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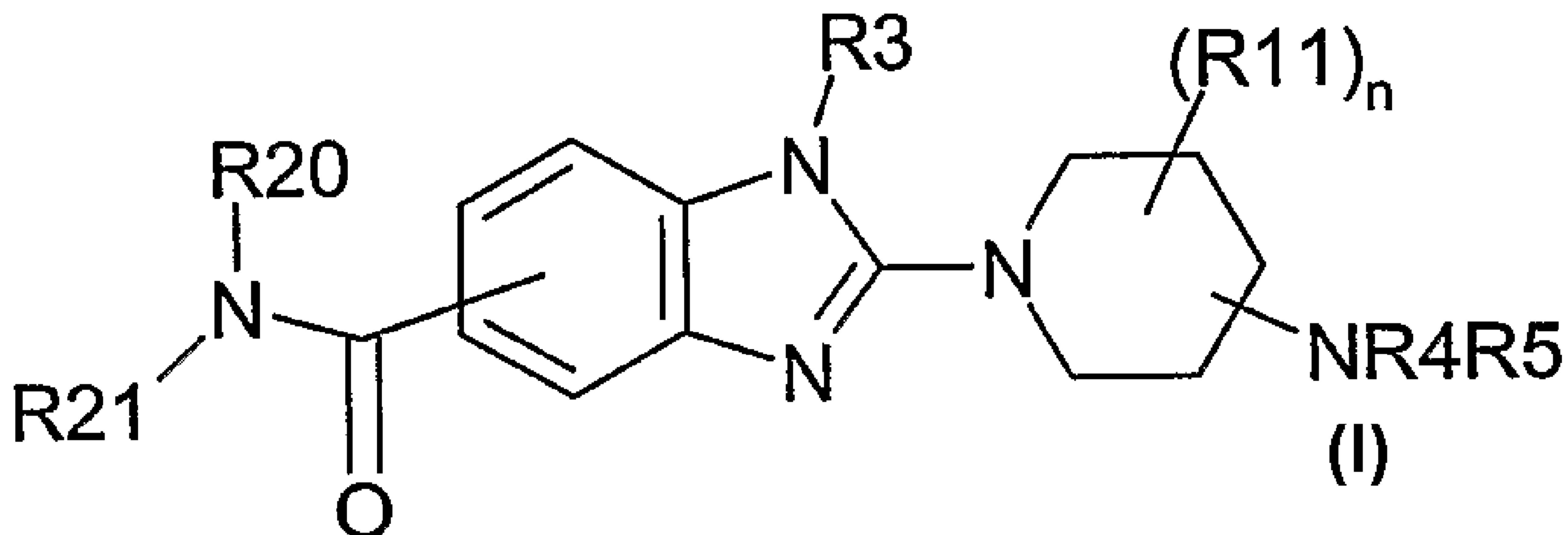
(71) Demandeur/Applicant:
SANOFI-AVENTIS, FR

(72) Inventeurs/Inventors:
DEFOSA, ELIZABETH, DE;
SCHOENAFINGER, KARL, DE;
JAEHNE, GERHARD, DE;
BUNNING, CHRISTIAN, DE;
TSCHANK, GEORG, DE;
WERNER, ULRICH, DE

(74) Agent: BERESKIN & PARR

(54) Titre : 8-N-BENZIMIDAZOLES A SUBSTITUTION AMIDE, LEUR PROCEDE DE PRODUCTION, ET LEUR UTILISATION EN TANT QUE MEDICAMENTS

(54) Title: AMIDE-SUBSTITUTED 8-N-BENZIMIDAZOLES, METHOD FOR THE PRODUCTION THEREOF, AND USE OF THE SAME AS MEDICAMENTS



(57) Abrégé/Abstract:

The invention relates to amide-substituted 8-N-benzimidazoles, and to the physiologically acceptable salts and physiologically functional derivatives thereof. The invention also relates to compounds of formula (I) wherein the radicals have the cited designations, and to the physiologically acceptable salts thereof. The compounds are suitable, for example, as medicaments for the prevention and treatment of diabetes type 2.

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(71) Applicant (for all designated States except US): SANOFI-AVENTIS DEUTSCHLAND GMBH [DE/DE]; Brüningstrasse 50, 65929 Frankfurt am Main (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DEFOSSA, Elizabeth [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). SCHOENAFINGER, Karl [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). JAEHNE, Gerhard [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). BUNNING, Christian [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). TSCHANK, Georg [AT/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). WERNER, Ulrich [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE).

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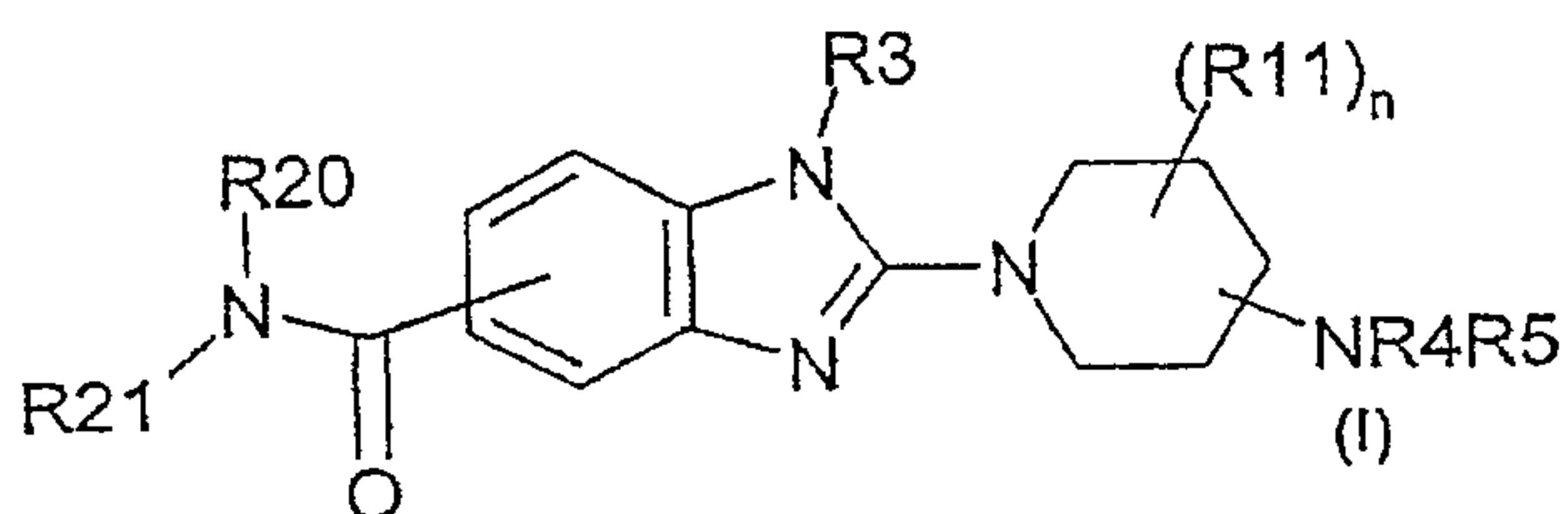
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(54) Title: AMIDE-SUBSTITUTED 8-N-BENZIMIDAZOLES, METHOD FOR THE PRODUCTION THEREOF, AND USE OF THE SAME AS MEDICAMENTS

(54) Bezeichnung: AMID SUBSTITUIERTE 8-N-BENZIMIDAZOLE, VERFAHREN ZU IHRER HERSTELLUNG UND IHRE VERWENDUNG ALS ARZNEIMITTEL



Description

Amide-substituted 8-N-benzimidazoles, method for the production thereof, and use of the same as medicaments

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The invention relates to amide-substituted 8-N-benzimidazoles and to the physiologically compatible salts and physiologically functional derivatives thereof.

EP 1069124 describes 2-benzimidazolylamines as ORL-1 receptor agonists.

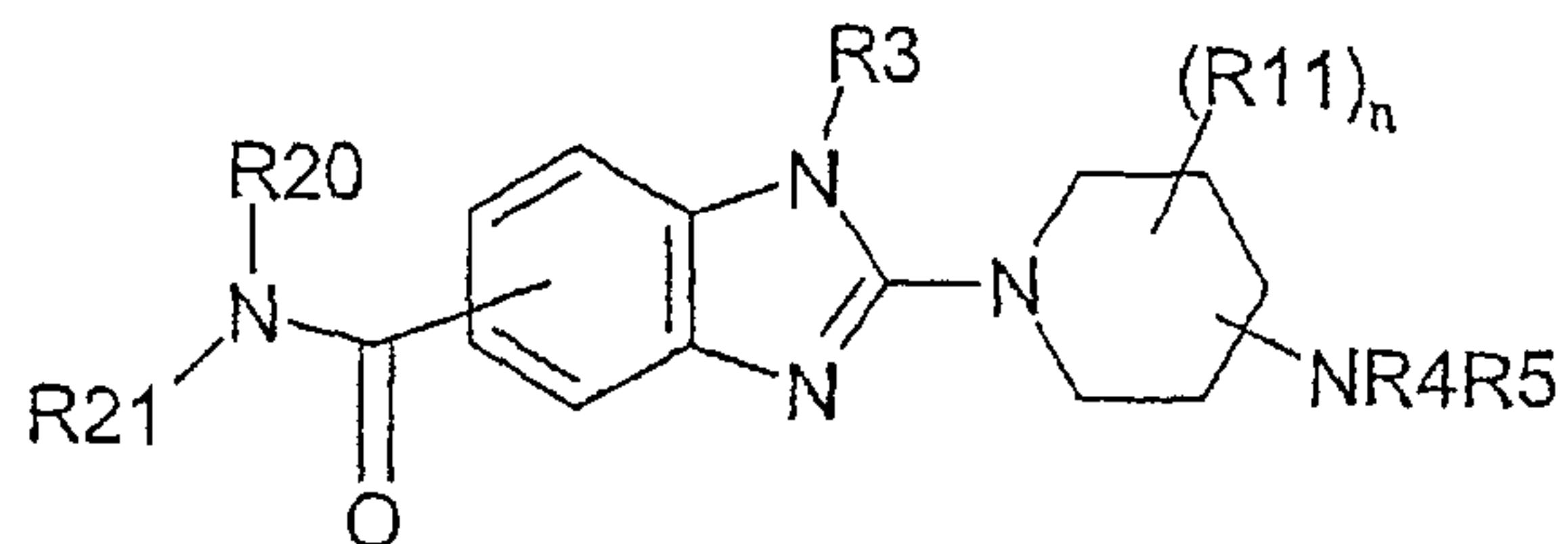
10 WO 97/12615 describes benzimidazole derivatives as 15-LO inhibitors.

WO 02/04425 describes structurally similar virus polymerase inhibitors.

WO 02/46168 describes benzimidazole derivatives for treating Alzheimer's disease.

15 It was therefore an object of the invention to provide compounds which display a therapeutically utilizable blood sugar-lowering action. These compounds should be particularly suitable for treating diabetes.

The invention therefore relates to compounds of the formula I



I

20

in which

R20 is H, (C₁-C₃)-alkyl, where (C₁-C₃)-alkyl is mono- or polysubstituted by CN, NO₂, SH, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl; (C₄-C₆)-alkyl, where (C₄-C₆)-alkyl is mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

(C₇-C₁₀)-alkyl, (C₃-C₁₀)-cycloalkyl, (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl (C₁-C₆)-alkylene-(C₆-C₁₀)-heterocyclyl or S(O)₂-aryl, where the alkyl, cycloalkyl, alkenyl, alkynyl, alkylene, aryl and heterocyclyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

5

R21 is (C₁-C₃)-alkyl, where (C₁-C₃)-alkyl is mono- or polysubstituted by CN, NO₂, SH, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

10

(C₄-C₆)-alkyl, where (C₄-C₆)-alkyl is mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl; (C₇-C₁₀)-alkyl, (C₃-C₁₀)-cycloalkyl, (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl (C₁-C₆)-alkylene-(C₆-C₁₀)-heterocyclyl or S(O)₂-aryl, where the alkyl, cycloalkyl, alkenyl, alkynyl, alkylene, aryl and heterocyclyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

15

excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

20

R3 is (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₃)-alkyl, phenyl, pyridyl, where the alkyl, cycloalkyl, cycloalkylalkyl, phenyl and pyridyl radicals are mono- or polysubstituted by CN, NO₂, -CF₃, -OCF₃, OR12, NR7R8, NR7CONR7R8, COR7, OCOR7, OCOOR7, COOR7, CONR7R8 or OCONR7R8;

25

(C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where the alkenyl, alkynyl, aryl, heterocyclyl and alkylenearyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, OH, (C₁-C₆)-alkyl, -CF₃, -OCF₃, OR7, NR7R8, NR7CONR7R8, COR7, OCOR7, OCOOR7, COOR7, CONR7R8 or OCONR7R8;

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excluding the definitions of unsubstituted phenyl and unsubstituted pyridyl, and also phenyl and pyridyl each substituted by F, Cl, Br, I, OH or (C₁-C₆)-alkyl, from the R3 radical;

R7, R8 are each independently H, (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR9R10, CONR9R10, (C₁-C₆)-alkylene-

5 COOR9, COOR9, COR9, (C₁-C₆)-alkylene-COR9, (C₁-C₆)-alkylene-OR9, (C₁-C₆)-alkylene-NR9R10, (C₁-C₆)-alkylene-SR9, (C₁-C₆)-alkylene-S(O)R9, (C₁-C₆)-alkylene-S(O)₂R9, S(O)R9, S(O)₂R9, (C₁-C₄)-alkylene-(C₆-C₁₀)-aryl or (C₁-C₄)-alkylene-heterocyclyl;

10

R9, R10 are each independently H, (C₁-C₆)-alkyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, -(C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-heterocyclyl;

15

R12 is (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR9R10, CONR9R10, (C₁-C₆)-alkylene-COOR9, COOR9, COR9, (C₁-C₆)-alkylene-COR9, (C₁-C₆)-alkylene-OR9, (C₁-C₆)-alkylene-NR9R10, (C₁-C₆)-alkylene-SR9, (C₁-C₆)-alkylene-S(O)R9, (C₁-C₆)-alkylene-S(O)₂R9, S(O)R9, S(O)₂R9, (C₂-C₄)-alkylene-(C₆-C₁₀)-aryl or (C₁-C₄)-alkylene-heterocyclyl;

20

R4, R5 are each independently H, (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl, where (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl may be substituted by F, Cl, Br, I, CN, aryl, heterocyclyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, OH, O(C₁-C₆)-alkyl, Oaryl, Oheteroaryl, S(C₁-C₆)-alkyl, S(O)(C₁-C₆)-alkyl or S(O)₂(C₁-C₆)-alkyl, where these alkyl groups may in turn be substituted by F, Cl, Br or I;

25

R11 is H, F, Cl, Br, I, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl, NH₂, NH(C₁-C₆)-alkyl, NH(C₃-C₇)-cycloalkyl, N((C₁-C₆)-alkyl)₂ or O-(C₁-C₆)-alkyl, where the alkyl groups may be mono- or polysubstituted by F, Cl, Br or I;

30

n is 0, 1 or 2;

and physiologically compatible salts thereof.

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

5 R20 is H;

10 R21 is (C₃-C₁₀)-cycloalkyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, phenyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-pyridyl, where the cycloalkyl, aryl and pyridyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;
excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

15 R3 is (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₃)-alkyl, phenyl, pyridyl, where the alkyl, cycloalkyl, cycloalkylalkyl, phenyl and pyridyl radicals are mono- or polysubstituted by CN, NO₂, -CF₃, -OCF₃, OR12, NR7R8, NR7CONR7R8, COR7, OCOR7, OCOOR7, COOR7, CONR7R8 or OCONR7R8;

20 (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where the alkenyl, alkynyl, aryl, heterocyclyl and alkylenearyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, OH, (C₁-C₆)-alkyl, -CF₃, -OCF₃, OR7, NR7R8, NR7CONR7R8, COR7, OCOR7, OCOOR7, COOR7, CONR7R8 or OCONR7R8;

25 excluding the definitions of unsubstituted phenyl and unsubstituted pyridyl, and also phenyl and pyridyl each substituted by F, Cl, Br, I, OH or (C₁-C₆)-alkyl, from the R3 radical;

30 R7, R8 are each independently H, (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR9R10, CONR9R10, (C₁-C₆)-alkylene-COOR9, COOR9, COR9, (C₁-C₆)-alkylene-COR9, (C₁-C₆)-alkylene-OR9, (C₁-C₆)-alkylene-NR9R10, (C₁-C₆)-alkylene-SR9, (C₁-C₆)-alkylene-S(O)R9,

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(C₁-C₆)-alkylene-S(O)₂R9, S(O)R9, S(O)₂R9, (C₁-C₄)-alkylene-(C₆-C₁₀)-aryl or (C₁-C₄)-alkylene-heterocyclyl;

R9, R10 are each independently H, (C₁-C₆)-alkyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, -(C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-heterocyclyl;

5 R12 is (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR9R10, CONR9R10, (C₁-C₆)-alkylene-COOR9, COOR9, COR9, (C₁-C₆)-alkylene-COR9, (C₁-C₆)-alkylene-OR9, (C₁-C₆)-alkylene-NR9R10, (C₁-C₆)-alkylene-SR9, (C₁-C₆)-alkylene-S(O)R9, (C₁-C₆)-alkylene-S(O)₂R9, S(O)R9, S(O)₂R9, (C₂-C₄)-alkylene-(C₆-C₁₀)-aryl or (C₁-C₄)-alkylene-heterocyclyl;

10 R4, R5 are each independently H, (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl, where (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl may be substituted by F, Cl, Br, I, CN, aryl, heterocyclyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, OH, O(C₁-C₆)-alkyl, Oaryl, Oheteroaryl, S(C₁-C₆)-alkyl, S(O)(C₁-C₆)-alkyl or S(O)₂(C₁-C₆)-alkyl, where these alkyl groups may in turn be substituted by F, Cl, Br or I;

15 R11 is H, F, Cl, Br, I, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl, NH₂, NH(C₁-C₆)-alkyl, NH(C₃-C₇)-cycloalkyl, N((C₁-C₆)-alkyl)₂ or O-(C₁-C₆)-alkyl, where the alkyl groups may be mono- or polysubstituted by F, Cl, Br or I;

20 n is 0, 1 or 2;

25

and physiologically compatible salts thereof.

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

30

R20 is H;

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R21 is (C_3-C_{10}) -cycloalkyl, (C_1-C_6) -alkylene- (C_6-C_{10}) -aryl, phenyl, (C_1-C_6) -alkylene- (C_6-C_{10}) -pyridyl, where the cycloalkyl, aryl and pyridyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C_1-C_6) -alkyl, O- (C_1-C_6) -alkyl or S- (C_1-C_6) -alkyl;

5 excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

R3 is independently (C_2-C_{10}) -alkenyl or (C_1-C_6) -alkylene- (C_6-C_{10}) -aryl, where the alkenyl and (C_1-C_6) -alkylene- (C_6-C_{10}) -aryl radicals may be mono- or 10 polysubstituted by F, Cl, Br;

R4, R5 are each H;

n is 0;

15

and physiologically compatible salts thereof.

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

20

R20 is H;

R21 is (C_3-C_{10}) -cycloalkyl, benzyl, pyridyl, phenyl, where the alkyl, cycloalkyl and benzyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, 25 OH, (C_1-C_6) -alkyl, O- (C_1-C_6) -alkyl or S- (C_1-C_6) -alkyl;

excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

R3 is independently (C_2-C_{10}) -alkenyl or (C_1-C_6) -alkylene- (C_6-C_{10}) -aryl, where the alkenyl and (C_1-C_6) -alkylene- (C_6-C_{10}) -aryl radicals may be mono- or 30 polysubstituted by F, Cl, Br;

R4, R5 are each H;

n is 0;

5 and physiologically compatible salts thereof.

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

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

Owing to their higher water solubility, pharmaceutically acceptable salts are particularly suitable for medical applications compared to the starting or base compounds. These salts must 15 have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the inventive compounds are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid and sulfuric acid, and organic acids, for example acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isethionic acid, lactic acid, 20 lactobionic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, p-toluenesulfonic acid and tartaric acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts) and salts of trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

25

Salts with a pharmaceutically unacceptable anion, for example trifluoroacetate, are likewise included in the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for the use in non-therapeutic, for example in vitro, applications.

30

The term "physiologically functional derivative" used here refers to any physiologically compatible derivative of an inventive compound of the formula I, for example an ester which,

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on administration to a mammal, for example the human, is capable (directly or indirectly) of forming a compound of the formula I or an active metabolite thereof.

The physiologically functional derivatives also include prodrugs of the inventive compounds.

5 Such prodrugs can be metabolized in vivo to give an inventive compound. These prodrugs may or may not themselves be active.

The inventive compounds may also be present in various polymorphic forms, for example as amorphous and crystalline polymorphic forms. All polymorphic forms of the inventive 10 compounds are included within the scope of the invention and are a further aspect of the invention.

Hereinafter, all references to "compound(s) of the formula (I)" relate to compound(s) of the formula I as described above, and also their salts, solvates and physiologically functional 15 derivatives as described herein.

An alkyl radical is understood to mean a straight-chain or branched hydrocarbon chain having one or more carbons, for example methyl, ethyl, isopropyl, tert-butyl, hexyl.

20 The alkyl radicals may be mono- or polysubstituted by suitable groups, for example: F, Cl, Br, I, CF₃, NO₂, N₃, CN, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, cycloalkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-aryl, O-CO-(C₁-C₆)-heterocycle; 25 PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-aryl, S-(CH₂)_n-heterocycle, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-aryl, SO-(CH₂)_n-heterocycle, SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)_n-aryl, SO₂-(CH₂)_n-heterocycle, SO₂-NH(CH₂)_n-aryl, SO₂-NH(CH₂)_n-heterocycle, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-aryl, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-heterocycle, SO₂-N((CH₂)_n-aryl)₂, SO₂-N((CH₂)_n-heterocycle)₂ where n may be 0 – 6 and the aryl radical or heterocyclic radical may be up to disubstituted by F, Cl, Br, OH, CF₃, NO₂, CN, 30 OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; C(=NH)(NH₂), NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH-CO-(C₁-C₆)-alkyl, NH-COO-(C₁-C₆)-alkyl, NH-CO-aryl, NH-CO-heterocycle, NH-COO-aryl, NH-COO-heterocycle, NH-

CO-NH-(C₁-C₆)-alkyl, NH-CO-NH-aryl, NH-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-COO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-aryl, N((C₁-C₆)-alkyl)-CO-heterocycle, N((C₁-C₆)-alkyl)-COO-aryl, N((C₁-C₆)-alkyl)-COO-heterocycle, N((C₁-C₆)-alkyl)-CO-NH-(C₁-C₆)-alkyl), N((C₁-C₆)-alkyl)-CO-NH-aryl, N((C₁-C₆)-alkyl)-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-aryl, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-heterocycle, N((C₁-C₆)-alkyl)-CO-N(aryl)₂, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-aryl, N((C₁-C₆)-alkyl)-CO-N(aryl)-heterocycle, N((C₁-C₆)-alkyl)-CO-N(aryl)-CO-N(aryl)₂, N((C₁-C₆)-alkyl)-CO-N(aryl)-CO-N(aryl)-heterocycle, N((C₁-C₆)-alkyl)-CO-N(aryl)-CO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-COO-(C₁-C₆)-alkyl, N(heterocycle)-COO-(C₁-C₆)-alkyl, N(aryl)-CO-aryl, N(heterocycle)-CO-aryl, N(aryl)-COO-aryl, N(heterocycle)-COO-aryl, N(aryl)-CO-NH-(C₁-C₆)-alkyl), N(heterocycle)-CO-NH-(C₁-C₆)-alkyl), N(aryl)-CO-NH-aryl, N(heterocycle)-CO-NH-aryl, N(aryl)-CO-N((C₁-C₆)-alkyl)₂, N(heterocycle)-CO-N((C₁-C₆)-alkyl)₂, N(aryl)-CO-N((C₁-C₆)-alkyl)-aryl, N(heterocycle)-CO-N((C₁-C₆)-alkyl)-aryl, N(aryl)-CO-N(aryl)₂, N(heterocycle)-CO-N(aryl)₂, aryl, O-(CH₂)_n-aryl and O-(CH₂)_n-heterocycle, where n may be 0 – 6, where the aryl radical or heterocyclic radical may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂.

An alkenyl radical is understood to mean a straight-chain or branched hydrocarbon chain having two or more carbons and one or more double bonds, for example vinyl, allyl, pentenyl, 2-methyl-but-2-en-4-yl.

The alkenyl radicals may be mono- or polysubstituted by suitable groups, for example: F, Cl, Br, I, CF₃, NO₂, N₃, CN, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, cycloalkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-aryl, O-CO-(C₁-C₆)-heterocycle; PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-aryl, S-(CH₂)_n-heterocycle, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-aryl, SO-(CH₂)_n-heterocycle, SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)_n-aryl, SO₂-(CH₂)_n-heterocycle, SO₂-NH(CH₂)_n-aryl, SO₂-NH(CH₂)_n-heterocycle, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-aryl, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-heterocycle, SO₂-N((CH₂)_n-aryl)₂, SO₂-N((CH₂)_n-heterocycle)₂ where n may be 0 – 6 and the aryl radical or heterocyclic radical may be up to disubstituted by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂;

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C(=NH)(NH₂), NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH-CO-(C₁-C₆)-alkyl, NH-COO-(C₁-C₆)-alkyl, NH-CO-aryl, NH-CO-heterocycle, NH-COO-aryl, NH-COO-heterocycle, NH-CO-NH-(C₁-C₆)-alkyl, NH-CO-NH-aryl, NH-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-COO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-aryl, N((C₁-C₆)-alkyl)-CO-heterocycle, N((C₁-C₆)-alkyl)-COO-aryl, N((C₁-C₆)-alkyl)-COO-heterocycle, N((C₁-C₆)-alkyl)-CO-NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-NH-aryl, N((C₁-C₆)-alkyl)-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)₂, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-aryl, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-heterocycle, N((C₁-C₆)-alkyl)-CO-N(aryl)₂, N((C₁-C₆)-alkyl)-CO-N-(heterocycle)₂, N(aryl)-CO-(C₁-C₆)-alkyl, N(heterocycle)-CO-(C₁-C₆)-alkyl, N(aryl)-COO-(C₁-C₆)-alkyl, N(heterocycle)-COO-(C₁-C₆)-alkyl, N(aryl)-CO-aryl, N(heterocycle)-CO-aryl, N(aryl)-COO-aryl, N(heterocycle)-COO-aryl, N(aryl)-CO-NH-(C₁-C₆)-alkyl, N(heterocycle)-CO-NH-(C₁-C₆)-alkyl, N(aryl)-CO-NH-aryl, N(heterocycle)-CO-NH-aryl, N(aryl)-CO-NH-alkyl, N(heterocycle)-CO-NH-alkyl, N(aryl)-CO-N((C₁-C₆)-alkyl)₂, N(heterocycle)-CO-N((C₁-C₆)-alkyl)₂, N(aryl)-CO-N((C₁-C₆)-alkyl)-aryl, N(heterocycle)-CO-N((C₁-C₆)-alkyl)-aryl, N(aryl)-CO-N(aryl)₂, N(heterocycle)-CO-N-(aryl)₂, aryl, O-(CH₂)_n-aryl and O-(CH₂)_n-heterocycle, where n may be 0 – 6, where the aryl radical or heterocyclic radical may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂.

20 An alkynyl radical is understood to mean a straight-chain or branched hydrocarbon chain having two or more carbons and one or more triple bonds, for example ethynyl, propynyl, butynyl, hexynyl.

The alkynyl radicals may be mono- or polysubstituted by suitable groups, for example:

25 F, Cl, Br, I, CF₃, NO₂, N₃, CN, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, cycloalkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-aryl, O-CO-(C₁-C₆)-heterocycle; PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-aryl, S-(CH₂)_n-heterocycle, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-aryl, SO-(CH₂)_n-heterocycle, 30 SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)_n-aryl, SO₂-(CH₂)_n-heterocycle, SO₂-NH(CH₂)_n-aryl, SO₂-NH(CH₂)_n-heterocycle, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-aryl, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-heterocycle, SO₂-N((CH₂)_n-aryl)₂, SO₂-N((CH₂)_n-heterocycle)₂ where n may be 0 – 6 and the

aryl radical or heterocyclic radical may be up to disubstituted by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂; C(=NH)(NH₂), NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH-CO-(C₁-C₆)-alkyl, NH-COO-(C₁-C₆)-alkyl, NH-CO-aryl, NH-CO-heterocycle, NH-COO-aryl, NH-COO-heterocycle, NH-5 CO-NH-(C₁-C₆)-alkyl, NH-CO-NH-aryl, NH-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-COO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-aryl, N((C₁-C₆)-alkyl)-CO-heterocycle, N((C₁-C₆)-alkyl)-COO-aryl, N((C₁-C₆)-alkyl)-COO-heterocycle, N((C₁-C₆)-alkyl)-CO-NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-NH-aryl, N((C₁-C₆)-alkyl)-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)₂, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-aryl, N((C₁-C₆)-alkyl)-CO-N(aryl)₂, 10 N((C₁-C₆)-alkyl)-CO-N-(heterocycle)₂, N(aryl)-CO-(C₁-C₆)-alkyl, N(heterocycle)-CO-(C₁-C₆)-alkyl, N(aryl)-COO-(C₁-C₆)-alkyl, N(heterocycle)-COO-(C₁-C₆)-alkyl, N(aryl)-CO-aryl, N(heterocycle)-CO-aryl, N(aryl)-COO-aryl, N(heterocycle)-COO-aryl, N(aryl)-CO-NH-(C₁-C₆)-alkyl, N(heterocycle)-CO-NH-(C₁-C₆)-alkyl, N(aryl)-CO-NH-aryl, N(heterocycle)-CO-15 NH-aryl, N(aryl)-CO-N((C₁-C₆)-alkyl)₂, N(heterocycle)-CO-N((C₁-C₆)-alkyl)₂, N(aryl)-CO-N((C₁-C₆)-alkyl)-aryl, N(heterocycle)-CO-N((C₁-C₆)-alkyl)-aryl, N(aryl)-CO-N(aryl)₂, N(heterocycle)-CO-N-(aryl)₂, aryl, O-(CH₂)_n-aryl and O-(CH₂)_n-heterocycle, where n may be 0 - 6, where the aryl radical or heterocyclic radical may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂.

An aryl radical is understood to mean a phenyl, naphthyl, biphenyl, tetrahydronaphthyl, alpha- or beta-tetralonyl, indanyl or indan-1-onyl radical.

25 The aryl radicals may be mono- or polysubstituted by suitable groups, for example: F, Cl, Br, I, CF₃, NO₂, N₃, CN, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, cycloalkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-aryl, O-CO-(C₁-C₆)-heterocycle; PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-aryl, S-(CH₂)_n-heterocycle, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-aryl, SO-(CH₂)_n-heterocycle, 30 SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)_n-aryl, SO₂-(CH₂)_n-heterocycle, SO₂-NH(CH₂)_n-aryl, SO₂-NH(CH₂)_n-heterocycle, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-aryl, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-

heterocycle, $\text{SO}_2\text{-N}((\text{CH}_2)_n\text{-aryl})_2$, $\text{SO}_2\text{-N}((\text{CH}_2)_n\text{-heterocycle})_2$ where n may be 0 – 6 and the aryl radical or heterocyclic radical may be up to disubstituted by F, Cl, Br, OH, CF_3 , NO_2 , CN, OCF_3 , O- $(\text{C}_1\text{-C}_6)$ -alkyl, $(\text{C}_1\text{-C}_6)$ -alkyl or NH_2 ;

$\text{C}(\text{=NH})(\text{NH}_2)$, NH_2 , $\text{NH-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})_2$, $\text{NH-CO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{NH-COO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, NH-CO-aryl , NH-CO-heterocycle , NH-COO-aryl , $\text{NH-COO-heterocycle}$, $\text{NH-CO-NH-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, NH-CO-NH-aryl , $\text{NH-CO-NH-heterocycle}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-COO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-aryl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-heterocycle}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-COO-aryl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-COO-heterocycle}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-NH-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-NH-aryl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-NH-heterocycle}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-N-}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-aryl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-N-}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-heterocycle}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-N-}(\text{aryl})_2$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-CO-N-}(\text{heterocycle})_2$, $\text{N}(\text{aryl})\text{-CO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}(\text{heterocycle})\text{-CO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}(\text{aryl})\text{-COO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}(\text{heterocycle})\text{-COO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}(\text{aryl})\text{-CO-aryl}$, $\text{N}(\text{heterocycle})\text{-CO-aryl}$, $\text{N}(\text{aryl})\text{-COO-aryl}$, $\text{N}(\text{heterocycle})\text{-COO-aryl}$, $\text{N}(\text{aryl})\text{-CO-NH-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}(\text{heterocycle})\text{-CO-NH-}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}(\text{aryl})\text{-CO-NH-aryl}$, $\text{N}(\text{heterocycle})\text{-CO-NH-aryl}$, $\text{N}(\text{aryl})\text{-CO-N-}((\text{C}_1\text{-C}_6)\text{-alkyl})_2$, $\text{N}(\text{heterocycle})\text{-CO-N-}((\text{C}_1\text{-C}_6)\text{-alkyl})_2$, $\text{N}(\text{aryl})\text{-CO-N-}((\text{C}_1\text{-C}_6)\text{-alkyl})\text{-aryl}$, $\text{N}(\text{aryl})\text{-CO-N-}(\text{aryl})_2$, $\text{N}(\text{heterocycle})\text{-CO-N-}(\text{aryl})_2$, aryl , $\text{O-}(\text{CH}_2)_n\text{-aryl}$ and $\text{O-}(\text{CH}_2)_n\text{-heterocycle}$, where n may be 0 – 6, where the aryl radical or heterocyclic radical may be mono- to trisubstituted by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , O- $(\text{C}_1\text{-C}_6)$ -alkyl, $(\text{C}_1\text{-C}_6)$ -alkyl, NH_2 , $\text{NH}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{N}((\text{C}_1\text{-C}_6)\text{-alkyl})_2$, $\text{SO}_2\text{-CH}_3$, COOH, $\text{COO-}(\text{C}_1\text{-C}_6)\text{-alkyl}$ or CONH_2 .

A cycloalkyl radical is understood to mean a ring system which comprises one or more rings and is present in saturated or partially unsaturated form (with one or two double bonds), and is formed exclusively from carbon atoms, for example cyclopropyl, cyclopentyl, cyclopentenyl, cyclohexyl or adamantyl.

The cycloalkyl radicals may be mono- or polysubstituted by suitable groups, for example:

F, Cl, Br, I, CF_3 , NO_2 , N_3 , CN, COOH, $\text{COO}(\text{C}_1\text{-C}_6)\text{-alkyl}$, CONH_2 , $\text{CONH}(\text{C}_1\text{-C}_6)\text{-alkyl}$, $\text{CON}[(\text{C}_1\text{-C}_6)\text{-alkyl}]_2$, cycloalkyl, $(\text{C}_2\text{-C}_6)$ -alkenyl, $(\text{C}_2\text{-C}_6)$ -alkynyl, O- $(\text{C}_1\text{-C}_6)$ -alkyl, O-CO- $(\text{C}_1\text{-C}_6)$ -alkyl, O-CO- $(\text{C}_1\text{-C}_6)$ -aryl, O-CO- $(\text{C}_1\text{-C}_6)$ -heterocycle;

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PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-aryl, S-(CH₂)_n-heterocycle, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-aryl, SO-(CH₂)_n-heterocycle, SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)_n-aryl, SO₂-(CH₂)_n-heterocycle, SO₂-NH(CH₂)_n-aryl, SO₂-NH(CH₂)_n-heterocycle, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-aryl, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-heterocycle, SO₂-N((CH₂)_n-aryl)₂, SO₂-N((CH₂)_n-heterocycle)₂ where n may be 0 – 6 and the aryl radical or heterocyclic radical may be up to disubstituted by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂;

C(=NH)(NH₂), NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH-CO-(C₁-C₆)-alkyl, NH-COO-(C₁-C₆)-alkyl, NH-CO-aryl, NH-CO-heterocycle, NH-COO-aryl, NH-COO-heterocycle, NH-10 CO-NH-(C₁-C₆)-alkyl, NH-CO-NH-aryl, NH-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-COO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-aryl, N((C₁-C₆)-alkyl)-CO-heterocycle, N((C₁-C₆)-alkyl)-COO-aryl, N((C₁-C₆)-alkyl)-COO-heterocycle, N((C₁-C₆)-alkyl)-CO-NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-NH-aryl, N((C₁-C₆)-alkyl)-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)₂, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-aryl, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-heterocycle, N((C₁-C₆)-alkyl)-CO-N(aryl)-CO-N(aryl)₂, N((C₁-C₆)-alkyl)-CO-N(aryl)-CO-N-(heterocycle)₂, N(aryl)-CO-(C₁-C₆)-alkyl, N(heterocycle)-CO-(C₁-C₆)-alkyl, N(aryl)-COO-(C₁-C₆)-alkyl, N(heterocycle)-COO-(C₁-C₆)-alkyl, N(aryl)-CO-aryl, N(heterocycle)-CO-aryl, N(aryl)-COO-aryl, N(heterocycle)-COO-aryl, N(aryl)-CO-NH-(C₁-C₆)-alkyl, N(heterocycle)-CO-NH-(C₁-C₆)-alkyl, N(aryl)-CO-NH-aryl, N(heterocycle)-CO-20 NH-aryl, N(aryl)-CO-N((C₁-C₆)-alkyl)₂, N(heterocycle)-CO-N((C₁-C₆)-alkyl)₂, N(aryl)-CO-N((C₁-C₆)-alkyl)-aryl, N(heterocycle)-CO-N((C₁-C₆)-alkyl)-aryl, N(aryl)-CO-N(aryl)₂, N(heterocycle)-CO-N(aryl)₂, aryl, O-(CH₂)_n-aryl and O-(CH₂)_n-heterocycle, where n may be 0 – 6, where the aryl radical or heterocyclic radical may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂.

Heterocyclyl, heterocycle and heterocyclic radical are understood to mean rings and ring systems which, apart from carbon, also contain heteroatoms, for example nitrogen, oxygen or sulfur. This definition also includes ring systems in which the heterocycle or the heterocyclic radical is fused to benzene rings. The heterocycle or the heterocyclic radical may be aromatic, saturated aliphatic or partially unsaturated aliphatic.

Suitable heterocyclyl radicals or “heterocyclic radicals” are acridinyl, azocinyl, benzimidazolyl, benzofuryl, benzothienyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazaliny, carbazolyl, 4aH-carbazolyl, carbolinyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxaliny, quinuclidinyl, chromanyl, 5 chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuran, furyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 10 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, 15 tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thienyl, triazolyl, tetrazolyl and xanthenyl.

Pyridyl is 2-, 3- or 4-pyridyl. Thienyl is 2- or 3-thienyl. Furyl is 2- or 3-furyl.

20 Also included are the corresponding N-oxides of these compounds, i.e., for example, 1-oxy-2-, -3- or -4-pyridyl.

Also included are mono- or polybenzofused derivatives of these heterocycles.

25 The heterocyclic rings or heterocyclic radicals may be mono- or polysubstituted by suitable groups, for example: F, Cl, Br, I, CF₃, NO₂, N₃, CN, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, cycloalkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-alkyl, O-CO-(C₁-C₆)-aryl, O-CO-(C₁-C₆)-heterocycle; 30 PO₃H₂, SO₃H, SO₂-NH₂, SO₂NH(C₁-C₆)-alkyl, SO₂N[(C₁-C₆)-alkyl]₂, S-(C₁-C₆)-alkyl, S-(CH₂)_n-aryl, S-(CH₂)_n-heterocycle, SO-(C₁-C₆)-alkyl, SO-(CH₂)_n-aryl, SO-(CH₂)_n-heterocycle, SO₂-(C₁-C₆)-alkyl, SO₂-(CH₂)_n-aryl, SO₂-(CH₂)_n-heterocycle, SO₂-NH(CH₂)_n-aryl, SO₂-

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NH(CH₂)_n-heterocycle, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-aryl, SO₂-N((C₁-C₆)-alkyl)(CH₂)_n-heterocycle, SO₂-N((CH₂)_n-aryl)₂, SO₂-N((CH₂)_n-heterocycle)₂ where n may be 0 – 6 and the aryl radical or heterocyclic radical may be up to disubstituted by F, Cl, Br, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl or NH₂;

5 C(=NH)(NH₂), NH₂, NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, NH-CO-(C₁-C₆)-alkyl, NH-COO-(C₁-C₆)-alkyl, NH-CO-aryl, NH-CO-heterocycle, NH-COO-aryl, NH-COO-heterocycle, NH-CO-NH-(C₁-C₆)-alkyl, NH-CO-NH-aryl, NH-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-COO-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-aryl, N((C₁-C₆)-alkyl)-CO-heterocycle, N((C₁-C₆)-alkyl)-COO-aryl, N((C₁-C₆)-alkyl)-COO-heterocycle, N((C₁-C₆)-alkyl)-CO-NH-(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)-CO-NH-aryl, N((C₁-C₆)-alkyl)-CO-NH-heterocycle, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)₂, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-aryl, N((C₁-C₆)-alkyl)-CO-N((C₁-C₆)-alkyl)-heterocycle, N((C₁-C₆)-alkyl)-CO-N(aryl)₂, N((C₁-C₆)-alkyl)-CO-N-(heterocycle)₂, N(aryl)-CO-(C₁-C₆)-alkyl, N(heterocycle)-CO-(C₁-C₆)-alkyl, N(aryl)-COO-(C₁-C₆)-alkyl, N(heterocycle)-COO-(C₁-C₆)-alkyl, N(aryl)-CO-aryl, N(heterocycle)-CO-aryl, N(aryl)-COO-aryl, N(heterocycle)-COO-aryl, N(aryl)-CO-NH-(C₁-C₆)-alkyl, N(heterocycle)-CO-NH-(C₁-C₆)-alkyl, N(aryl)-CO-NH-aryl, N(heterocycle)-CO-NH-aryl, N(aryl)-CO-NH-aryl, N(heterocycle)-CO-NH-aryl, N(aryl)-CO-N((C₁-C₆)-alkyl)₂, N(heterocycle)-CO-N((C₁-C₆)-alkyl)₂, N(aryl)-CO-N((C₁-C₆)-alkyl)-aryl, N(heterocycle)-CO-N((C₁-C₆)-alkyl)-aryl, N(aryl)-CO-N(aryl)₂, N(heterocycle)-CO-N(aryl)₂, aryl, O-(CH₂)_n-aryl and O-(CH₂)_n-heterocycle, where n may be 0 – 6, where the aryl radical or heterocyclic radical may be mono- to trisubstituted by F, Cl, Br, I, OH, CF₃, NO₂, CN, OCF₃, O-(C₁-C₆)-alkyl, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, SO₂-CH₃, COOH, COO-(C₁-C₆)-alkyl or CONH₂.

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

The amount of a compound of the formula I which is required in order to achieve the desired biological effect is dependent upon a series of factors, for example the specific compound selected, the intended use, the mode of administration and the clinical condition of the patient. 30 The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day per kilogram of bodyweight, for example 3-10 mg/kg/day. An intravenous dose may, for example, be in the range from 0.3 mg to 1.0 mg/kg and may suitably be administered as an

infusion of from 10 ng to 100 ng per kilogram per minute. Suitable infusion solutions for these purposes may, for example, contain from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. Ampoules for injections may therefore contain, for example, from 1 mg to 100 mg, and single 5 dose formulations which can be administered orally, for example tablets or capsules, may contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. The compounds of the formula I may be used for therapy of the abovementioned conditions as the compounds themselves, although they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier of course has to be acceptable, in the sense that it is compatible 10 with the other constituents of the composition and is not damaging to the health of the patient. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05 to 95% by weight of the active ingredient. Further pharmaceutically active substances may likewise be present, including further compounds of the formula I. The inventive pharmaceutical compositions may 15 be produced by one of the known pharmaceutical methods which consist essentially in mixing the constituents with pharmacologically acceptable carriers and/or excipients.

Inventive pharmaceutical compositions are those which are suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, 20 intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the condition to be treated and on the type of the compound of the formula I used in each case. Coated formulations and coated slow-release formulations are also encompassed by the scope of the invention. Preference is given to acid- and gastric fluid-resistant formulations. Suitable gastric fluid-resistant coatings 25 include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical preparations for oral administration may be in the form of separate units, for example capsules, cachets, lozenges or tablets, each of which contains a certain 30 amount of the compound of the formula I; as powder or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method

which includes a step in which the active ingredient and the carrier (which may consist of one or more additional constituents) are brought into contact. In general, the compositions are prepared by uniform and homogeneous mixing of the active ingredient with a liquid carrier and/or finely divided solid carrier, after which the product is shaped if necessary. For example, 5 a tablet can thus be produced by compressing or shaping a powder or granules of the compound, optionally with one or more additional constituents. Compressed tablets can be prepared by tableting the compound in free-flowing form, for example a powder or granules, optionally mixed with a binder, lubricant, inert diluent and/or one (or more) surfactants/dispersants in a suitable machine. Shaped tablets can be prepared by shaping the 10 pulverulent compound moistened with an inert liquid diluent in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges which contain a compound of the formula I with a flavoring, customarily sucrose, and gum arabic or tragacanth, and pastilles which include the compound in an inert base, such as 15 gelatin and glycerol or sucrose and gum arabic.

Suitable pharmaceutical compositions for parenteral administration include preferably sterile aqueous preparations of a compound of the formula I which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, 20 although the administration may also be subcutaneous, intramuscular or intradermal as an injection. These preparations can preferably be produced by mixing the compound with water and making the solution obtained sterile and isotonic with the blood. Injectable compositions according to the invention generally contain from 0.1 to 5% by weight of the active compound.

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

30 Suitable pharmaceutical compositions for topical application on the skin are preferably in the form of an ointment, cream, lotion, paste, spray, aerosol or oil. Useful carriers include petroleum jelly, lanolin, polyethylene glycols, alcohols and combinations of two or more of

these substances. The active ingredient is generally present in a concentration of from 0.1 to 15% by weight of the composition, preferably from 0.5 to 2%.

Transdermal administration is also possible. Suitable pharmaceutical compositions for 5 transdermal applications may be in the form of single plasters which are suitable for long-term close contact with the epidermis of the patient. Such plasters suitably contain the active ingredient in an optionally buffered aqueous solution, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active ingredient concentration is from approx. 1% to 10 35%, preferably from approx. 3% to 15%. A particular means of releasing the active ingredient may be by electrotransport or iontophoresis, as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The compounds of the formula I may be administered alone or else also in combination with further active ingredients. Further useful active ingredients for combination products are as 15 follows:

All antidiabetics mentioned in the Rote Liste 2001, chapter 12. They can be combined with the inventive compounds of the formula I, in particular for synergistic enhancement of action. The active ingredient combination can be administered either by separately administering the active 20 ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. Most of the active ingredients listed hereinbelow are disclosed in USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives, for example Lantus® (see 25 www.lantus.com) or Apidra®, fast-acting insulins (see US 6,221,633), GLP-1 derivatives, for example those disclosed in WO 98/08871 of Novo Nordisk A/S, and orally active hypoglycemic active ingredients.

The orally active hypoglycemic active ingredients preferably include sulfonylureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, 30 glucagon antagonists, GLP-1 agonists, potassium channel openers, for example those disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S, insulin sensitizers, inhibitors of liver enzymes which are involved in the stimulation of gluconeogenesis and/or glycogenolysis,

modulators of glucose uptake, compounds which alter lipid metabolism such as antihyperlipidemic active ingredients and antilipidemic active ingredients, compounds which reduce food intake, PPAR and PXR agonists and active ingredients which act on the ATP-dependent potassium channel of the beta cells (PPAR = peroxisome proliferator-activated receptor, PXR = pregnane X receptor, ATP = adenosine triphosphate).
5

In one embodiment of the invention, the compounds of the formula I are administered in combination with an HMG-CoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin (HMG-CoA = 3-hydroxy-
10 3-methylglutaryl coenzyme A).

In one embodiment of the invention, the compounds of the formula I are administered in combination with a cholesterol absorption inhibitor, for example, ezetimibe, tiqueside, pamaqueside, or with a compound as described in PCT/EP 2004/00269, WO 2004/000804,
15 WO 2004/000803, WO 2004/000805, EP 0114531, US 6,498,156.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a PPAR gamma agonist, for example, rosiglitazone, pioglitazone, JTT-501,
20 Gl 262570.

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a mixed PPAR alpha/gamma agonist, for example, GW 1536, AVE 8042,
25 AVE 8134, AVE 0847, or as described in WO 00/64888, WO 00/64876, DE10142734.4.

In one embodiment of the invention, the compounds of the formula I are administered in combination with a fibrate, for example fenofibrate, clofibrate, bezafibrate.
30

In one embodiment of the invention, the compounds of the formula I are administered in combination with an MTP inhibitor, for example implitapide, BMS-201038, R-103757 (MTP = microsomal triglyceride transfer protein).

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

10 In one embodiment of the invention, the compounds of the formula I are administered in combination with a CETP inhibitor, for example JTT-705 (CETP = cholestryl ester transfer protein).

15 In one embodiment of the invention, the compounds of the formula I are administered in combination with a polymeric bile acid adsorber, for example cholestyramine, colestevlam.

In one embodiment of the invention, the compounds of the formula I are administered in combination with an LDL receptor inducer (see US 6,342,512), for example HMR1171, HMR1586 (LDL = low density lipids).

20 In one embodiment of the invention, the compounds of the formula I are administered in combination with an ACAT inhibitor, for example avasimibe (ACAT = acyl coenzyme A: cholesterol acyl transferase).

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

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

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

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

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

In one embodiment of the invention, the compounds of the formula I are administered in combination with a lipase inhibitor, for example orlistat.

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

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

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

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

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

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

In one embodiment, the compounds of the formula I are administered in combination with adenosine A1 agonists, for example those which are described in WO 2004/003002.

In one embodiment, the compounds of the formula I are administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, for 30 example tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment, the compounds of the formula I are administered in combination with more than one of the abovementioned compounds, for example in combination with a sulfonylurea

and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

In a further embodiment, the compounds of the formula I are administered in combination with

5 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 (NPY = neuropeptide Y), e.g. naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]cyclohexyl-methyl}amide hydrochloride (CGP 71683A)), MC4 agonists (MC4 = melanocortin 4 receptor, 10 e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxo-ethyl]amide; (WO 01/91752)), orexin antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea; hydrochloride (SB-334867-A)), H3 agonists (H3 = histamine receptor, e.g. 15 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 (TNF = tumor necrosis factor), CRF antagonists (CRF = corticotropin releasing factor, e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585)), CRF BP antagonists (CRF BP = corticotropin releasing factor binding protein, e.g. urocortin), urocortin agonists, β 3 agonists (e.g. 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-20 6-yloxy)ethylamino]ethanol hydrochloride (WO 01/83451)), CB1 (cannabinoid receptor 1) receptor antagonists (e.g. rimonabant or the active ingredients specified in WO 02/28346), MSH (melanocyte-stimulating hormone) agonists, CCK-A (CCK-A = cholecystokinin-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)), 25 serotonin reuptake inhibitors (e.g. dexfenfluramine), mixed serotonergic and noradrenergic compounds (e.g. WO 00/71549), 5HT agonists (serotonin mimetics) e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111), bombesin agonists, galanin antagonists, growth hormone (e.g. human growth hormone), growth hormone-releasing compounds (6-benzyloxy-1-(2-diisopropylaminoethyl-carbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-30 butyl ester (WO 01/85695)), TRH agonists (TRH = TSH releasing hormone; TSH = thyroid-stimulating hormone; thyrotropin), 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 (DA = dopamine autoreceptor, for example bromocriptine, doprexin), lipase/amylase inhibitors (e.g. WO 00/40569), PPAR modulators (e.g. WO 00/78312), RXR (RXR = retinoid X receptor) modulators or TR- β agonists.

In one embodiment of the invention, the other active ingredient is leptin; see, for example, "Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi, Javier; Frühbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

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

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

In yet another embodiment, the other active ingredient is sibutramine.

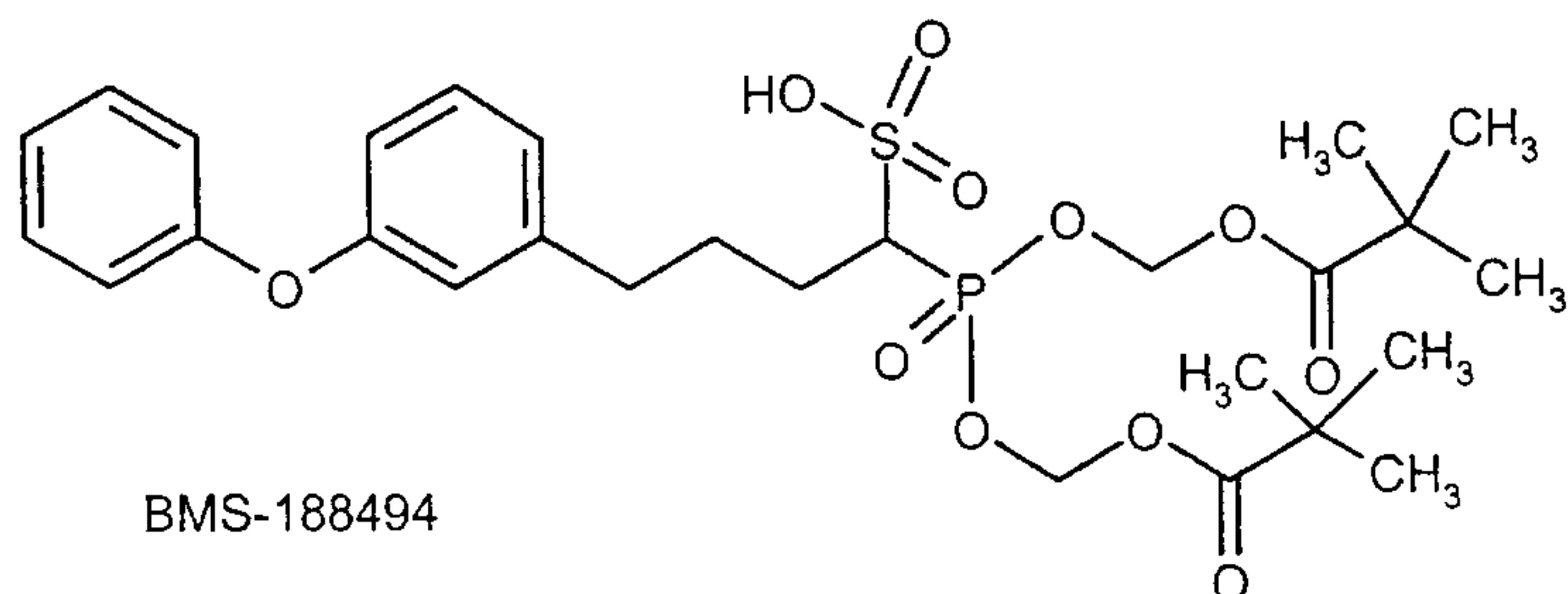
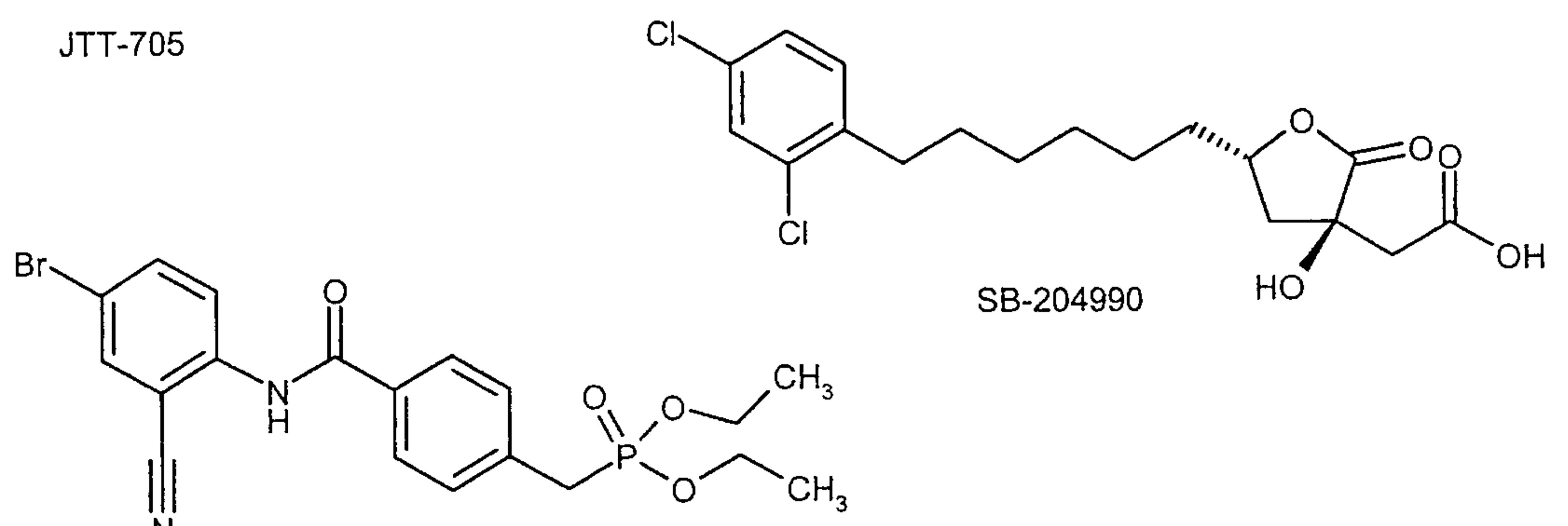
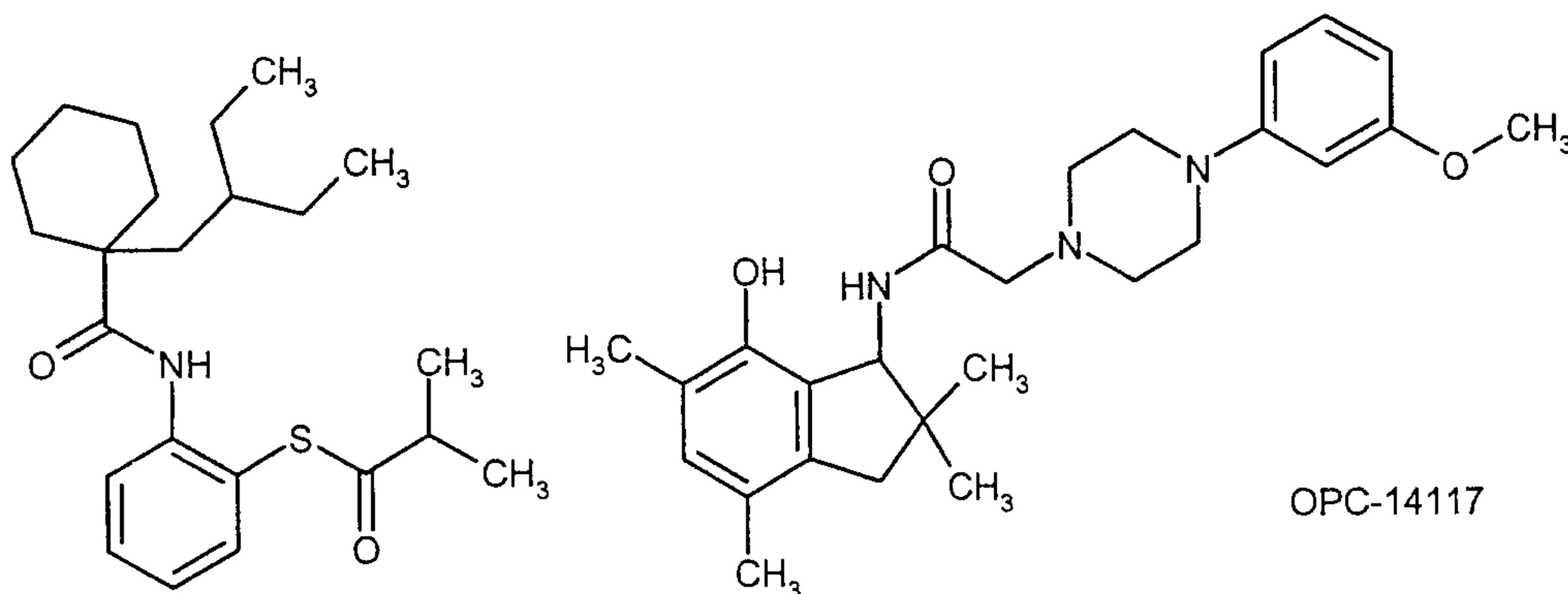
In one embodiment, the other active ingredient is orlistat.

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

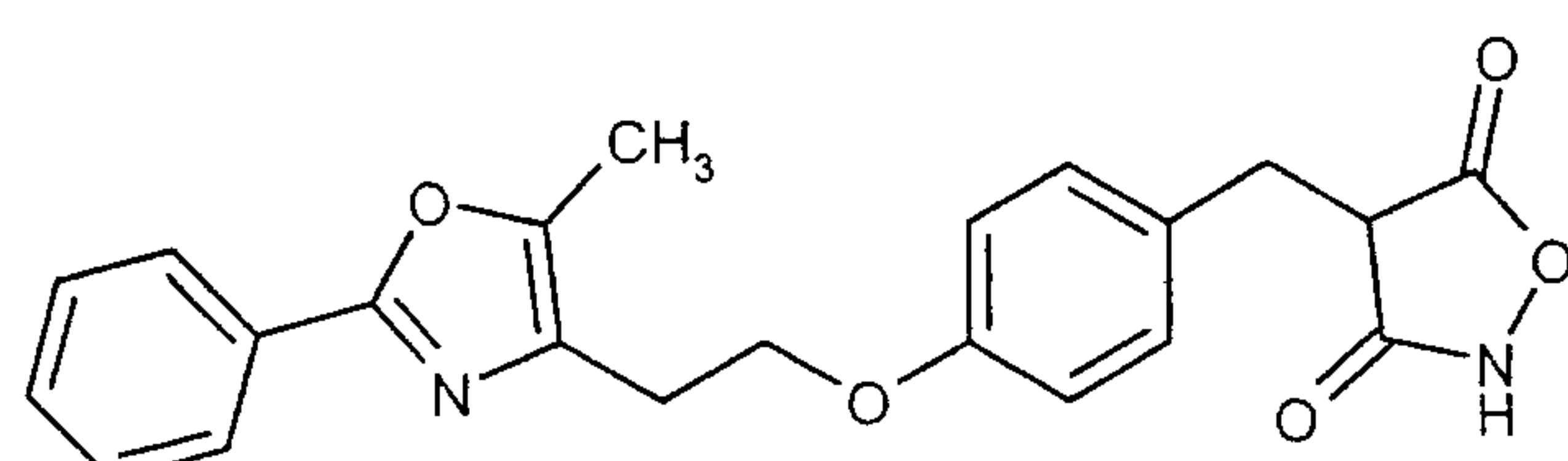
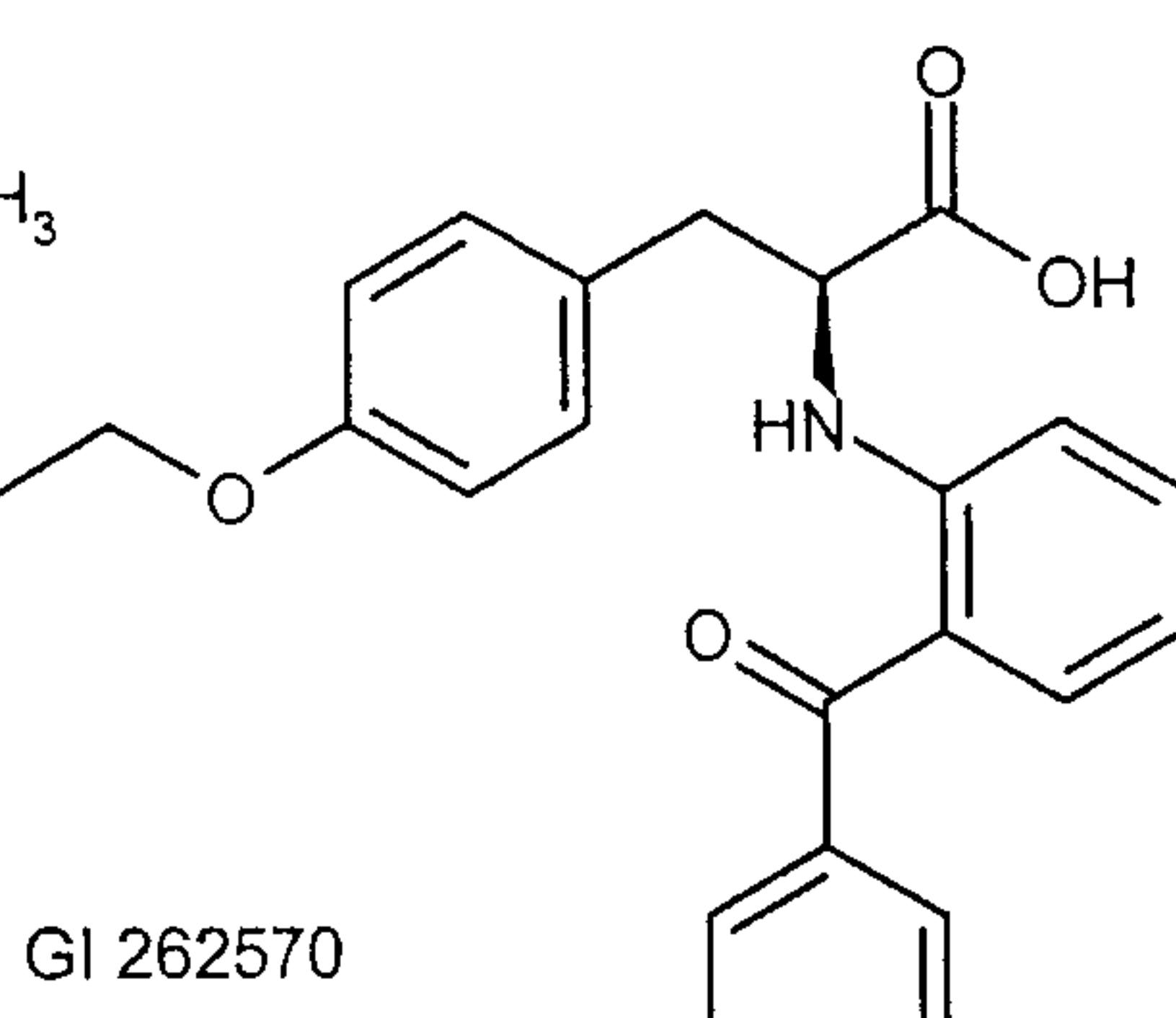
In another embodiment, the other active ingredient is rimonabant.

In one embodiment, the compounds of the formula I are administered in combination with 20 dietary fiber materials, preferably insoluble dietary fiber materials (see, for example, Carob/Caromax[®] (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6.); Caromax is a carob-containing product supplied by Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main)). Combination with Caromax[®] is possible 25 in one preparation or by separate administration of compounds of the formula I and Caromax[®]. Caromax[®] can also be administered in the form of foodstuffs, for example, in bakery products or muesli bars.

It will be appreciated that any suitable combination of the compounds according to the 30 invention with one or more of the abovementioned compounds and optionally one or more further pharmacologically active substances is regarded as being covered by the scope of protection of the present invention.

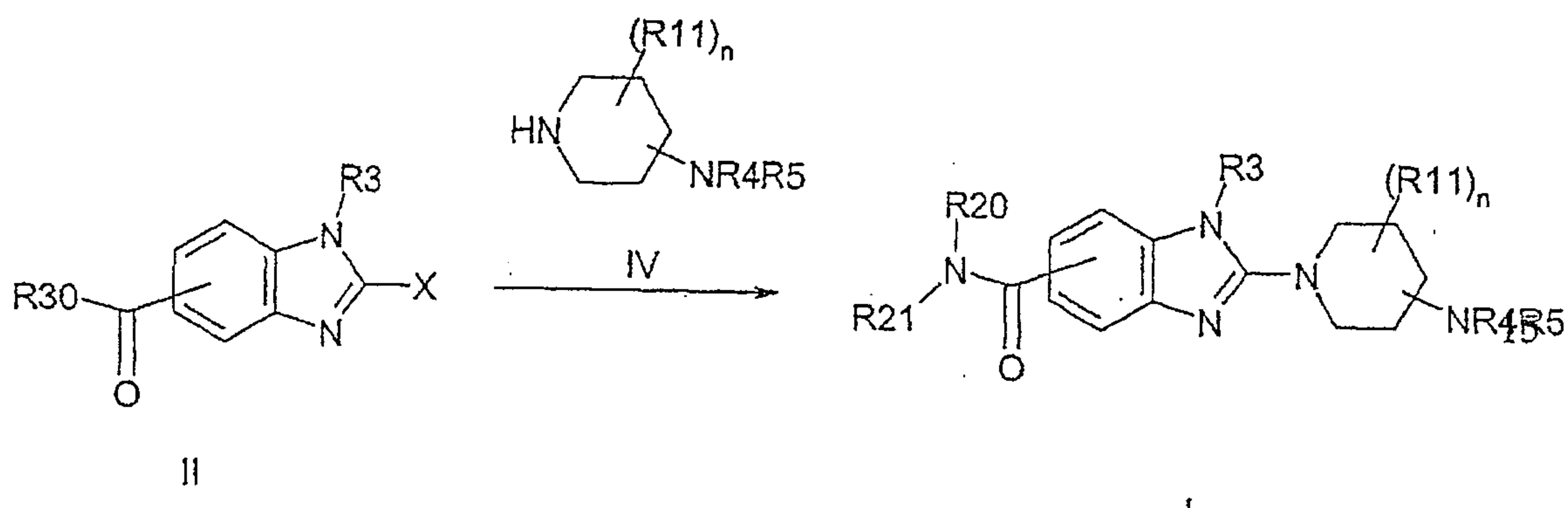


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The compounds of the formula I can be prepared by reacting suitable starting materials of the formula II in which X is a leaving group, such as chlorine, bromine, iodine, sulfonyloxy, sulfinyl or sulfoxyl, and R₃₀ is an ester or an amide, with a compound of the formula IV optionally in the presence of suitable bases and in suitable solvents.



5

In the cases where R₄ and R₅ are simultaneously hydrogen, it may be appropriate to use the radical IV in a form protected on the nitrogen function and to detach the protecting group again on completion of reaction with II. Such suitable protecting groups and the processes for their introduction and detachment are known (see: Theodora W. Greene and Peter G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, Inc., New York, 1999).

The halogen compounds of the formula II can be obtained by known processes, for example by halogenating the corresponding H, hydroxyl or thio compound (formula II, X = H, OH or SH).
 Suitable halogenating agents may, by way of example, be halogens such as chlorine and bromine, N-bromosuccinimide, phosphorus pentachloride or phosphorus oxychloride. The synthesis of compounds of the formula II is described in the literature. They may be prepared, for example, by condensing substituted diaminobenzene derivatives with aldehydes in the presence of an oxidizing agent (for example atmospheric oxygen, oxygen, iodine, oxone, quinones, peroxides, etc.), or alternatively with carboxylic acids, nitriles or amides, without or in the presence of a catalyst.

The amines IV can be synthesized by processes known from the literature.

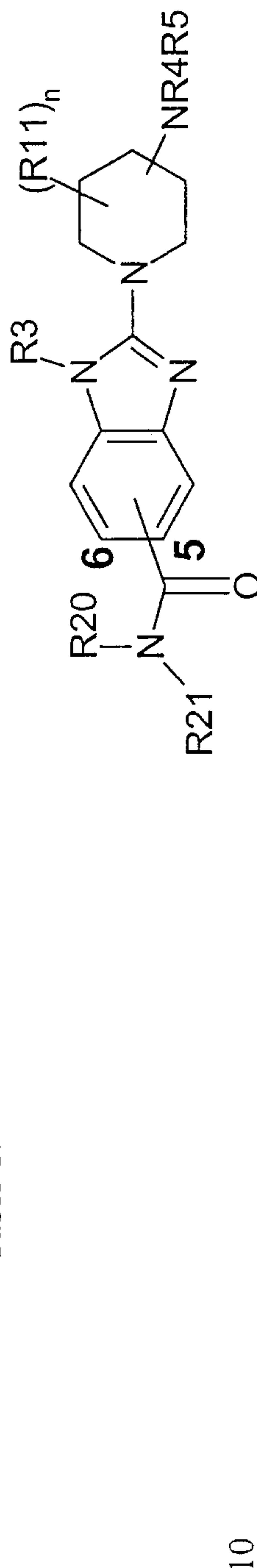
Some derivatives of the formula IV, for example piperidin-3-ylamines are commercially available.

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The esters or amides CO-R30 can be converted to the amides CO-NR20R21 by methods known from the literature.

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

Table 1:



Ex.	A No.	Binding site C=O-NR20R21	R20	R21	R3	NR4R5	n	R11
1	A003394933A	6	H	4-Cl-Benzyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
2	A003394934A	6	H	3-CF ₃ -Benzyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
3	A003394935A	6	H	2-Cl-Benzyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
4	A003394936A	6	H	Cyclohexyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
5	A003394937A	6	H	3-Pyridyl-CH ₂ -	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
6	A003395756A	5	H	4-Cl-Benzyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
7	A003395757A	5	H	2-Cl-Benzyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
8	A003395758A	5	H	3-Pyridyl-(CH ₂) ₂ -	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
9	A003395760A	5	H	3-Cl-Benzyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-
10	A003401196A	6	H	Cyclopentyl-	-CH ₂ -CH=C(CH ₃) ₂	3-R-NH ₂ x HCl	0	-
11	A003401273A	6	H	4-F-Phenyl-	-CH ₂ -CH=C(CH ₃) ₂	3-R-NH ₂ x HCl	0	-
12	A003401848A	6	H	4-F-Phenyl-	4-F-Benzyl	3-R-NH ₂ x HCl	0	-

The compounds of the formula I feature favorable effects on lipid and carbohydrate metabolism; in particular, they lower the blood sugar level and are suitable for the treatment of type II diabetes, of insulin resistance, of dislipidemias and of metabolic syndrome/syndrome X. Moreover, the compounds are suitable for the treatment and prophylaxis of arteriosclerotic 5 manifestations. The compounds can be used alone or in combination with further blood sugar-lowering active ingredients. The compounds act as DPP IV (dipeptidyl peptidase IV) inhibitors and are also suitable for the treatment of disorders of perception and other psychiatric indications, for example depressions, anxiety states, anxiety neuroses, schizophrenia, and for the treatment of disorders associated with the circadian rhythm, for weight reduction in 10 mammals, for the treatment of immune disorders and for the treatment of drug abuse.

They are additionally suitable for the treatment of cancer, arthritis, osteoarthritis, osteoporosis, sleep disorders, sleep apnea, masculine and feminine sexual disorders, inflammations, acne, pigmentation of the skin, disorders of steroid metabolism, skin diseases, psoriasis, mycoses, neurodegenerative disorders, multiple sclerosis and Alzheimer's disease.

15

The efficacy of the compounds was tested as follows:

Measurement of the DPP-IV activity:

20 Material:

DPP-IV from porcine kidneys (Sigma, Munich)

H-Ala-Pro-AFC (Bachem, Weil am Rhein)

25 Test conditions:

DPP-IV (1 mU/ml, end concentration)

H-Ala-Pro-AFC (15 μ m end concentration)

in Tris/HCl (40 mM, pH 7.4), total volume 0.2 ml

30 The reaction was performed at room temperature for different periods (typically 10 minutes) and stopped at the end of the reaction by adding 20 μ l of ZnCl₂ (1 M). The conversion of H-Ala-Pro-AFC was determined fluorimetrically by measuring the emission at 535 nm on

excitation at 405 nm. In the case of addition of inhibitors, the buffer volume added was adjusted such that a total volume of the test mixture of 200 μ l was maintained.

IC₅₀ values for inhibitors were determined by varying the inhibitor concentrations at the given substrate concentration of 15 μ M. K_i and K_m values were determined by corresponding

5 variation of substrate and inhibitor concentration as described (Dixon, M. and Webb, E.C. (1979) Enzymes, third edition, pp. 47-206, Academic Press). The values for K_m, IC₅₀ and K_i were calculated using a commercially available software package (Leatherbarrow, R.J. (1992) GraFit Version 3.0, Erihacus Software Ltd. Staines, U.K.).

10 Table 2: Biological activity of the examples:

Example	IC ₅₀ [μ M]
2	1.0
5	2.5
6	4.3
11	1.8

It can be seen from the table that the compounds of the formula I inhibit the activity of the DPP-IV (dipeptidyl peptidase IV) and are thus very suitable for lowering the blood sugar level.

15 The preparation of some working examples will be described in detail hereinafter; the other compounds of the formula I were obtained analogously:

Example 1

20 N-(4-Chlorobenzyl)-R-2-(3-aminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxamide hydrochloride

a) Methyl 2-hydroxy-1H-benzimidazole-5-carboxylate

The solution of 5.9 g of carbonyldiimidazole in 10 ml of N-methylpyrrolidone is added

25 dropwise to the solution of 5 g of methyl 3,4-diaminobenzoate in 10 ml of N-methylpyrrolidone, and the mixture is heated to 100°C for 2 hours. After cooling to 60°C, 5 ml of methanol were added dropwise and then the mixture was stirred at room temperature

with 150 ml of water, and the precipitate was filtered off with suction, washed with isopropanol and dried under reduced pressure.

Yield: 4.0 g m.p.: 312°C

5 b) Methyl 2-chloro-1H-benzimidazole-5-carboxylate

3.9 g of methyl 2-hydroxy-1H-benzimidazole-5-carboxylate and 50 ml of phosphorus oxychloride are stirred at 100°C for 6 hours. The resulting thick slurry is, after cooling, stirred cautiously into 500 ml of ice-water, and the solid is filtered off with suction after one hour, washed with water and dried under reduced pressure.

10 Yield: 4.3 g m.p.: 276°C

c) Mixture of methyl 2-chloro-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxylate and methyl 2-chloro-1-(4-fluorobenzyl)-1H-benzimidazole-5-carboxylate

4.3 g of methyl 2-chloro-1H-benzimidazole-6-carboxylate are dissolved in 15 ml of

15 N-methylpyrrolidone, admixed with 4.2 g of potash and stirred at room temperature for 60 minutes. 4.86 g of 4-fluorobenzyl bromide are then added and the mixture is stirred at 70°C for 4 hours, cooled and stirred with 50 ml of water and 10 ml of glacial acetic acid. The solid is filtered off with suction and dried under reduced pressure.

Yield: 4.0 g m.p. resin

20

d) Mixture of methyl R-2-(3-tert-butoxycarbonylaminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxylate and methyl 2-(3-tert-butoxycarbonylaminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-5-carboxylate

The mixture of methyl 2-chloro-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxylate and

25 methyl 2-chloro-1-(4-fluorobenzyl)-1H-benzimidazole-5-carboxylate (2 g in total), 15 ml of N-methylpyrrolidone, 3 ml of triethylamine and 2.5 g of tert-butyl R-piperidin-3-ylcarbamate is heated to 100°C for 6 hours. After being allowed to cool, the mixture is admixed with 50 ml of water and stirred. The liquid is decanted off from the semi-solid precipitate which is taken up again in 5 ml of methanol and precipitated again with 30 ml of water and stirred. The solid is 30 filtered off with suction and dried under reduced pressure.

Yield: 2.1 g m.p.: resin

e) R-2-(3-tert-Butoxycarbonylaminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxylic acid

The mixture of a total of 2 g of R-2-(3-tert-butoxycarbonylaminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxylate and methyl R-2-(3-tert-

5 butoxycarbonylaminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-5-carboxylate in the solvent mixture of 10 ml of methanol, 20 ml of water and 10 ml of tetrahydrofuran is admixed with 500 mg of lithium hydroxide and stirred at room temperature for 24 hours. After adding 2 ml of glacial acetic acid, the volatile fractions were removed under reduced pressure, the residue was stirred with water, and the solid was filtered off with suction and then separated by 10 column chromatography (silica gel, eluent: methylene chloride:isopropanol = 94:6), the 5-isomer being eluted first.

Yield: 980 mg m.p.: resin

f) tert-Butyl R-{1-[6-(4-chlorobenzylcarbamoyl)-1-(4-fluorobenzyl)-1H-benzimidazol-2-yl]-15 piperidin-3-yl} carbamate (F-34529-074)

The solution of 50 mg of R-2-(3-tert-butoxycarbonylaminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxylic acid in 1.5 ml of dimethylformamide was admixed successively with 40.6 mg of HATU, 18 μ l of triethylamine and 14 μ l of 4-chlorobenzylamine, and stirred at room temperature overnight. The mixture was then diluted with 5 ml of water and 20 the precipitate was filtered off with suction and dried at 40°C under reduced pressure.

Yield: 30 mg m.p.: resin

g) N-(4-Chlorobenzyl)-R-2-(3-aminopiperidin-1-yl)-1-(4-fluorobenzyl)-1H-benzimidazole-6-carboxamide hydrochloride (F-34529-083)

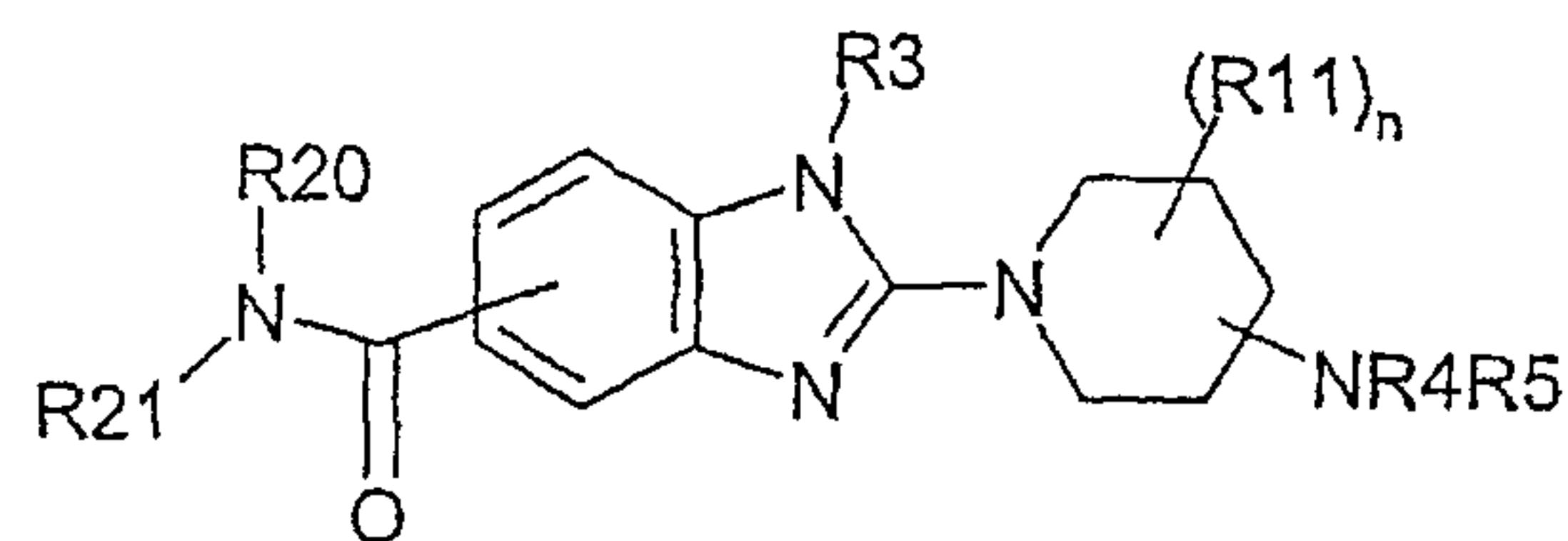
25 The solution of 63 mg of tert-butyl R-{1-[6-(4-chlorobenzylcarbamoyl)-1-(4-fluorobenzyl)-1H-benzimidazol-2-yl]-piperidin-3-yl} carbamate in 1 ml of ethyl acetate is admixed with 0.2 ml of a saturated HCl solution in ethyl acetate and left to stand at room temperature overnight. The volatile fractions were removed on a rotary evaporator and the residue was dissolved in a little methylene chloride and precipitated with diisopropyl ether. The solid was filtered off with 30 suction and dried at 40°C under reduced pressure.

Yield: 15 mg m.p.: 197.1°C

Claims:

1. A compound of the formula I

5



I

I

in which

10

R20 is H, (C₁-C₃)-alkyl, where (C₁-C₃)-alkyl is mono- or polysubstituted by CN, NO₂, SH, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl; (C₄-C₆)-alkyl, where (C₄-C₆)-alkyl is mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl; (C₇-C₁₀)-alkyl, (C₃-C₁₀)-cycloalkyl, (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl (C₁-C₆)-alkylene-(C₆-C₁₀)-heterocyclyl or S(O)₂-aryl, where the alkyl, cycloalkyl, alkenyl, alkynyl, alkylene, aryl and heterocyclyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

15

20

R21 is (C₁-C₃)-alkyl, where (C₁-C₃)-alkyl is mono- or polysubstituted by CN, NO₂, SH, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl; (C₄-C₆)-alkyl, where (C₄-C₆)-alkyl is mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl; (C₇-C₁₀)-alkyl, (C₃-C₁₀)-cycloalkyl, (C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where (C₁-C₆)-alkylene-

25

(C₆-C₁₀)-aryl (C₁-C₆)-alkylene-(C₆-C₁₀)-heterocyclyl or S(O)₂-aryl, where the alkyl, cycloalkyl, alkenyl, alkynyl, alkylene, aryl and heterocyclyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

5 excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

R3 is (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₃)-alkyl, phenyl, pyridyl, where the alkyl, cycloalkyl, cycloalkylalkyl, phenyl and pyridyl radicals are mono- or polysubstituted by CN, NO₂, -CF₃, -OCF₃, OR12, NR7R8, 10 NR7CONR7R8, COR7, OCOR7, OCOOR7, COOR7, CONR7R8 or OCONR7R8;

(C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where the alkenyl, alkynyl, aryl, heterocyclyl and alkylenearyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, 15 OH, (C₁-C₆)-alkyl, -CF₃, -OCF₃, OR7, NR7R8, NR7CONR7R8, COR7, OCOR7, OCOOR7, COOR7, CONR7R8 or OCONR7R8;

excluding the definitions of unsubstituted phenyl and unsubstituted pyridyl, and also phenyl and 20 pyridyl each substituted by F, Cl, Br, I, OH or (C₁-C₆)-alkyl, from the R3 radical;

R7, R8 are each independently H, (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-25 aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR9R10, CONR9R10, (C₁-C₆)-alkylene-COOR9, COOR9, COR9, (C₁-C₆)-alkylene-COR9, (C₁-C₆)-alkylene-OR9, (C₁-C₆)-alkylene-NR9R10, (C₁-C₆)-alkylene-SR9, (C₁-C₆)-alkylene-S(O)R9, (C₁-C₆)-alkylene-S(O)₂R9, S(O)R9, S(O)₂R9, (C₁-C₄)-alkylene-(C₆-C₁₀)-aryl or (C₁-C₄)-alkylene-heterocyclyl;

R9, R10 are each independently H, (C₁-C₆)-alkyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, 30 -(C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-heterocyclyl;

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R12 is (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR₉R₁₀, CONR₉R₁₀, (C₁-C₆)-alkylene-COOR₉, COOR₉, COR₉, (C₁-C₆)-alkylene-COR₉, (C₁-C₆)-alkylene-OR₉, (C₁-C₆)-alkylene-NR₉R₁₀, (C₁-C₆)-alkylene-SR₉, (C₁-C₆)-alkylene-S(O)R₉, (C₁-C₆)-alkylene-S(O)₂R₉, S(O)R₉, S(O)₂R₉, (C₂-C₄)-alkylene-(C₆-C₁₀)-aryl or (C₁-C₄)-alkylene-heterocyclyl;

5 R4, R5 are each independently H, (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl, where (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl may be substituted by F, Cl, Br, I, CN, aryl, heterocyclyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, OH, O(C₁-C₆)-alkyl, 10 Oaryl, Oheteroaryl, S(C₁-C₆)-alkyl, S(O)(C₁-C₆)-alkyl or S(O)₂(C₁-C₆)-alkyl, where these alkyl groups may in turn be substituted by F, Cl, Br or I;

15 R11 is H, F, Cl, Br, I, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl, NH₂, NH(C₁-C₆)-alkyl, NH(C₃-C₇)-cycloalkyl, N((C₁-C₆)-alkyl)₂ or O-(C₁-C₆)-alkyl, where the alkyl groups may be mono- or polysubstituted by F, Cl, Br or I;

n is 0, 1 or 2;

20 and physiologically compatible salts thereof.

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

25 R20 is H;

R21 is (C₃-C₁₀)-cycloalkyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, phenyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-pyridyl, where the cycloalkyl, aryl and pyridyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

30 excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

R3 is (C₁-C₆)-alkyl, (C₃-C₇)-cycloalkyl, (C₃-C₇)-cycloalkyl-(C₁-C₃)-alkyl, phenyl, pyridyl, where the alkyl, cycloalkyl, cycloalkylalkyl, phenyl and pyridyl radicals are mono- or polysubstituted by CN, NO₂, -CF₃, -OCF₃, OR12, NR7R8, NR7CONR7R8, COR7, OCOR7, OCOOR7, COOR7, CONR7R8 or

5 OCONR7R8;

(C₂-C₁₀)-alkenyl, (C₂-C₁₀)-alkynyl, (C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where the alkenyl, alkynyl, aryl, heterocyclyl and alkylenearyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, OH, (C₁-C₆)-alkyl, -CF₃, -OCF₃, OR7, NR7R8, NR7CONR7R8, COR7,

10 OCOR7, OCOOR7, COOR7, CONR7R8 or OCONR7R8;

excluding the definitions of unsubstituted phenyl and unsubstituted pyridyl, and also phenyl and pyridyl each substituted by F, Cl, Br, I, OH or (C₁-C₆)-alkyl, from the R3 radical;

15 R7, R8 are each independently H, (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR9R10, CONR9R10, (C₁-C₆)-alkylene-COOR9, COOR9, COR9, (C₁-C₆)-alkylene-COR9, (C₁-C₆)-alkylene-OR9, (C₁-C₆)-alkylene-NR9R10, (C₁-C₆)-alkylene-SR9, (C₁-C₆)-alkylene-S(O)R9, (C₁-C₆)-alkylene-S(O)₂R9, S(O)R9, S(O)₂R9, (C₁-C₄)-alkylene-(C₆-C₁₀)-aryl or

20 (C₁-C₄)-alkylene-heterocyclyl;

R9, R10 are each independently H, (C₁-C₆)-alkyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, -(C₆-C₁₀)-aryl, heterocyclyl or (C₁-C₆)-alkylene-heterocyclyl;

25 R12 is (C₁-C₆)-alkyl, -CF₃, (C₃-C₁₀)-cycloalkyl, (C₆-C₁₀)-aryl, heterocyclyl, (C₁-C₆)-alkylene-CONR9R10, CONR9R10, (C₁-C₆)-alkylene-COOR9, COOR9, COR9, (C₁-C₆)-alkylene-COR9, (C₁-C₆)-alkylene-OR9, (C₁-C₆)-alkylene-NR9R10, (C₁-C₆)-alkylene-SR9, (C₁-C₆)-alkylene-S(O)R9, (C₁-C₆)-alkylene-S(O)₂R9, S(O)R9, S(O)₂R9, (C₂-C₄)-alkylene-(C₆-C₁₀)-aryl or (C₁-C₄)-alkylene-

30 heterocyclyl;

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R4, R5 are each independently H, (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl, where (C₁-C₆)-alkyl or (C₃-C₈)-cycloalkyl may be substituted by F, Cl, Br, I, CN, aryl, heterocyclyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂, OH, O(C₁-C₆)-alkyl, Oaryl, Oheteroaryl, S(C₁-C₆)-alkyl, S(O)(C₁-C₆)-alkyl or S(O)₂(C₁-C₆)-alkyl, where these alkyl groups may in turn be substituted by F, Cl, Br or I;

5

R11 is H, F, Cl, Br, I, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl, NH₂, NH(C₁-C₆)-alkyl, NH(C₃-C₇)-cycloalkyl, N((C₁-C₆)-alkyl)₂ or O-(C₁-C₆)-alkyl, where the alkyl groups may be mono- or polysubstituted by F, Cl, Br or I;

10

n is 0, 1 or 2;

and physiologically compatible salts thereof.

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

R20 is H;

R21 is (C₃-C₁₀)-cycloalkyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, phenyl, (C₁-C₆)-alkylene-(C₆-C₁₀)-pyridyl, where the cycloalkyl, aryl and pyridyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, CF₃, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

20 excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

25

R3 is independently (C₂-C₁₀)-alkenyl or (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where the alkenyl and (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl radicals may be mono- or polysubstituted by F, Cl, Br;

30 R4, R5 are each H;

n is 0;

and physiologically compatible salts thereof.

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

5 R20 is H;

R21 is (C₃-C₁₀)-cycloalkyl, benzyl, pyridyl, phenyl, where the alkyl, cycloalkyl and benzyl radicals may be mono- or polysubstituted by F, Cl, Br, I, CN, NO₂, SH, OH, (C₁-C₆)-alkyl, O-(C₁-C₆)-alkyl or S-(C₁-C₆)-alkyl;

10 excluding the definitions of unsubstituted phenyl and unsubstituted benzyl from the R21 radical;

R3 is independently (C₂-C₁₀)-alkenyl or (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl, where the alkenyl and (C₁-C₆)-alkylene-(C₆-C₁₀)-aryl radicals may be mono- or 15 polysubstituted by F, Cl, Br;

R4, R5 are each H;

n is 0;

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and physiologically compatible salts thereof.

? A compound as claimed in one or more of claims 1 to 3 for use as a medicament.

25 5. A medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 3.

6. A medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 3 and at least one further active ingredient.

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7. A medicament as claimed in claim 6, which comprises, as a further active ingredient, one or more antidiabetics, active hypoglycemic ingredients, HMG-CoA reductase inhibitors,

cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, CETP inhibitors, polymeric bile acid adsorbers, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP citrate lyase inhibitors, squalene synthetase 5 inhibitors, lipoprotein(a) antagonists, lipase inhibitors, insulins, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α -glucosidase inhibitors, active ingredients which act on the ATP-dependent potassium channel of the beta cells, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRIB antagonists, urocortin agonists, β 3 agonists, CB1 receptor antagonists, MSH (melanocyte-stimulating 10 hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed serotonin 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 (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR- β agonists or amphetamines.

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8. The use of the compounds as claimed in one or more of claims 1 to 3 for producing a medicament for lowering blood sugar.

9. The use of the compounds as claimed in one or more of claims 1 to 3 for producing a 20 medicament for treating type II diabetes.

10. The use of the compounds as claimed in one or more of claims 1 to 3 for producing a medicament for treating lipid and carbohydrate metabolism disorders.

25 11. The use of the compounds as claimed in one or more of claims 1 to 3 for producing a medicament for treating arteriosclerotic manifestations.

12. The use of the compounds as claimed in one or more of claims 1 to 3 for producing a medicament for treating insulin resistance.

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13. A process for producing a medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 3, which comprises mixing the active ingredient with a

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pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.

