ok	
93	2-Br, 5-Cl, H, H	H	H	OCH ₃	H	H	H	-	ok	
94	2-CH ₃ , 5-CH ₃ , H, H	H	H	OCH ₃	H	H	H	-	ok	
95	2-CH ₃ , 5-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
96	2-F, 4-F, 5-F	H	H	OCH ₃	H	H	H	-	ok	
97	2-CH ₃ , 4-F, H, H	H	H	OCH ₃	H	H	H	-	ok	
98	2-CH ₃ , 5-Cl, H, H	H	H	OCH ₃	H	H	H	-	ok	
99	2-Cl, 4-F, 5-F, H	H	H	NHCH ₂ CH ₃	H	H	H	-	ok	300
100	2-Cl, 4-F, 5-F, H	H	H	OCH ₃	H	H	NH ₂	-	ok	
101	2-Cl, 4-F, 5-F, H	H	H	OCH(CH ₃) ₂	H	H	H	-	ok	261

* Decomposition

** The information "MS is OK" is understood as meaning that a mass spectrum or HPLC/MS was measured and the molar peak (molar mass + H⁺) was detected in this spectrum

Example 5 from EP 0 193 249 was synthesized as comparative example A. Example A has the structure:



5

The compounds of the formula I are characterized by advantageous effects on sugar metabolism; in particular, they lower the blood sugar level and are suitable for treating type 2 diabetes. The compounds can therefore be used on their own or in combination with other blood sugar-lowering active compounds (antidiabetics).

10

The compounds of formula I are furthermore suitable for treating late damage in diabetes, such as nephropathy, retinopathy, neuropathy and cardiac infarction, myocardial infarction, peripheral arterial occlusion diseases, thromboses, arteriosclerosis, syndrome X, obesity, inflammations, immune diseases, autoimmune diseases, such as AIDS, asthma, osteoporosis, cancer, psoriasis, Alzheimer's disease, schizophrenia and infectious diseases.

15

The activity of the compounds was tested as follows:

20

Glycogen phosphorylase a activity test

25

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 the reactions were carried out as duplicate determinations in 96-well microtiter plates (Half Area Plates, Costar No. 3696), with the change in absorption due to the formation of the reaction product being measured, at the wavelength specified below, in a Multiscan Ascent Elisa Reader (Lab Systems, Finland). In order to measure the enzymic activity of GPa in the reverse direction, the conversion of glucose 1-phosphate into glycogen and inorganic phosphate was measured in accordance with the general method of Engers et al. (Engers HD, Shechosky S, Madsen NB, Can J Biochem 1970 Jul;48(7): 746-754)

30

but 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 with buffer T (50 mM Hepes, pH 7.0, 100 mM KCl, 2.5 mM EDTA, 2.5 mM $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$), and addition of 5 mg of glycogen/ml, to a concentration of 10 μg of protein/ml. Test substances were prepared as a 10 mM solution in DMSO and diluted down to 50 μM with buffer solution T. 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 glucose 1-phosphate, 2.5 mM, were added to 10 ml of the solution. The basal value of the activity of the 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 inorganic phosphate which was released was measured using the general method of Drueckes et al. (Drueckes P, Schinzel R, Palm D, *Anal Biochem* 1955 Sep 1;230(10):173-177) but with the following modifications: 50 μl of a stop solution of 7.3 mM ammonium molybdate, 10.9 mM zinc acetate, 3.6% ascorbic acid, 0.9% SDS are added to 50 μl of the enzyme mixture. After 60 minutes of incubation at 45°C, the absorption was measured at 820 nm. In order to determine the background absorption, the stop solution was added immediately after adding the glucose 1-phosphate solution in a separate assay. This test was carried out using a 10 μM concentration 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.	% inhibition at 10 μ M	Ex.	% inhibition at 10 μ M
1	71	52	96
2	85	53	93
3	93	54	91
4	56	55	100
5	80	56	96
6	89	57	99
7	93	58	91
8	96	59	92
9	100	60	41
10	95	61	85
11	95	62	59
12	82	63	92
13	74	64	40
14	70	65	56
15	90	66	97
16	89	67	92
17	75	68	54
18	64	69	99
19	94	70	100
20	85	71	95
21	81	72	99
22	79	73	85
23	59	74	47
24	87	75	84
25	82	76	98
26	81	77	96
27	90	78	69
28	91	79	58
29	72	80	65
30	95	81	49
31	98	82	40
32	98	83	34
33	100	84	98
34	59	85	98

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Ex.	% inhibition at 10 μ M
35	94
36	96
37	91
38	103
39	98
40	92
41	101
42	99
43	100
44	101
45	96
46	92
47	98
48	99
49	103
50	108
51	96

Ex.	% inhibition at 10 μ M
86	99
87	102
88	99
89	102
90	95
91	94
92	95
93	96
94	88
95	96
96	90
97	97
98	95
99	95
100	95
101	100

Comparative Example A exhibits 3% inhibition at 10 μ M.

5 It can be seen from the table that the compounds of the formula I inhibit the activity of glycogen phosphorylase a and are therefore well suited for lowering the blood sugar level. In particular, the compounds of formula I exhibit an effect which is from 14- to 36-fold higher than that of comparative example A.

10 The preparation of one example is described in detail below;
The remaining compounds of formula I were obtained in an analogous manner, where appropriate using customary protective-group techniques:

Experimental section:

Example 1:

5 a) 2-Chlorobenzoyl isocyanate

1.03 g (6.6 mmol) of 2-chlorobenzamide were suspended in 3 ml of dichloromethane. After 1.17 g (9.2 mmol) of oxalyl chloride had been added, the mixture was heated to reflux for 17 hours. The reaction mixture
10 was then concentrated under high vacuum and reacted in step b without any further purification.

b) 3-[3-(2,4-Dichlorobenzoyl)ureido]-4-methoxybenzoic acid

15 2-Chlorobenzoyl isocyanate (step a) was taken up in 8 ml of acetonitrile, and a suspension of 1.1 g (6 mmol) of 4-amino-3-nitrobenzoic acid in 24 ml of acetonitrile was added. The mixture was heated to reflux for 3.5 hours and, after it had been cooled down, the precipitate was filtered off, washed with acetonitrile and dried in vacuo. 1.68 g (77%) of the desired product
20 were obtained.

M.p.: 240°C (decomposition)

Example 2:

25 a) 4-[3-(2-Chloro-4,5-difluorobenzoyl)ureido]-3-trifluoromethoxybenzoic acid

The compound was prepared in a one-pot reaction.

30.0 g (155.8 mmol) of 2-chloro-4,5-difluorobenzoic acid were initially
30 introduced, under a protective gas atmosphere, in a 1 l round-bottomed flask fitted with a gastight mechanical stirrer and a distillation head. After 300 ml of toluene had been added, 29.01 ml of thionyl chloride were added while stirring and the mixture was heated to 60°C. At 60°C, the reaction mixture was subsequently stirred for 1.5 h, after which 0.1 ml of pyridine
35 was added. After a further 1.5 h at 60°C, 90 ml of liquid were distilled off from the mixture under normal pressure (maximum bath temperature, 125°C). The reaction solution was then cooled down to 20°C and ammonia gas was passed in at 20-35°C (cooling with an ice bath) until the solution was saturated. After that, 160 ml of THF and 120 ml of deionized water

were added to the mixture at 20°C. The aqueous phase was separated off and the organic phase was washed with a 5% aqueous solution of sodium hydrogen carbonate. The organic phase was then azeotropically dried by distilling off 250 ml of liquid in vacuo at 50°C. 17 ml of oxalyl chloride were added to the reaction suspension, which had been cooled down to 20°C. The mixture was subsequently stirred at 20°C for 2 h and then stirred at 50°C for 4 h. 200 ml of liquid were distilled off from the mixture in vacuo at 50°C, after which 200 ml of toluene were added and 200 ml of liquid were once again distilled off in vacuo at 50°C. The mixture was cooled down to 20°C and a solution of 26.49 g (119.8 mmol) of 4-amino-3-(trifluoromethoxy)benzoic acid in 75 ml of THF was added. The product was separated off by filtration through a glass suction filter and dried to constant weight in vacuo at 50°C. 52.6 g of the desired product were obtained.

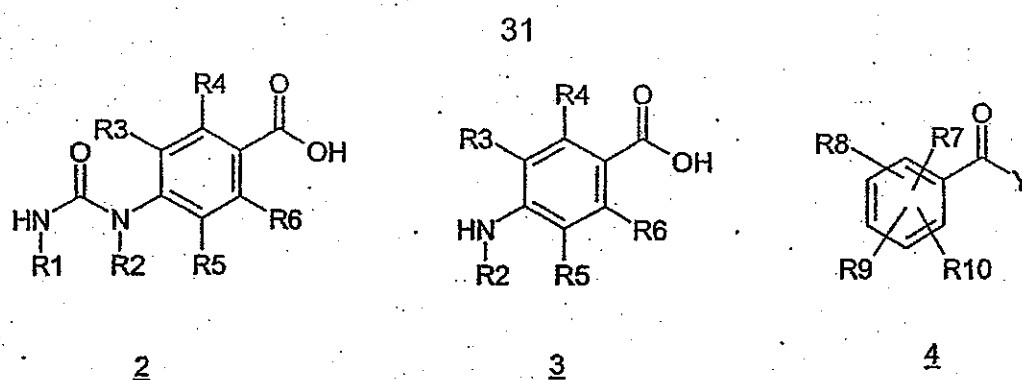
M.p.: 236°C

b) 4-[3-(2-Chloro-4,5-difluorobenzoyl)ureido]-3-trifluoromethoxybenzoic acid TRIS salt

A mixture of 10.0 g (22.79 mmol) of 4-[3-(2-chloro-4,5-difluorobenzoyl)ureido]-3-trifluoromethoxybenzoic acid and 3.0 g of α,α,α -tris(hydroxymethyl)methylamine were heated to reflux in 400 ml of 2-propanol until a clear solution was formed. The solution was filtered in the hot and concentrated down to a volume of 310 ml. The product crystallized from the solution on cooling down to 20°C. 10.4 g of the desired product were obtained.

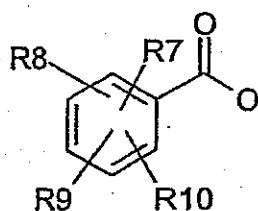
M.p.: 176°C

The compounds of formula I can be prepared by reacting ureas of the formula 2 or aniline derivatives of the formula 3 with aroyl isocyanates, with reactive acid derivatives, with acid chlorides or with anhydrides, of the formula 4,



in which R1 to R6 have the abovementioned meanings. The resulting free acids of the formula I can then be converted, with the corresponding bases,
 5 into the corresponding physiologically tolerated salts of the compounds of the formula I.

For clarification: if formula 4 is an acid chloride, Y is Cl, if 4 is an isocyanate, Y is N=C=O, and if 4 is an anhydride, Y is

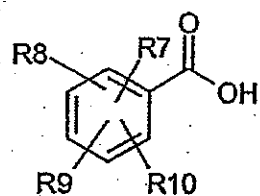


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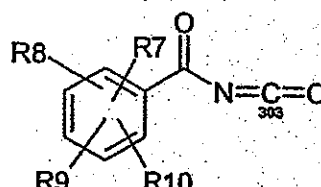
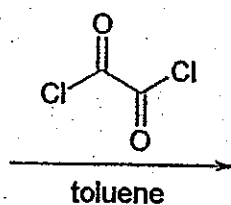
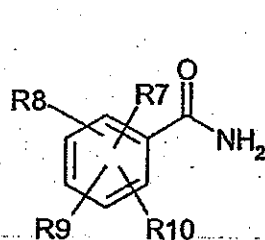
Preference is given to the method of preparing the compounds of the formula I by way of the aroyl isocyanate 4a, as depicted in the following scheme:

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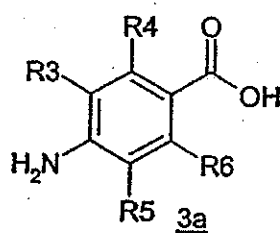
for example:



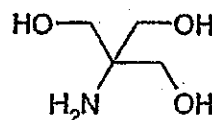
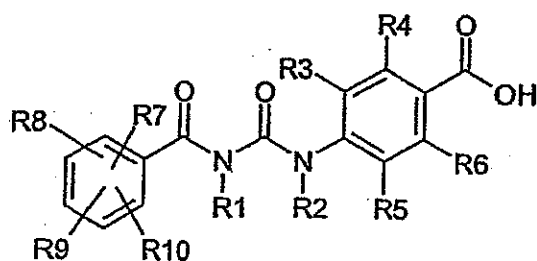
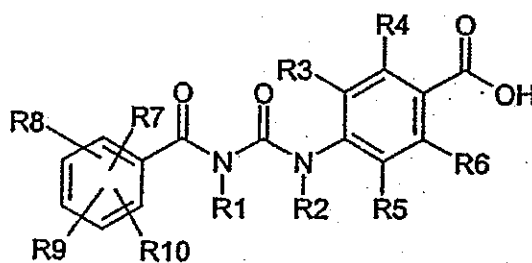
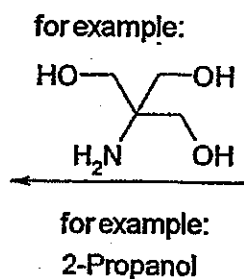
1. SOCl_2 , toluene
2. $\text{NH}_3(\text{g})$
3. THF, H_2O
4. $\text{NaHCO}_3(\text{aq})$



not isolated



1. Toluene/THF
2. H_2O

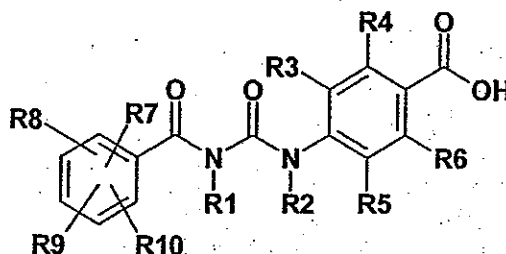


The preparation of I can, in a general manner, take place in a one-pot

process, thereby greatly simplifying its industrial-scale preparation. For this, 4b is converted into the acid chloride in a suitable solvent, for example toluene, using a suitable reagent, such as thionyl chloride or oxalyl chloride. As required, a suitable catalyst, such as pyridine, NMP or DMF, is added for the purpose of completing the reaction. After the unreacted reagent (such as thionyl chloride) has been removed, the acid chloride is converted into the acid amide 4b using suitable reagents, such as passing ammonia gas into the reaction solution or adding a solution of ammonia in a suitable solvent, such as THF. Sufficient water and a suitable solvent, such as THF, are added to the reaction mixture to ensure that any solid goes into solution. After the phases have separated, washing takes place with sodium hydrogen carbonate solution and the organic phase is subsequently dried. The acid amide 4b is converted into the aroyl isocyanate 4a by adding oxalyl chloride and then heating. After the unreacted oxalyl chloride has been removed, the aniline 3a is dissolved in a suitable solvent, such as THF, and added to the solution of the aroyl isocyanate 4a, with the reaction product precipitating from the solution. The compound of the formula I is separated off by filtration. The TRIS salt of the compound of the formula I crystallizes after the compound of the formula I has been dissolved with TRIS at boiling heat in a suitable solvent, such as 2-propanol, when the solution is subsequently cooled.

Patent Claims:

1. A compound of the formula I,



in which

R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br, OH, NO₂, CN, O-(C₁-C₆)-alkyl, O-(C₂-C₆)-alkenyl, O-(C₂-C₆)-alkynyl, O-SO₂-(C₁-C₄)-alkyl, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl or (C₂-C₆)-alkynyl, where alkyl, alkenyl and alkynyl can be substituted, once or more than once, by F, Cl or Br;

R1 and R2 are, independently of each other, H, (C₁-C₆)-alkyl, where alkyl can be substituted by OH, O-(C₁-C₄)-alkyl, NH₂, NH(C₁-C₄)-alkyl or N[(C₁-C₆)-alkyl]₂, O-(C₁-C₆)-alkyl, CO-(C₁-C₆)-alkyl, COO-(C₁-C₆)-alkyl, (C₁-C₆)-alkylene-COOH or (C₁-C₆)-alkylene-COO-(C₁-C₆)-alkyl;

R3 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);

R4 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);

- 5 R5 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);
- 10 R6 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11, COOR11 or N(R16)(R17);
- 15 R11 is H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl or (C₂-C₈)-alkynyl, where alkyl, alkenyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OH or O-(C₁-C₄)-alkyl;
- 20 R12 and R13 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl, phenyl or SO₂-phenyl, where the phenyl ring can be substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;
- 25 or R12 and R13 form, together with the nitrogen atom to which they are bonded, a 3-7-membered, saturated heterocyclic ring which can contain up to 2 further heteroatoms from the group N, O or S and where the heterocyclic ring can be substituted, up to four times, by F, Cl, Br, OH, Oxo, (C₁-C₄)-alkyl or N(R14)(R15);
- 30 R14 and R15 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl, phenyl or SO₂-phenyl, where the phenyl ring can be substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl,
- 35

O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO(C₁-C₆)-alkyl or CONH₂;

5 R16 and R17 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl, phenyl or SO₂-phenyl, where the phenyl ring can be substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂;

10 or R16 and R17 form, together with the nitrogen atom to which they are bonded, a 3-7-membered, saturated heterocyclic ring which can contain up to 2 further heteroatoms from the group N, O or S and where the heterocyclic ring can be substituted, up to four times, by F, Cl, Br, OH, Oxo, (C₁-C₄)-alkyl or N(R14)(R15);

15 it always being the case that at least one of the radicals R3, R7, R8, R9 and R10 is not hydrogen,

20 and the physiologically tolerated salts thereof.

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

25 R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br, OH, NO₂, CN, (C₁-C₆)-alkyl or O-(C₁-C₆)-alkyl, where alkyl can be substituted, once or more than once, by F;

30 R1 and R2 are H;

R3 is H, F, Cl, Br, NO₂, CN, O-R11, unsubstituted O-phenyl, S-R11, COOR11, N(R12)(R13), (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₃-C₇)-cycloalkyl or (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkylene, where alkyl, cycloalkyl and alkynyl can be substituted, once or more than once, by F, Cl, Br, OR11 or COOR11;

R4 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted, once or more than once, by F;

- R5 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted, once or more than once, by F;
- 5 R6 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted, once or more than once, by F;
- R11 is H, (C₁-C₈)-alkyl, (C₁-C₈)-alkylene-O-(C₁-C₈)-alkyl or (C₁-C₈)-alkyl-OH, where alkyl can be substituted, once or
10 more than once, by F;
- R12 and R13 are, independently of each other, H or (C₁-C₈)-alkyl;
or R12 and R13 form, together with the nitrogen atom to which they are
bonded, a 3-7-membered, saturated heterocyclic ring which
15 can contain up to 2 further heteroatoms from the group N, O
or S and where the heterocyclic ring can be substituted, up to
four times, by F, Cl, Br, OH, Oxo, (C₁-C₄)-alkyl or
N(R14)(R15);
- 20 R14 and R15 are, independently of each other, H, (C₁-C₈)-alkyl, (C₂-C₈)-
alkenyl, (C₂-C₈)-alkynyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-
(C₁-C₄)-alkylene, COO-(C₁-C₄)-alkyl, COO-(C₂-C₄)-alkenyl,
phenyl or SO₂-phenyl, where the phenyl ring can be
substituted, up to two times, by F, Cl, CN, OH, (C₁-C₆)-alkyl,
25 O-(C₁-C₆)-alkyl, CF₃, OCF₃, COOH, COO(C₁-C₆)-alkyl or
CONH₂;

and the physiologically tolerated salts thereof.

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

R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br,
CH₃ or CF₃;

- 35 R1, R2, R5 are H;

R3 is H, F, Cl, NO₂, CF₃, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl,
where alkyl can be substituted once or more than once by F;

- R4 is H, F, Cl, NO₂, CF₃, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted once or more than once by F;
- 5 R6 is H, F, Cl, NO₂, CF₃, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted once or more than once by F;
- R11 is H or (C₁-C₈)-alkyl, where alkyl can be substituted once or more than once by F,
- 10 R12 and R13 are H or (C₁-C₈)-alkyl;
- or the two radicals R12 and R13 form, together with the nitrogen atom to which they are bonded, a 5-6-membered, saturated heterocyclic ring which can contain a further oxygen atom;
- 15 and the physiologically tolerated salts thereof.
4. A compound of the formula I as claimed in one or more of claims 1 to 3, wherein
- 20 R7, R8, R9 and R10 are, independently of each other, H, F, Cl, Br, CH₃ or CF₃;
- R1, R2, R4, R5 and R6 are H;
- 25 R3 is H, F, Cl, NO₂, O-R11, N(R12)(R13) or (C₁-C₆)-alkyl, where alkyl can be substituted once or more than once by F;
- R11 is H or (C₁-C₈)-alkyl, where alkyl can be substituted once or more than once by F,
- 30 R12 and R13 are H or (C₁-C₈)-alkyl;
- or the two radicals R12 and R13 form, together with the nitrogen atom to which they are bonded, a 5-6-membered, saturated heterocyclic ring which can contain a further oxygen atom;
- 35 and the physiologically tolerated salts thereof.
5. A compound of the formula I as claimed in one or more of claims 1

to 4, wherein it is, in each case, the tromethamol salt.

6. A pharmaceutical which comprises one or more of the compounds as claimed in one or more of claims 1 to 5.

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7. A pharmaceutical which comprises one or more of the compounds as claimed in one or more of claims 1 to 5 and one or more blood sugar-lowering active compounds.

10

8. A pharmaceutical which comprises one or more of the compounds as claimed in one or more of claims 1 to 5 and one or more statins.

9. The use of the compounds as claimed in one or more of claims 1 to 5 for producing a medicament for treating type 2 diabetes.

15

10. The use of the compounds as claimed in one or more of claims 1 to 5 for producing a medicament for lowering blood sugar.

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11. The use of the compounds as claimed in one or more of claims 1 to 5 in combination with at least one further blood sugar-lowering active compound for producing a medicament for treating type 2 diabetes.

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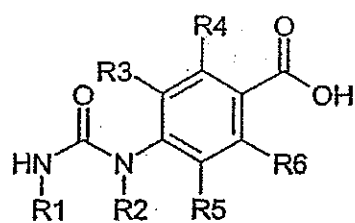
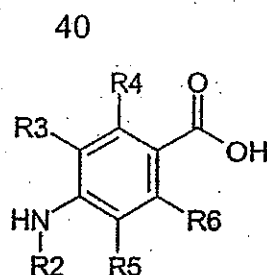
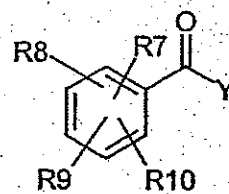
12. The use of the compounds as claimed in one or more of claims 1 to 5 in combination with at least one further blood sugar-lowering active compound for producing a medicament for lowering blood sugar.

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13. A process for producing a pharmaceutical which comprises one or more of the compounds as claimed in one or more of claims 1 to 5, which comprises mixing the active compound with a pharmaceutically suitable excipient and bringing this mixture into a form which is suitable for administration.

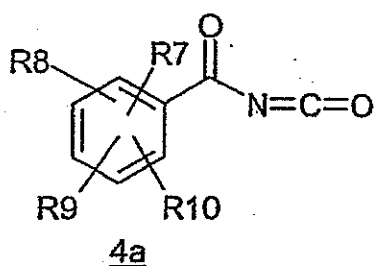
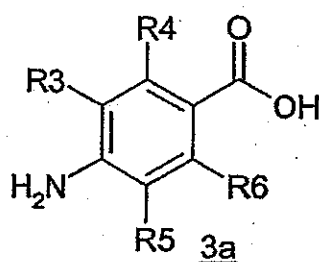
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14. A process for preparing the compounds of the formula 1, which comprises reacting ureas of the formula 2 or aniline derivatives of the formula 3 with aroyl isocyanates, with reactive acid derivatives, with acid chlorides or with anhydrides, of the formula 4,

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in which R1 to R10 have the meanings given in claim 1.

- 5 15. The process for preparing the compounds of the formula I as claimed in claim 14, wherein aroyl isocyanate of the formula 4a is reacted with acid of the formula 3a,

4a3a

10

in which R1 to R10 have the meanings given in claim 1.

16. A process for preparing the physiologically tolerated salts of the compounds of the formula I, which comprises reacting the free acids of the compounds of the formula I with a corresponding base.

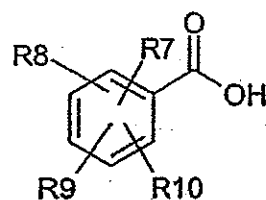
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17. The process as claimed in claim 16, wherein the base is α,α,α -tris-(hydroxymethyl)methylamine (tromethamol).

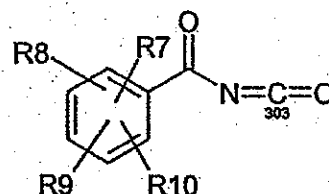
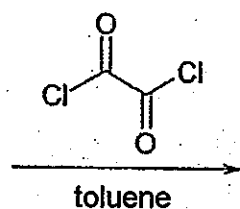
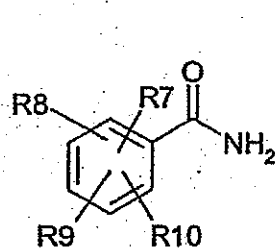
- 20 18. A process for preparing the compounds of the formula I, which comprises, in accordance with the following reaction scheme in which R1 to R10 have the meanings given in claim 1,

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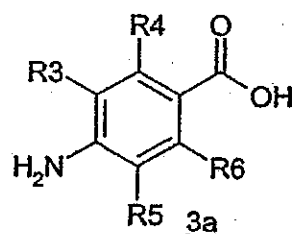
for example:



1. SOCl_2 , toluene
2. $\text{NH}_3(\text{g})$
3. THF, H_2O
4. $\text{NaHCO}_3(\text{aq})$



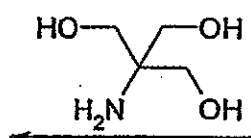
not isolated



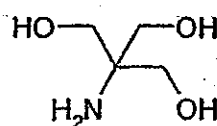
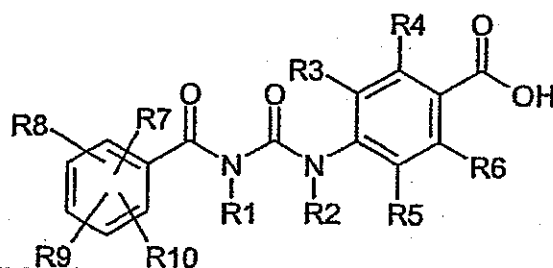
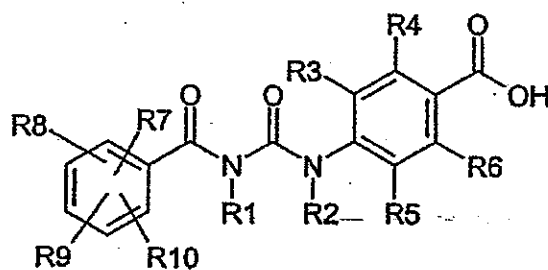
for example:

1. Toluene/THF
2. H_2O

for example:



for example:
2-Propanol



in a first step, using a suitable reagent to convert the compound 4b, in a solvent which is suitable for the purpose, into the acid chloride, and

5 in a second step, using a suitable reagent to convert the resulting acid chloride, in a solvent which is suitable for the purpose, into the acid amide 4b, and

10 in a third step, converting the acid amide 4b, by reacting it with oxalyl chloride, into the aroyl isocyanate 4a, and

in a fourth step, reacting the aroyl isocyanate 4a with the aniline 3a, in a suitable solvent, to give the free acid of the compound of the formula I, and

15 in a fifth step, reacting the free acid of the compound of the formula I with a base to give a physiologically tolerated salt of the compound of the formula 1.