

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2007321496 B2**

- (54) Title
Novel 1,4-benzothiepin-1,1-dioxide derivatives which are substituted with benzyl groups, method for producing drugs containing said compounds and use thereof
- (51) International Patent Classification(s)
C07H 5/06 (2006.01) **A61K 31/7028** (2006.01)
- (21) Application No: **2007321496** (22) Date of Filing: **2007.10.30**
- (87) WIPO No: **WO08/058628**
- (30) Priority Data
- | | | |
|--------------------------|-------------------|--------------|
| (31) Number | (32) Date | (33) Country |
| 10 2006 053 635.5 | 2006.11.14 | DE |
- (43) Publication Date: **2008.05.22**
(44) Accepted Journal Date: **2012.07.26**
- (71) Applicant(s)
Sanofi-Aventis Deutschland GmbH
- (72) Inventor(s)
Schaefer, Hans-Ludwig;Glombik, Heiner;Heuer, Hubert;Theis, Stefan;Kramer, Werner;Frick, Wendelin
- (74) Agent / Attorney
Watermark Patent and Trade Marks Attorneys, Level 2 302 Burwood Road, Hawthorn, VIC, 3122
- (56) Related Art
WO 2003/018024
US 2004/087648

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro



(43) Internationales Veröffentlichungsdatum
22. Mai 2008 (22.05.2008)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2008/058628 A1

(51) Internationale Patentklassifikation:

C07H 5/06 (2006.01) A61K 31/7028 (2006.01)

(21) Internationales Aktenzeichen: PCT/EP2007/009393

(22) Internationales Anmeldedatum:

30. Oktober 2007 (30.10.2007)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:

10 2006 053 635.5

14. November 2006 (14.11.2006) DE

(71) Anmelder (für alle Bestimmungsstaaten mit Ausnahme von US): **SANOFI-AVENTIS DEUTSCHLAND GMBH** [DE/DE]; Brüningstrasse 50, 65929 Frankfurt am Main (DE).

(72) Erfinder; und

(75) Erfinder/Anmelder (nur für US): **FRICK, Wendelin** [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **GLOMBIK, Heiner** [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **THEIS, Stefan** [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **HEUER, Hubert** [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE).

SCHAEFER, Hans-Ludwig [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **KRAMER, Werner** [DE/DE]; c/o Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE).

(81) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

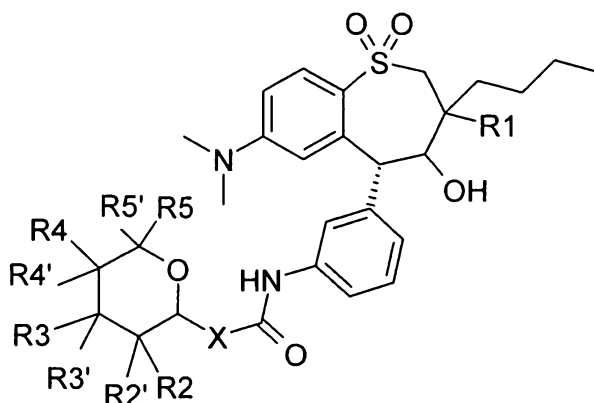
(84) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare regionale Schutzrechtsart): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:

— mit internationalem Recherchenbericht

(54) Title: NOVEL 1,4-BENZOTHIEPIN-1,1-DIOXIDE DERIVATIVES WHICH ARE SUBSTITUTED WITH BENZYL GROUPS, METHOD FOR PRODUCING DRUGS CONTAINING SAID COMPOUNDS AND USE THEREOF

(54) Bezeichnung: NEUE MIT BENZYLRESTEN SUBSTITUIERTE 1,4-BENZOTHIEPIN-1,1-DIOXIDDERIVATE, VERFAHREN ZU DEREN HERSTELLUNG, DIESE VERBINDUNGEN ENTHALTENDE ARZNEIMITTEL UND DEREN VERWENDUNG



(57) Abstract: The invention relates to the compounds of formula (I) and to the physiologically acceptable salts thereof. These compounds are suitable, for example, as hypolipidemics.

(57) Zusammenfassung: Die Erfindung betrifft die Verbindungen der Formel I, sowie deren physiologisch verträgliche Salze. Die Verbindungen eignen sich z.B. als Hypolipidämika.

WO 2008/058628 A1

Description

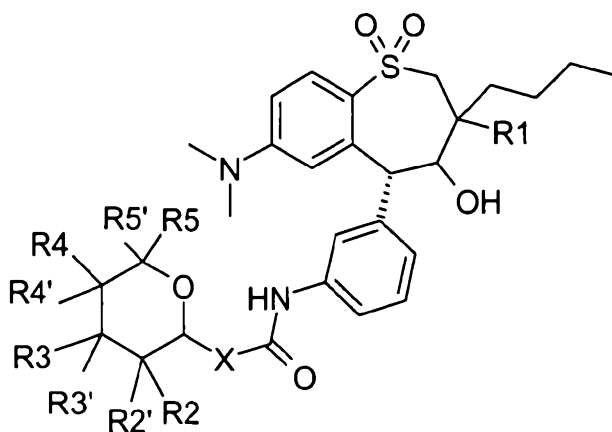
Novel 1,4-benzothiepine 1,1-dioxide derivatives substituted by benzyl radicals,
method for their preparation, pharmaceuticals comprising these compounds, and the
use thereof

The invention relates to 1,4-benzothiepine 1,1-dioxide derivatives substituted by benzyl radicals, and the physiologically tolerated salts thereof.

10 1,4-Benzothiepine 1,1-dioxide derivatives of similar structure have previously been described (US 5,994,391).

The invention was based on the object of providing further compounds which show a hypolipidemic effect.

The invention therefore relates to the compound of the formula I



1

in which the meanings are

X O, NH, CH₂ or a bond;

R1 (C₁-C₆)-alkyl;

R2, R2', R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH,

5 -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine;

10 phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

15 where always at least one of the radicals R2, R2', R3, R3', R4, R4', R5, R5' has the meaning of -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl where the phenyl ring may be substituted one to 3 times 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, CONH₂;

20

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

25 m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

30

Preference is given to compounds of the formula I in which the meanings are

X NH;

R1 (C₁-C₆)-alkyl;

R2, R2', R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH,
 5 -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-
 S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl,
 CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl,
 (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than
 10 one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine;
 phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl,
 -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one
 to 3 times 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, CONH₂;

15 where always at least one of the radicals R2, R2', R3, R3', R4, R4', R5, R5' has the
 meaning of S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6 or
 (C₁-C₆)-alkylene-O-S(O)_p-R6 and another has the meaning of
 -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may
 20 be substituted one to 3 times 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, CONH₂;

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

30 p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

Particular preference is given to compounds of the formula I in which the meanings are

X NH;

5

R1 (C₁-C₆)-alkyl;

R2, OH;

10 R2' H;

R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH,

CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6,

(C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)-alkyl, CONH₂,

15

CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl,

(C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all

hydrogen(s) in the alkyl radicals may be replaced by fluorine;

phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl,

-(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one

20

to 3 times 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, CONH₂;

where always at least one of the radicals R3, R3', R4, R4', R5, R5' has the meaning

25

of (S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6 or (C₁-C₆)-

alkylene-O-S(O)_p-R6 and another has the meaning of -O-(CH₂)_m-phenyl

or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted

one to 3 times 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,

30

COO-(C₁-C₆)-alkyl, CONH₂;

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

5 p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

Particular preference is further given to compounds of the formula I in which the
10 meanings are

X NH;

15 R1 (C₁-C₆)-alkyl;

R2, OH;

R2' H;

20 R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all
25 hydrogen(s) in the alkyl radicals may be replaced by fluorine; phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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,
30 COO-(C₁-C₆)-alkyl, CONH₂;

where always at least one of the radicals R3, R3', R4, R4', R5, R5' has the meaning of (C₁-C₆)-alkylene-O-S(O)_p-R6 and another has the meaning of

-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

5

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

10 m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

15

Particular preference is further given to compounds of the formula I in which the meanings are

X NH;

20

R1 (C₁-C₆)-alkyl;

R2, OH;

25 R2' H;

R5' (C₁-C₆)-alkylene-O-S(O)₂-R6;

30

R3, R3', R4, R4', R5 independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in

the alkyl radicals may be replaced by fluorine;

phenyl, $-(CH_2)$ -phenyl, $-(CH_2)_n$ -phenyl, O-phenyl, $O-(CH_2)_m$ -phenyl, $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$, SO_2-CH_3 , $COOH$, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

where always at least one of the radicals R_3 , R_3' , R_4 , R_4' , R_5 , R_5' has the meaning of $-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$, SO_2-CH_3 , $COOH$, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

R_6 H, OH, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$;

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

and the pharmaceutically acceptable salts thereof.

Preference is further given to compounds of the formula I in which one, two or three of the radicals R_2 , R_2' , R_3 , R_3' , R_4 , R_4' , R_5 , R_5' have the meaning OH.

Compounds of the formula I which are preferred in one embodiment are those in which the radical X is equal to O.

Compounds of the formula I which are preferred in one embodiment are those in which the radical X is equal to NH.

Compounds of the formula I which are preferred in one embodiment are those in which the radical X is equal to CH_2 .

Compounds of the formula I which are preferred in one embodiment are those in which the radical R1 is equal to butyl.

- 5 Compounds of the formula I which are preferred in one embodiment are those in which the radical R1 is equal to ethyl.

Compounds of the formula I which are preferred in one embodiment are those in which the radical R2 is equal to OH.

10

Compounds of the formula I which are preferred in one embodiment are those in which the radical of at least one of the radicals R2, R2', R3, R3', R4, R4', R5 or R5' is equal to -O-benzyl.

- 15 Compounds of the formula I which are preferred in one embodiment are those in which the radical R3 is equal to -O-benzyl.

Compounds of the formula I which are preferred in one embodiment are those in which the radical R4 is equal to OH or OSO₂OH.

20

Compounds of the formula I which are preferred in one embodiment are those in which the radical R4 is equal to OH.

- 25 Compounds of the formula I which are preferred in one embodiment are those in which at least one of the radicals R2, R2', R3, R3', R4, R4', R5 or R5' is equal to CH₂OSO₂OH.

Compounds of the formula I which are preferred in one embodiment are those in which at least one of the radicals R5 or R5' is equal to CH₂OH or CH₂Obenzyl.

30

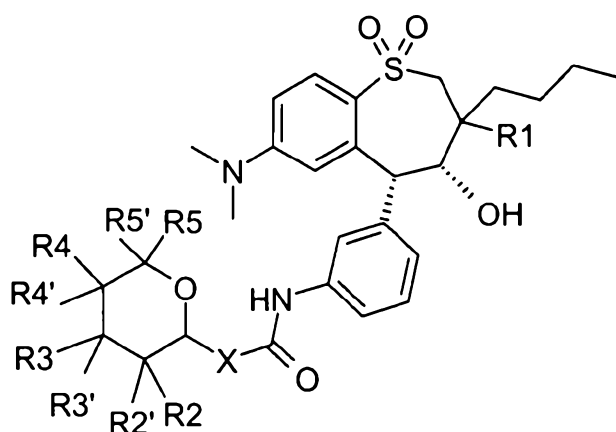
Compounds of the formula I which are preferred in one embodiment are those in which at least one of the radicals R5 or R5' is equal to CH₂OSO₂OH.

Compounds of the formula I which are preferred in one embodiment are those in which R5 is equal to CH₂OSO₂OH.

Compounds of the formula I which are preferred in one embodiment are those in which R5 is equal to CH₂OSO₂OH and R5' is equal to H.

Compounds of the formula I which are preferred in one embodiment are those in which R1 is equal to ethyl and R5 is equal to CH₂OSO₂OH.

Compounds of the formula I which are preferred in one embodiment are those in which the structure of the formula I is present as follows:



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

The alkyl, alkenyl, alkynyl, alkylene, alkenylene and alkynylene radicals in the radicals R₁, R₂, R₂', R₃, R₃', R₄, R₄', R₅, R₅' and R₆ may be either straight-chain or branched.

The invention relates to compounds of the formula I in the form of their tautomers, racemates, racemic mixtures, mixtures of stereoisomers, pure stereoisomers, mixtures of diastereoisomers, pure diastereoisomers. The mixtures are separated for example by chromatographic means.

Pharmaceutically acceptable salts are, because their solubility in water is greater than that of the initial or basic compounds, particularly suitable for medical applications. These salts must have a pharmaceutically acceptable anion or cation.

Suitable pharmaceutically acceptable acid addition salts of the compounds of the

- 5 invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acids. Suitable pharmaceutically acceptable
- 10 basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts), alkaline earth metal salts (such as magnesium and calcium salts), trometamol (2-amino-2-hydroxymethyl-1,3-propanediol), diethanolamine, lysine or ethylenediamine.

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

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

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

- An alkyl radical means a straight-chain or branched hydrocarbon chain having up to
- 30 eight carbons, such as, for example, methyl, ethyl, isopropyl, tert-butyl, hexyl, heptyl, octyl. The alkyl radicals may be substituted once or more than once as described above.

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

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.3 mg to 100 mg (typically from 3 mg and 50 mg) per day and per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose may be for example in the range from 0.3 mg to 1.0 mg/kg, which can suitably be administered as infusion of from 10 ng to 100 ng per kilogram per minute. Suitable infusion solutions for these purposes may comprise for example from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may comprise for example from 1 mg to 10 g of the active ingredient. Thus, ampoules for injections may comprise for example from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, may comprise for example from 1.0 to 1000 mg, typically from 10 to 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including other compounds of formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral, rectal, topical, peroral (for example sublingual) and parenteral (for example subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of

the condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Preference is given to acid- and gastric juice-resistant formulations. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contains a defined amount of the compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients.

Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

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

Pharmaceutical compositions suitable for parenteral administration comprise preferably sterile aqueous preparations of a compound of formula I, which are

preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also take place by subcutaneous, intramuscular or intradermal injection. These preparations can preferably be produced by mixing the compound with water and making the resulting
5 solution sterile and isotonic with blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

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

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

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

30 Further active ingredients suitable for combination products are:
All antidiabetics which are mentioned in the Rote Liste 2006, chapter 12; all weight-reducing agents/appetite suppressants which are mentioned in the Rote Liste 2006, chapter 1; all lipid-lowering agents which are mentioned in the Rote Liste 2006,

chapter 58. They may be combined with the compound of the invention of the formula I in particular for a synergistic improvement in the effect. The active ingredient combination can be administered either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients is present in a pharmaceutical preparation. Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives such as, for example, Lantus[®] (see www.lantus.com) or HMR 1964 or Levemir[®] (insulin detemir) or those described in WO2005005477 (Novo Nordisk), fast-acting insulins (see US 6,221,633), inhalable insulins such as, for example, Exubera[®] or oral insulins such as, for example, IN-105 (Nobex) or Oral-lyn[™] (Generex Biotechnology), GLP-1 derivatives such as, for example, exenatide, liraglutide or those which have been disclosed in WO98/08871, WO2005027978, WO2006037811 or WO2006037810 of Novo Nordisk A/S, in WO01/04156 of Zealand or in WO00/34331 of Beaufour-Ipsen, pramlintide acetate (Symlin; Amylin Pharmaceuticals), and orally effective hypoglycemic active ingredients.

The orally effective hypoglycemic active ingredients include preferably sulfonylureas,

biguanidines,

meglitinides,

oxadiazolidinediones,

thiazolidinediones,

glucosidase inhibitors,

inhibitors of glycogen phosphorylase,

glucagon antagonists,

glucokinase activators,

inhibitors of fructose-1,6-bisphosphatase,

modulators of glucose transporter 4 (GLUT4),

inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT),

GLP-1 agonists, potassium channel openers such as, for example, those which have been disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S, or those

- which are disclosed in WO2006045799 (Solvay),
inhibitors of dipeptidylpeptidase IV (DPP-IV),
insulin sensitizers,
inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or
5 glycogenolysis,
modulators of glucose uptake, of glucose transport and of glucose reabsorption,
inhibitors of 11 β -HSD1,
inhibitors of protein tyrosine phosphatase 1B (PTP1B),
modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2),
10 compounds which alter lipid metabolism such as antihyperlipidemic active
ingredients and antilipidemic active ingredients,
compounds which reduce food intake,
compounds which increase thermogenesis,
PPAR and RXR modulators and
15 active ingredients which act on the ATP-dependent potassium channel of the beta
cells.

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

In one embodiment of the invention, the compound of the formula I is administered
in combination with a cholesterol absorption inhibitor such as, for example,
ezetimibe, tiqueside, pamaqueside, FM-VP4 (sitostanol/campesterol ascorbyl
25 phosphate; Forbes Medi-Tech, WO2005042692, WO2005005453), MD-0727
(Microbia Inc., WO2005021497, WO2005021495) or with compounds as described
in WO2002066464 (Kotobuki Pharmaceutical Co. Ltd.), or WO2005044256 or
WO2005062824 (Merck & Co.) or WO2005061451 and WO2005061452
(AstraZeneca AB), and WO2006017257 (Phenomix) or WO2005033100 (Lipideon
30 Biotechnology AG).

In one embodiment of the invention, the compound of the formula I is administered
in combination with Vytorin™, a fixed combination of ezetimibe and simvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with a fixed combination of ezetimibe with fenofibrate.

- 5 In a further embodiment of the invention, the compound of the formula I is administered in combination with a fixed combination of fenofibrate and rosuvastatin.

In one embodiment of the invention, the compound of the formula I is administered in combination with ISIS-301012, an antisense oligonucleotide able to regulate the
10 apolipoprotein B gene.

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR gamma agonist such as, for example, rosiglitazone, pioglitazone, JTT-501, GI 262570, R-483, CS-011 (rivoglitazone).
15

In one embodiment of the invention, the compound of the formula I is administered in combination with Competact™, a fixed combination of pioglitazone hydrochloride with metformin hydrochloride.

- 20 In one embodiment of the invention, the compound of the formula I is administered in combination with duetact™, a fixed combination of pioglitazone hydrochloride with glimepiride.

In one embodiment of the invention, the compound of the formula I is administered
25 in combination with Avandamet®, a fixed combination of rosiglitazone maleate with metformin hydrochloride.

In one embodiment of the invention, the compound of the formula I is administered in combination with a PPAR alpha agonist such as, for example, GW9578, GW-
30 590735, K-111, LY-674, KRP-101, DRF-10945.

In one embodiment of the invention, the compound of the formula I is administered in combination with a mixed PPAR alpha/gamma agonist such as, for example,

naveglitazar, LY-510929, ONO-5129, E-3030, AVE 8042, AVE 8134, AVE 0847, or as described in PCT/US 00/11833, PCT/US 00/11490, DE10142734.4 or in J.P. Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

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

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

In a further embodiment of the invention, the compound of the formula I is administered in combination with an activator of AMP-activated protein kinase (AMPK) such as, for example, A-769662 or those compounds described in
15 US 20050038068.

In one embodiment of the invention, the compound of the formula I is administered in combination with a fibrate such as, for example, fenofibrate, clofibrate or bezafibrate.
20

In one embodiment of the invention, the compound of the formula I is administered in combination with an MTP inhibitor such as, for example, implitapide, BMS-201038, R-103757 or those described in WO2005085226, WO2005121091, WO2006010423.
25

In one embodiment of the invention, the compound of the formula I is administered in combination with a CETP inhibitor such as, for example, torcetrapib or JTT-705 or those described in WO2006002342, WO2006010422, WO2006012093.

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

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

5

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

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

15 In one embodiment of the invention, the compound of the formula I is administered in combination with an ACAT inhibitor such as, for example, avasimibe or SMP-797.

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

20

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

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

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

30

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

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

5

In one embodiment of the invention, the compound of the formula I is administered in combination with an agonist of GPR109A (HM74A receptor agonist) such as, for example, nicotinic acid or extended release niacin in conjunction with MK-0524A or those compounds described in WO2006045565, WO2006045564, WO2006069242.

10

In another embodiment of the invention, the compound of the formula I is administered in combination with an agonist of GPR116 as are described for example in WO2006067531, WO2006067532.

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

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

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

25

In one embodiment, the compound of the formula I is administered in combination with a substance enhancing insulin secretion, such as, for example, KCP-265 (WO2003097064).

In one embodiment, the compound of the formula I is administered in combination
30 with agonists of the glucose-dependent insulinotropic receptor (GDIR) such as, for example, APD-668.

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

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

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

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

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

20 In one embodiment, the compound of the formula I is administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

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

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

In one embodiment, the compound of the formula I is administered in combination with activators of glucokinase, such as, for example, LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50 or those as are described for example in

5 WO2004072031, WO2004072066, WO2005080360, WO2005044801, WO2006016194, WO2006058923.

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

10

In one embodiment, the compound of the formula I is administered in combination with inhibitors of fructose-1,6-bisphosphatase (FBPase), such as, for example, CS-917 (MB-06322) or MB-07803 or those described in WO2006023515.

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

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

In one embodiment, the compound of the formula I is administered in combination with inhibitors of dipeptidylpeptidase IV (DPP-IV), such as, for example, vildagliptin
25 (LAF-237), sitagliptin (MK-0431), saxagliptin (BMS-477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200, GW-825964X, KRP-104, DP-893 or as are described in WO2003074500, WO2003106456, WO200450658, WO2005058901, WO2005012312, WO2005/012308, WO2006039325, WO2006058064, PCT/EP2005/007821, PCT/EP2005/008005,
30 PCT/EP2005/008002, PCT/EP2005/008004, PCT/EP2005/008283, DE 10 2005 012874.2 or DE 10 2005 012873.4.

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

with Januvia™, a fixed combination of sitagliptin phosphate with metformin hydrochloride.

In one embodiment, the compound of the formula I is administered in combination
5 with inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11 β -HSD1), such as, for
example, BVT-2733, JNJ-25918646, INCB-13739 or those as are described for
example in WO200190090-94, WO200343999, WO2004112782, WO200344000,
WO200344009, WO2004112779, WO2004113310, WO2004103980,
WO2004112784, WO2003065983, WO2003104207, WO2003104208,
10 WO2004106294, WO2004011410, WO2004033427, WO2004041264,
WO2004037251, WO2004056744, WO2004058730, WO2004065351,
WO2004089367, WO2004089380, WO2004089470-71, WO2004089896,
WO2005016877, WO2005097759, WO2006010546, WO2006012227,
WO2006012173, WO2006017542, WO2006034804, WO2006040329,
15 WO2006051662, WO2006048750, WO2006049952, WO2006048331,
WO2006050908, WO2006024627, WO2006040329, WO2006066109.

In one embodiment, the compound of the formula I is administered in combination
with inhibitors of protein tyrosine phosphatase 1B (PTP1B), as are described for
20 example in WO200119830-31, WO200117516, WO2004506446, WO2005012295,
WO2005116003, PCT/EP2005/005311, PCT/EP2005/005321,
PCT/EP2005/007151, PCT/EP2005/01294 or DE 10 2004 060542.4.

In one embodiment, the compound of the formula I is administered in combination
25 with modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1,
SGLT2), such as, for example, KGA-2727, T-1095, SGL-0010, AVE 2268 and
SAR 7226 or as are described for example in WO2004007517, WO200452903,
WO200452902, PCT/EP2005/005959, WO2005085237, JP2004359630,
WO2005121161, WO2006018150, WO2006035796, WO2006062224,
30 WO2006058597 or by A. L. Handlon in Expert Opin. Ther. Patents (2005) 15(11),
1531-1540.

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

with modulators of GPR40.

In one embodiment, the compound of the formula I is administered in combination with modulators of GPR119b as are described for example in WO2004041274.

5

In one embodiment, the compound of the formula I is administered in combination with modulators of GPR119 as are described for example in WO2005061489 (PSN-632408).

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

15 In one embodiment, the compound of the formula I is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC), such as, for example, those as described in WO199946262, WO200372197, WO2003072197, WO2005044814, WO2005108370, JP2006131559.

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

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

30

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

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

5

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

- 10 In one embodiment, the compound of the formula I is administered in combination with modulators of the glucocorticoid receptor, like those described for example in WO2005090336.

- In a further embodiment, the compound of the formula I is administered in
15 combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone and Metabolic Research (2001), 33(9), 554-558);
NPY antagonists such as, for example, naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]cyclohexylmethyl}amide hydrochloride
20 (CGP 71683A);
NPY-5 receptor antagonists such as L-152804, S-2367 or as are described for example in WO2006001318;
Peptide YY 3-36 (PYY3-36) or analogous compounds, such as, for example, CJC-1682 (PYY3-36 conjugated with human serum albumin via Cys34), CJC-1643
25 (derivative of PYY3-36 which conjugates in vivo to serum albumin) or those as are described in WO2005080424;
CB1R (cannabinoid receptor 1) antagonists (such as, for example, rimonabant, SR147778, SLV-319, AVE-1625, MK-0364 or salts thereof, or those as are described for example in EP 0656354, WO 00/15609, WO2001/64632,
30 WO2001/64633, WO2001/64634, WO02/076949, WO2005080345, WO2005080328, WO2005080343, WO2005075450, WO2005080357, WO200170700, WO2003026647-48, WO200302776, WO2003040107, WO2003007887, WO2003027069, US6,509,367, WO200132663, WO2003086288,

- WO2003087037, WO2004048317, WO2004058145, WO2003084930,
WO2003084943, WO2004058744, WO2004013120, WO2004029204,
WO2004035566, WO2004058249, WO2004058255, WO2004058727,
WO2004069838, US20040214837, US20040214855, US20040214856,
5 WO2004096209, WO2004096763, WO2004096794, WO2005000809,
WO2004099157, US20040266845, WO2004110453, WO2004108728,
WO2004000817, WO2005000820, US20050009870, WO200500974,
WO2004111033-34, WO200411038-39, WO2005016286, WO2005007111,
WO2005007628, US20050054679, WO2005027837, WO2005028456,
10 WO2005063761-62, WO2005061509, WO2005077897, WO2006047516,
WO2006060461, WO2006067428, WO2006067443);
MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]amide; (WO 01/91752)) or LB53280, LB53279, LB53278 or
15 THIQ, MB243, RY764, CHIR-785, PT-141 or those that are described in
WO2005060985, WO2005009950, WO2004087159, WO2004078717,
WO2004078716, WO2004024720, US20050124652, WO2005051391,
WO2004112793, WO20050222014, US20050176728, US20050164914,
US20050124636, US20050130988, US20040167201, WO2004005324,
20 WO2004037797, WO2005042516, WO2005040109, WO2005030797,
US20040224901, WO200501921, WO200509184, WO2005000339, EP1460069,
WO2005047253, WO2005047251, EP1538159, WO2004072076, WO2004072077
or WO2006021655-57;
orexin receptor antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-
25 ylurea hydrochloride (SB-334867-A) or those as are described for example in
WO200196302, WO200185693, WO2004085403, WO2005075458 or
WO2006067224);
histamine H3 receptor agonists (e.g. 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208) or
30 those as are described in WO200064884, WO2005082893);
CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585));
CRF BP antagonists (e.g. urocortin);

- urocortin agonists;
agonists of the beta-3 adrenoceptor such as, for example, 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol hydrochloride (WO 01/83451); or Solabegron
- 5 (GW-427353) or N-5984 (KRP-204) or those described in JP2006111553;
MSH (melanocyte-stimulating hormone) agonists;
MCH (melanin-concentrating hormone) receptor antagonists (such as, for example, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 or compounds such as are described in WO2003/15769, WO2005085200,
- 10 WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2004039780, WO2003033476, WO2002006245, WO2002089729, WO2002002744, WO2003004027, FR2868780, WO2006010446, WO2006038680, WO2006044293, WO2006044174);
- 15 CCK-A agonists (such as, for example, {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525), SR-146131 (WO 0244150) or SSR-125180 or those which are described in WO2005116034);
serotonin reuptake inhibitors (e.g. dexfenfluramine);
- 20 mixed serotoninergic and noradrenergic compounds (e.g. WO 00/71549);
5-HT receptor agonists, e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111);
5-HT_{2C} receptor agonists (such as, for example, lorcaserin hydrochloride (APD-356), BVT-933 or those as are described in WO200077010, WO20077001-02,
- 25 WO2005019180, WO2003064423, WO200242304 or WO2005082859);
5-HT₆ receptor antagonists as are described for example in WO2005058858;
bombesin receptor agonists (BRS-3 agonists);
galanin receptor antagonists;
growth hormone (e.g. human growth hormone or AOD-9604);
- 30 growth hormone-releasing compounds (tertiary butyl 6-benzyloxy-1-(2-diisopropyl-aminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695));
growth hormone secretagogue receptor antagonists (ghrelin antagonists) such as, for example, A-778193 or those as are described in WO2005030734;

- TRH agonists (see, for example, EP 0 462 884);
uncoupling protein 2 or 3 modulators;
leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.;
Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential
5 approach to the treatment of obesity. *Drugs of the Future* (2001), 26(9), 873-881);
DA agonists (bromocriptine or Doprexin);
lipase/amylase inhibitors (for example WO 00/40569);
inhibitors of diacylglycerol O-acyltransferases (DGATs) such as BAY-74-4113 or as
described for example in US2004/0224997, WO2004094618, WO200058491,
10 WO2005044250, WO2005072740, JP2005206492, WO2005013907,
WO2006004200, WO2006019020, WO2006064189;
inhibitors of fatty acid synthase (FAS) such as, for example, C75 or those as
described in WO2004005277;
oxyntomodulin;
15 oleoyl-estrone
or thyroid hormone receptor agonists such as, for example: KB-2115 or those as
described in WO20058279, WO200172692, WO200194293, WO2003084915,
WO2004018421 or WO2005092316.
- 20 In one embodiment, the further active ingredient is varenicline tartrate, a partial
agonist of the alpha 4-beta 2 nicotinic acetylcholine receptor.
- In one embodiment, the further active ingredient is trodusquemine.
- 25 In one embodiment, the further active ingredient is a modulator of the SIRT1
enzyme, a member of the human sirtuin enzyme family.
- In one embodiment, the further active ingredient is leptin; see, for example,
"Perspectives in the therapeutic use of leptin", Salvador, Javier; Gomez-Ambrosi,
30 Javier; Fruhbeck, Gema, *Expert Opinion on Pharmacotherapy* (2001), 2(10),
1615-1622.

In one embodiment, the further active ingredient is dexamphetamine or

amphetamine.

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

In another embodiment, the further active ingredient is sibutramine.

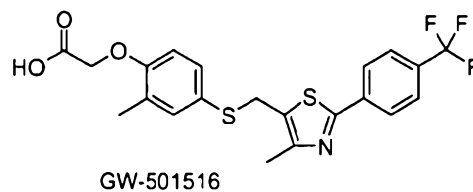
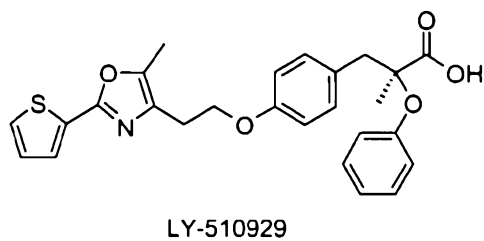
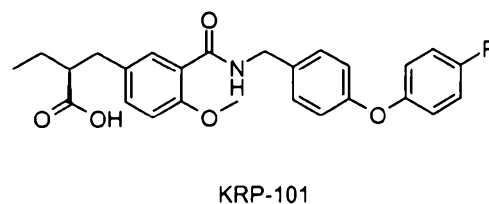
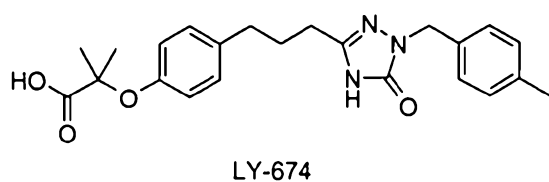
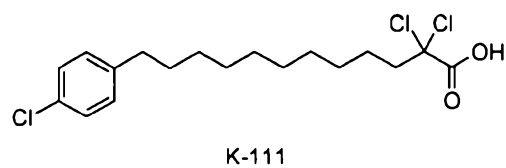
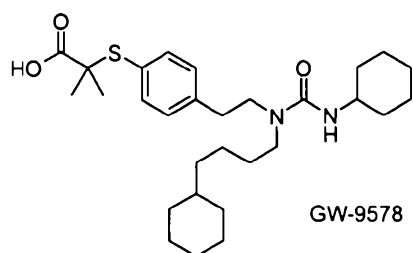
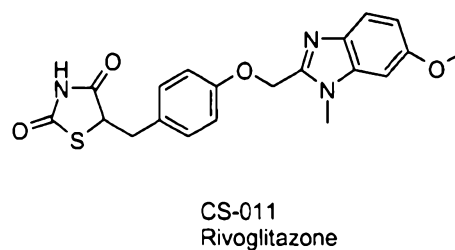
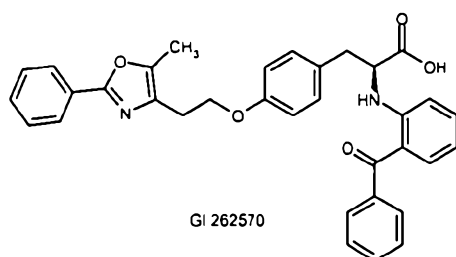
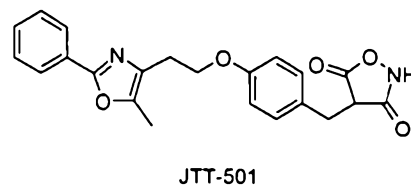
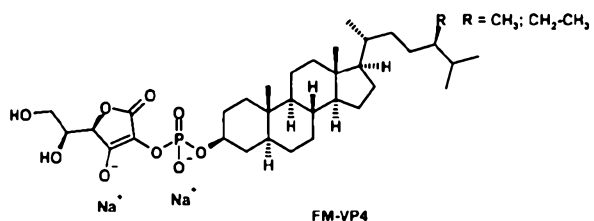
In one embodiment, the further active ingredient is mazindole or phentermine.

5

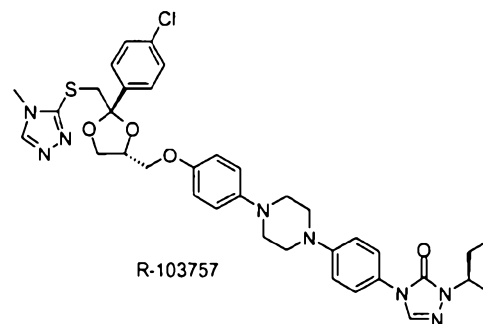
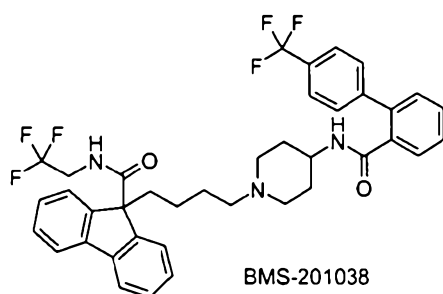
In one embodiment, the further active ingredient is a diphenylazetidinone derivative as described, for example, in US 6,992,067 or US 7,205,290.

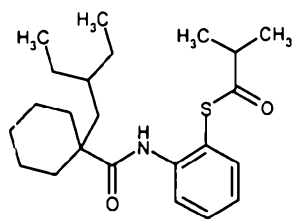
10 In one embodiment, the compound of the formula I is administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, Carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6).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

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

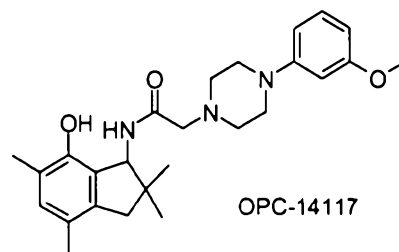


5

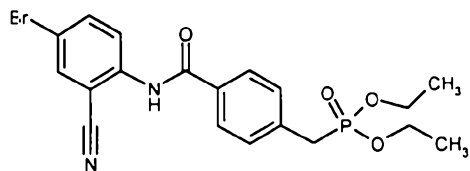




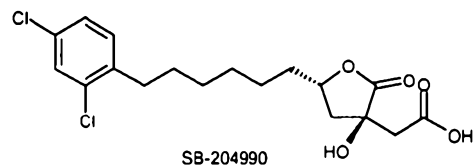
JTT-705



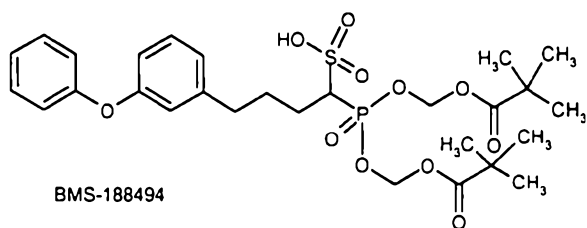
OPC-14117



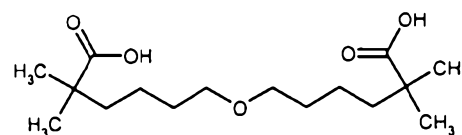
NO-1886



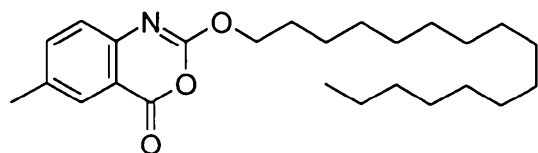
SB-204990



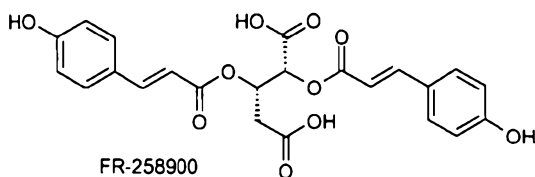
BMS-188494



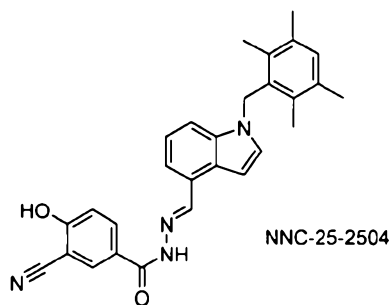
CI-1027



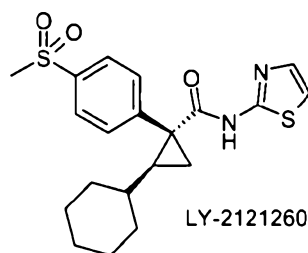
ATL-962



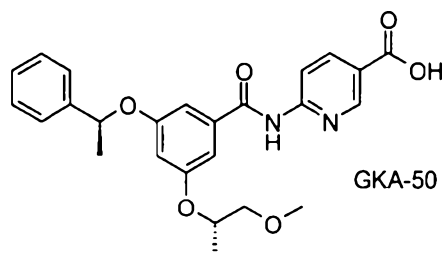
FR-258900



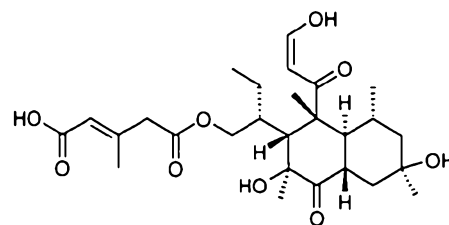
NNC-25-2504



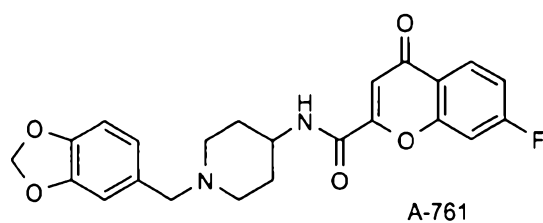
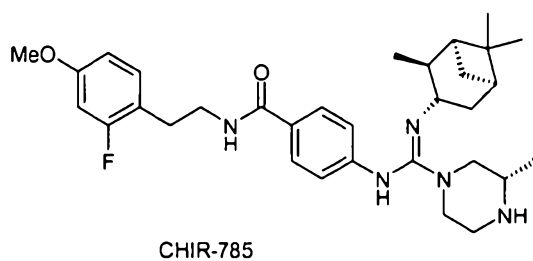
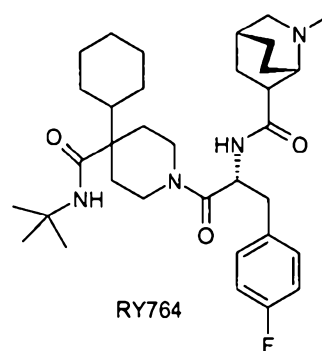
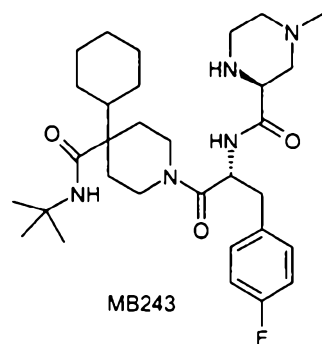
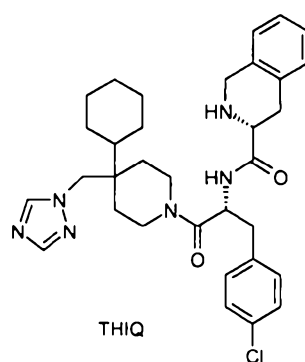
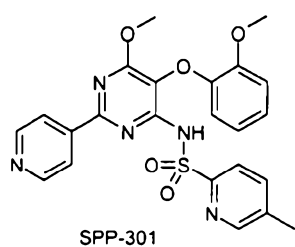
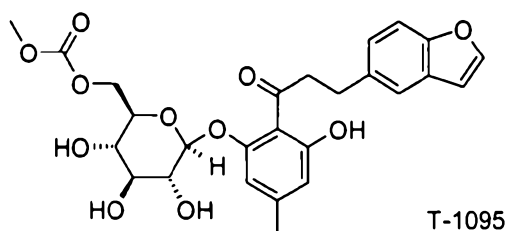
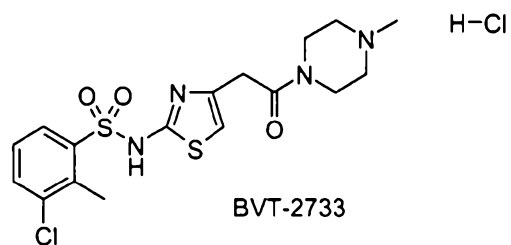
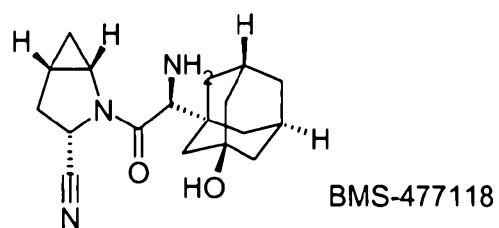
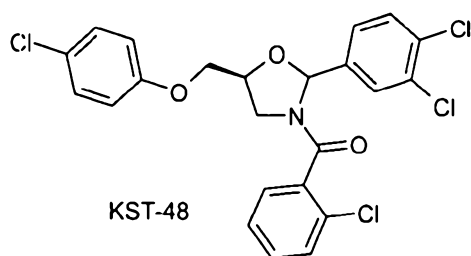
LY-2121260



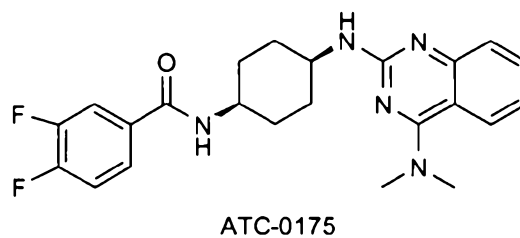
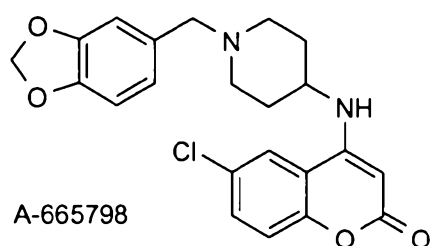
GKA-50



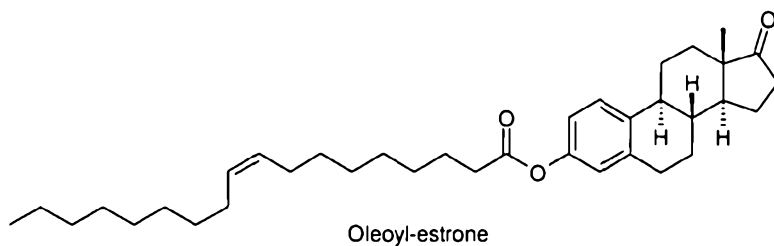
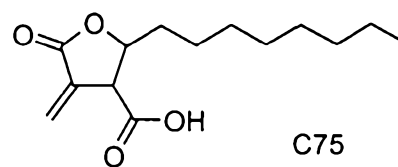
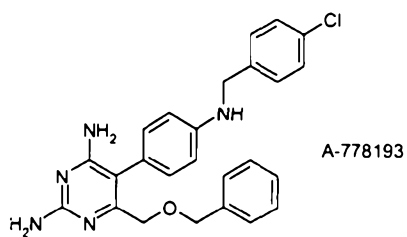
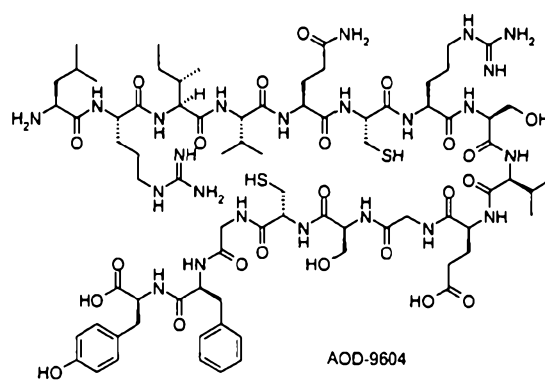
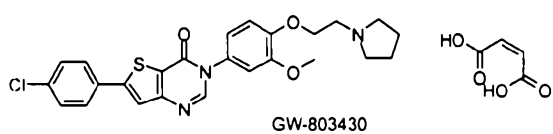
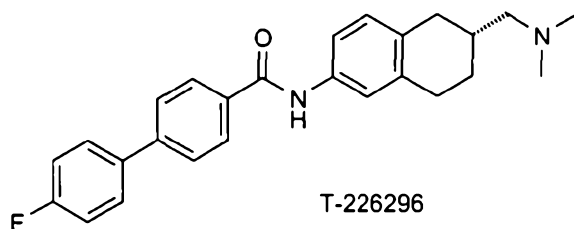
FR-225654



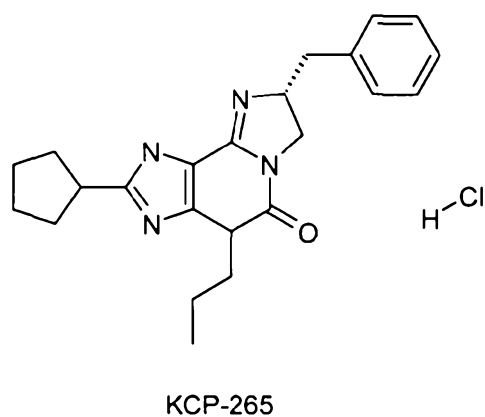
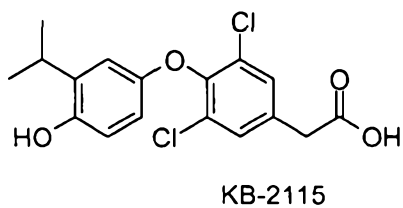
5



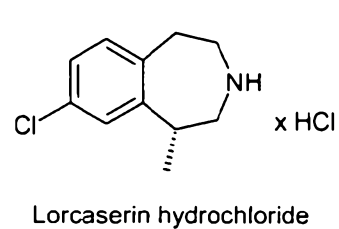
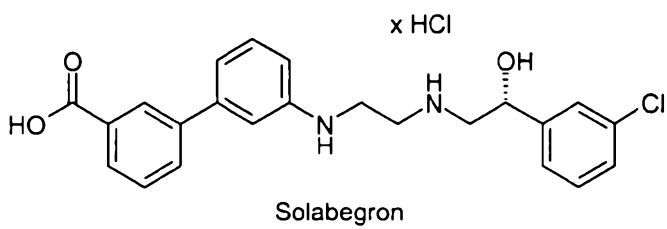
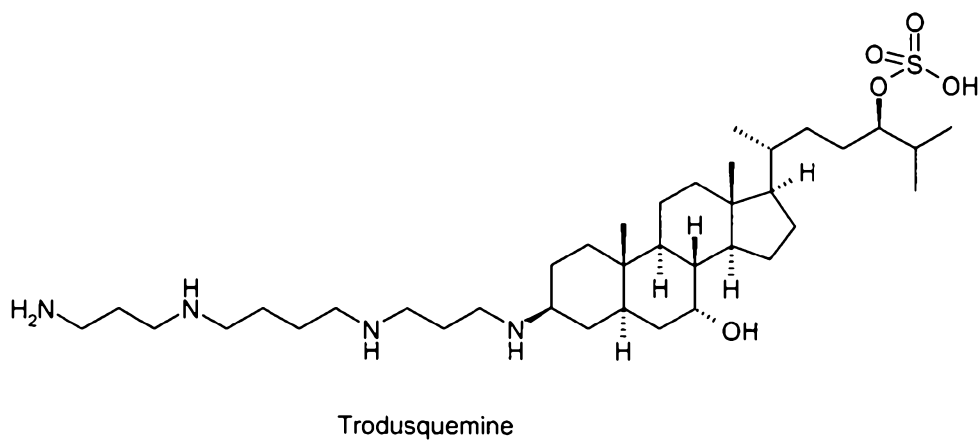
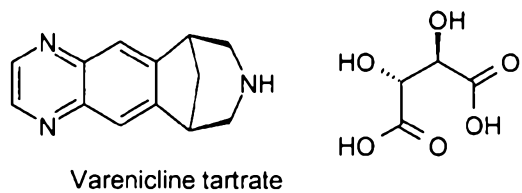
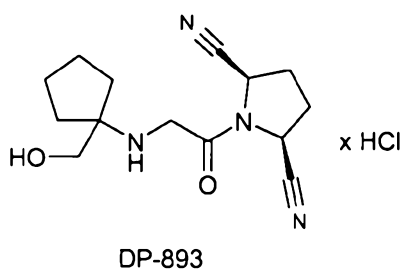
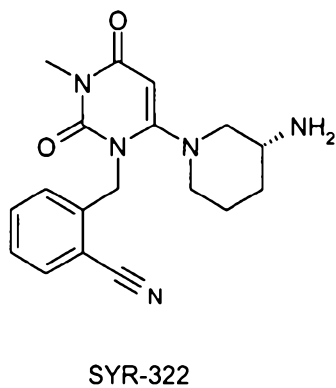
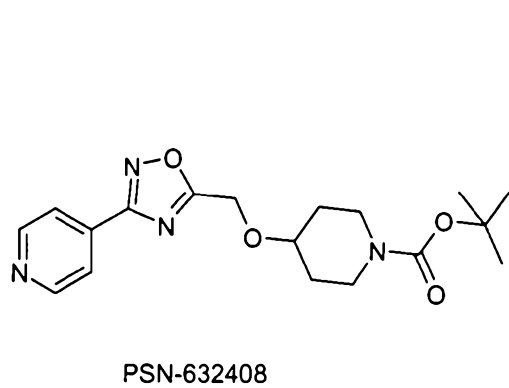
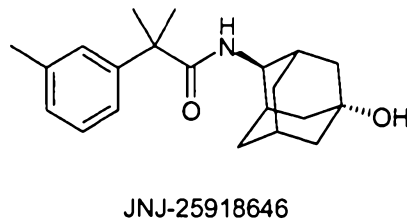
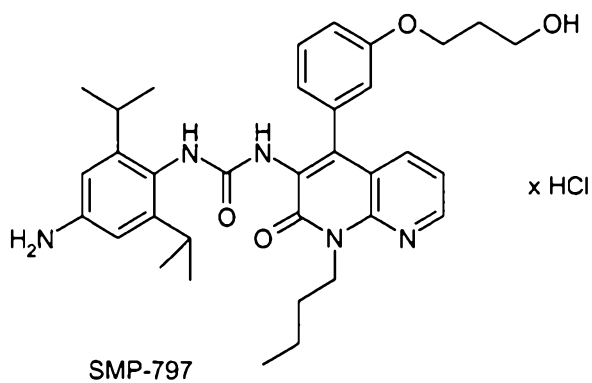
32

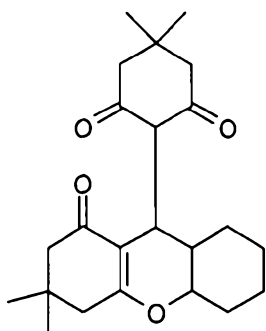


5

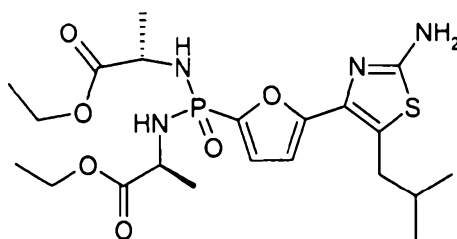


33

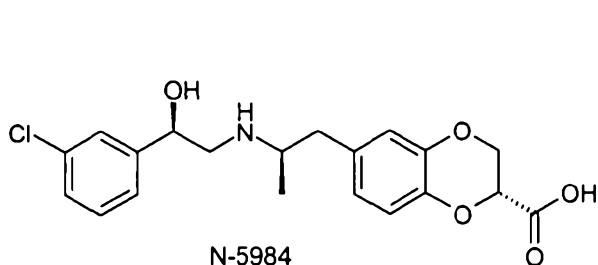




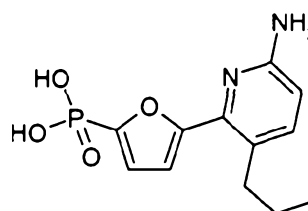
L-152804



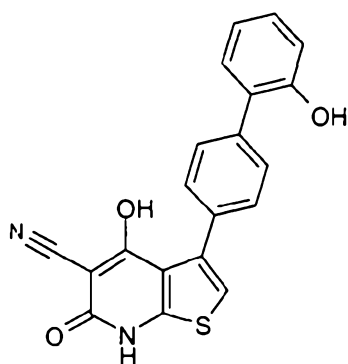
MB-06322



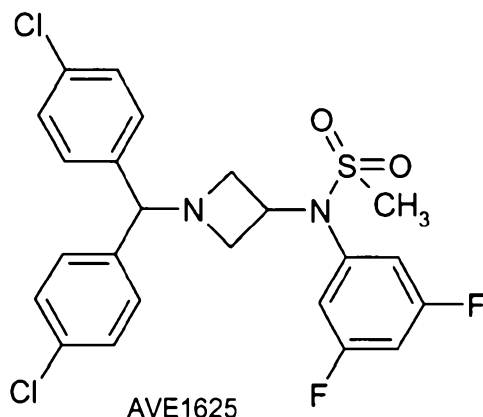
N-5984



MB-07803



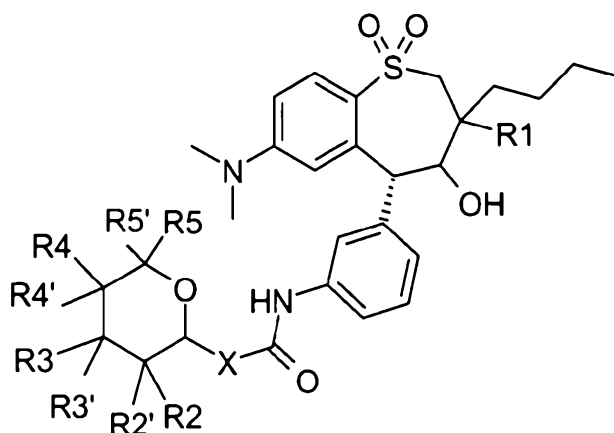
A-769662



AVE1625

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

Table 1:



5

Ex.	R1	R2, R2'	R3, R3'	R4, R4'	R5, R5'	X
1	Et	OH, H	OBn, H	OH, H	CH ₂ OH, H	NH
2	n-Bu	OH, H	OBn, H	OH, H	CH ₂ OH, H	NH
3	Et	OH, H	OBn, H	OH, H	CH ₂ OBn, H	NH
4	Et	OH, H	OBn, H	OH, H	CH ₂ OSO ₂ OH, H	NH
5	Et	OH, H	OBn, H	OSO ₂ OH, H	CH ₂ OSO ₂ OH, H	NH
6	n-Bu	OH, H	OBn, H	OH, H	CH ₂ OSO ₂ OH, H	NH

Et = Ethyl, Bu = n-Butyl, Bn = Benzyl

The activity of the compounds was assayed as follows:

10

Preparation and procedure for the *in vitro* IBAT inhibition assay:

1. Cloning of an expression vector for human IBAT

The cDNA (complementary deoxyribonucleic acid) of human IBAT was cloned by standard methods of molecular biology as described for example in Molecular Cloning: A Laboratory Manual by Joseph Sambrook and David Russell, and introduced into the pcDNA1 vector from Invitrogen. The subsequent sequencing of the insert revealed complete identity with bases 599 to 1645 of the base sequence for human IBAT which was described by P.A. Dawson and is deposited in the GenBank sequence database (GenBank Accession Number: U10417). Bases 599 to 1645 correspond to the complete coding region of human IBAT.

10 2. Preparation of a recombinant cell line with constitutive expression of human IBAT

The expression vector for human IBAT was introduced by stable transfection into CHO (chinese hamster ovary) cells. To select single cell clones, 400 µg/ml Geneticin was added to the cell culture medium (Ham's F12 medium supplemented with 10% fetal calf serum, 100 units/ml penicillin, 100 units/ml streptomycin). The functionality of the single cell clones resulting from the selection was assayed via their uptake activity for radiolabeled taurocholic acid ([³H]-TCA). The cell clone with the highest uptake activity for [³H]-TCA, referred to hereinafter as CHO-hIBAT, was selected for the further assays and further cultured in the presence of 400 µg/ml Geneticin.

3. Measurement of the inhibitory effect of the compound of the invention on the IBAT-dependent uptake of taurocholic acid into cells

25 CHO-hIBAT cells were seeded in a concentration of 40 000 cells per well in poly-D-lysine-coated 96-well plates in cell culture medium and cultured for 24 h. The cells were then washed once with sodium-free transport assay buffer (140 mM choline chloride, 2 mM potassium chloride, 1 mM magnesium chloride, 1 mM calcium chloride, 10 mM HEPES/Tris, pH 7.5) and subsequently incubated either with sodium-free transport assay buffer as negative control or with sodium-containing transport assay buffer (140 mM sodium chloride, 2 mM potassium chloride, 1 mM magnesium chloride, 1 mM calcium chloride, 10 mM HEPES/Tris, pH 7.5) as positive control at room temperature for 30 min. At the same time, the assay wells were also

incubated in the presence of the compound to be investigated in varying concentration in sodium-containing transport assay buffer at room temperature for 30 min. The test substances were appropriately diluted in transport assay buffer (40 µl/well) starting from a 10 mM stock solution in dimethyl sulfoxide. The assay
5 was then started by adding 10 µl/well of a mixture of radiolabeled taurocholic acid ([³H]-TCA) and unlabeled taurocholic acid. The final concentration of taurocholic acid in the assay was 10 µM. After an incubation time of 60 min at room temperature, the reaction was stopped by adding 100 µl/well of sodium-free transport assay buffer (4°C), and each well was washed three times with sodium-free transport assay
10 buffer. Finally, 100 µl of scintillation fluid were added to each well, and the radioactivity taken up into the cells was determined in a MicroBeta Scintillation Microplate Reader from Wallac.

The half-maximum inhibitory effect of the test compound (IC₅₀ value, inhibitory concentration 50) was determined in the following way:

15

1. Determination of the value for 0% inhibition. This is the measurement in the absence of substance, measured in sodium-containing transport assay buffer.
2. Determination of the value for 100% inhibition. This is the measurement in the absence of substance, measured in sodium-free transport assay buffer.
- 20 3. Calculation of the percentage inhibitions of those measurements carried out in the presence of various concentrations of the compound to be investigated. It was then possible to find therefrom the concentration of the compound which reduces the uptake of taurocholic acid by 50% (IC₅₀ value).

Table 2: Biological activity

Ex.	IC-50 (human IBAT) µM
1	0.0044
2	0.0069
3	0.0035
4	0.0024
5	0.0020
6	0.0107

It can be inferred from the measured data that the compounds of the invention of the formula I are very suitable for the treatment of hyperlipidemia.

5 The use of the compounds of the formula I for the treatment or prevention of further diseases is likewise conceivable. Examples of such diseases are:

1. - disorders of fatty acid metabolism and glucose utilization disorders
- disorders in which insulin resistance is involved
- 10 2. Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith.
- Particular aspects in this connection are
- hyperglycemia,
- improvement in insulin resistance,
15 - improvement in glucose tolerance,
- protection of the pancreatic β cells
- prevention of macro- and microvascular disorders
- 20 3. Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors:
- high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations,
- low HDL cholesterol concentration
25 - low apoA lipoprotein concentrations
- high LDL cholesterol concentrations
- small dense LDL cholesterol particles
- high apoB lipoprotein concentrations
- desaturation index (e.g. ratio 18:1 / 18:0n-9, 16:1 / 16:0 n-7 or 18:1n-9 + 16:1n-7 /
30 16:0 fatty acids)
4. Various other conditions which may be associated with the metabolic syndrome or syndrome X, such as:

- increased abdominal girth
- dyslipidemia (e.g. hypertriglyceridemia and / or low HDL)
- insulin resistance
- hypercoagulability
- 5 - hyperuricemia
- microalbuminemia
- thromboses, hypercoagulable and prothrombotic states (arterial and venous)
- high blood pressure
- heart failure such as, for example (but not restricted thereto), following
- 10 myocardial infarction, hypertensive heart disease or cardiomyopathy

5. Hepatic disorders and conditions related thereto

- fatty liver
- hepatic steatosis
- 15 - non-alcoholic hepatitis
- non-alcoholic steatohepatitis (NASH)
- alcoholic hepatitis
- acute fatty liver
- fatty liver of pregnancy
- 20 - drug-induced hepatitis
- iron overload disorders
- hepatic fibrosis
- hepatic cirrhosis
- hepatoma
- 25 - viral hepatitis

6. Skin disorders and conditions and those associated with polyunsaturated fatty acids

- eczema
- acne
- 30 - psoriasis
- keloid scar formation or prevention
- other diseases related to mucous membrane fatty acid composition

7. Primary hypertriglyceridemia or secondary hypertriglyceridemias following

- familial histiocytic reticulosis
- lipoprotein lipase deficiency
- hyperlipoproteinemias
- 5 - apolipoprotein deficiency (e.g. apoCII or apoE deficiency)

8. Diseases or conditions related to neoplastic cellular proliferation

- benign or malignant tumors
- cancer
- 10 - neoplasia
- metastases
- carcinogenesis

9. Diseases or conditions related to neurological, psychiatric or immune disorders or
15 conditions10. Other diseases or conditions in which inflammatory reactions or cell differentiation
may for example be involved are:

- 20 - atherosclerosis such as, for example (but not restricted thereto), coronary
sclerosis including angina pectoris or myocardial infarction, stroke, ischemic
stroke and transient ischemic attack (TIA)
- peripheral occlusive disease
- vascular restenosis or reocclusion
- 25 - chronic inflammatory bowel diseases such as, for example, Crohn's disease and
ulcerative colitis
- pancreatitis
- sinusitis
- other inflammatory conditions
- 30 - retinopathy, ischemic retinopathy
- adipose cell tumors
- lipomatous carcinomas such as, for example, liposarcomas
- solid tumors and neoplasms such as, for example (but not restricted thereto),

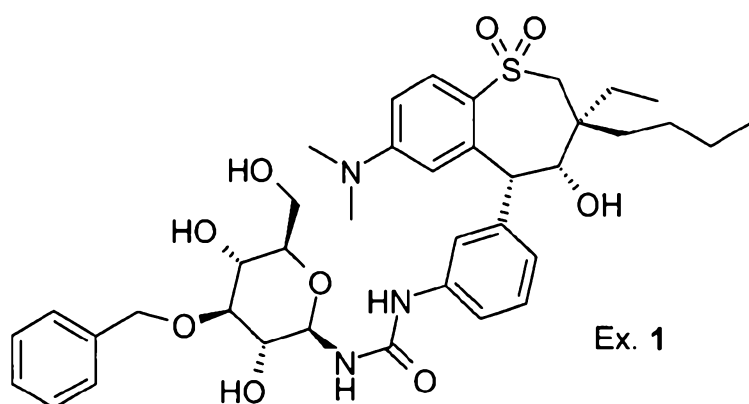
carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumors, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas, etc

- acute and chronic myeloproliferative disorders and lymphomas
- 5 - angiogenesis
- neurodegenerative disorders
- Alzheimer's disease
- multiple sclerosis
- Parkinson's disease
- 10 - erythematous-squamous dermatoses such as, for example, psoriasis
- acne vulgaris
- other skin disorders and dermatological conditions which are modulated by PPAR
- eczemas and neurodermatitis
- 15 - dermatitis such as, for example, seborrheic dermatitis or photodermatitis
- keratitis and keratoses such as, for example, seborrheic keratoses, senile keratoses, actinic keratoses, photo-induced keratoses or keratosis follicularis
- keloids and keloid prophylaxis
- warts, including condylomata or condylomata acuminata
- 20 - human papilloma viral (HPV) infections such as, for example, venereal papillomata, viral warts such as, for example, molluscum contagiosum, leukoplakia
- papular dermatoses such as, for example, lichen planus
- skin cancer such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas
- 25 - localized benign epidermal tumors such as, for example, keratoderma, epidermal naevi
- chilblains
- high blood pressure
- 30 - syndrome X
- polycystic ovary syndrome (PCOS)
- asthma
- cystic fibrosis

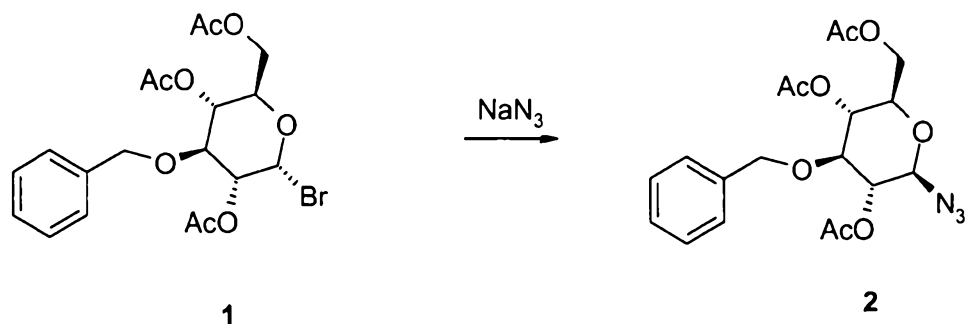
- osteoarthritis
- lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis
- vasculitis
- 5 - wasting (cachexia)
- gout
- ischemia/reperfusion syndrome
- acute respiratory distress syndrome (ARDS)
- viral diseases and infections
- 10 - lipodystrophy and lipodystrophic conditions, also for treating adverse drug effects (e.g. after taking medicaments for treating HIV or tumors)
- myopathies and lipid myopathies (such as carnitine palmitoyltransferase I or II deficiency)
- 15 The preparation of some examples is described in detail below; the other compounds of the formula I were obtained analogously:

Experimental section:

20 Example 1



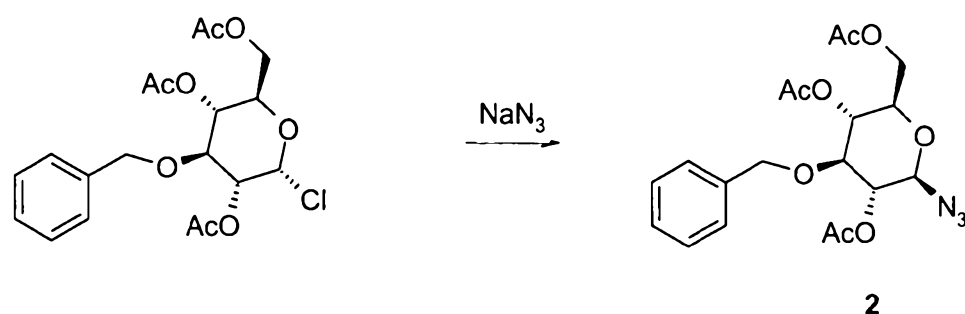
Synthesis of compound 2:



15.0 g (32.7 mmol) of bromide **1** (Eur. J. Med. Chem, (1996) 31, 557-574) are dissolved in 250 ml of dimethylformamide. Addition of 7.5 g of sodium azide is followed by stirring at room temperature for 1 hour. The reaction solution is extracted with water and ethyl acetate, and the organic phase is washed twice with saturated sodium chloride solution, filtered through a little silica gel and concentrated. The residue is purified by flash chromatography (n-heptane/ethyl acetate) to result in 11.1 g (81% yield) of azide **2** as colorless oil, which solidifies on prolonged standing.

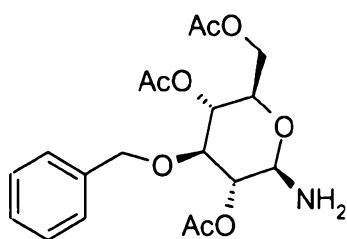
TLC (n-heptane/ethyl acetate 2:1). $R_f = 0.4$. $C_{19}H_{23}N_3O_8$ (421.41). MS $(M+H)^+ = 422.3$.

Alternative synthesis of compound **2** via the glucosyl chloride



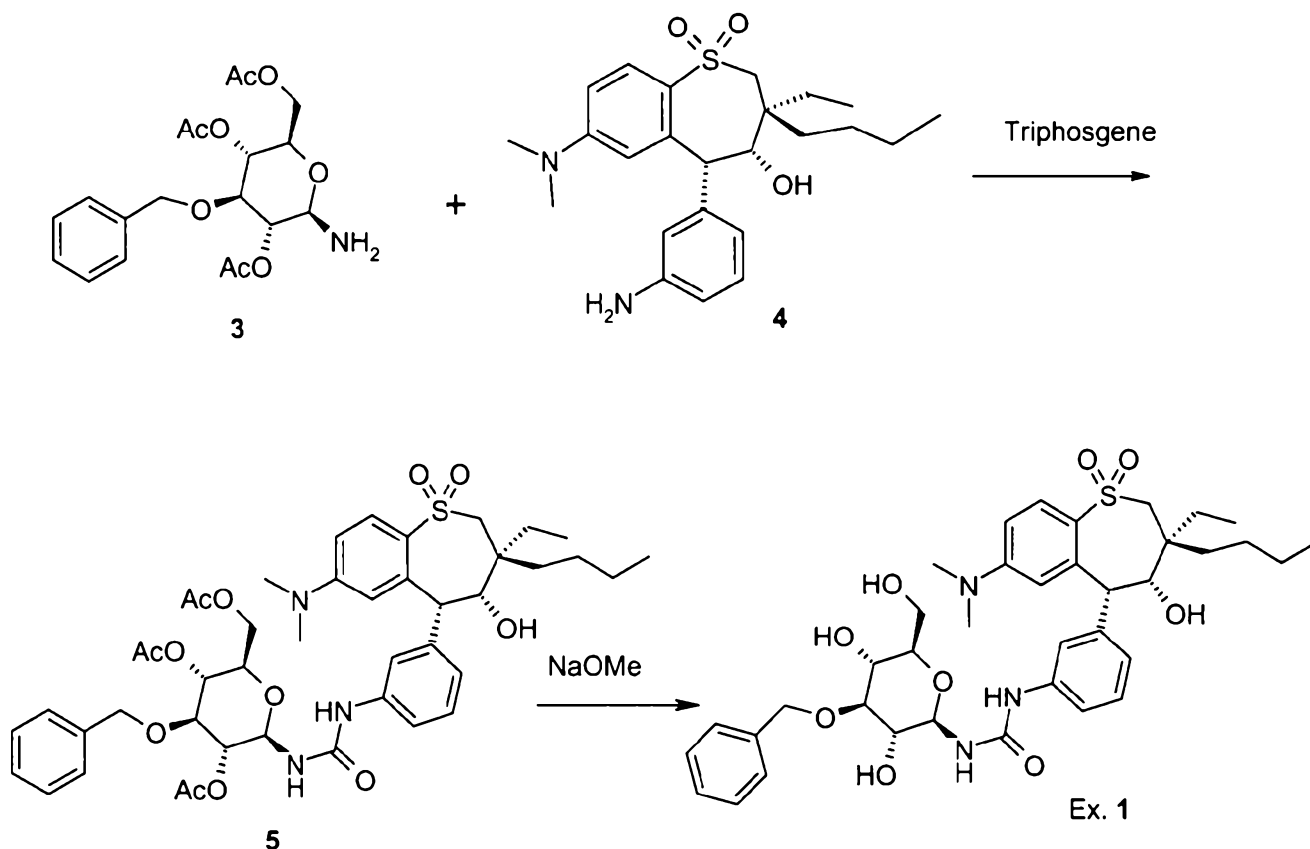
1.5 g of 2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranosyl chloride (J. Org. Chem (1997), 62(9) 2832-46) are reacted in analogy to a synthesis of the glucosyl bromide. The reaction temperature must in this case be raised to 60°C. 1.3 g (86%) of azide **2** are obtained.

Synthesis of compound **3**:

**3**

8.8 g (20.9 mmol) of azide **2** are dissolved in 100 ml of methylene chloride and 2 ml of triethylamine. Addition of 300 mg of 10% palladium on activated carbon is followed by hydrogenation under a pressure of 4 bar of hydrogen for 1 hour. The catalyst is removed on a little silica gel, and the silica gel is washed with ethyl acetate. The solution is concentrated until crystallization starts. In total, 6.9 g of crystalline solid **3** are obtained (83% yield). TLC (ethyl acetate). $R_f = 0.2$. $C_{19}H_{25}NO_8$ (395.41). MS $(M+H)^+ = 396.3$.

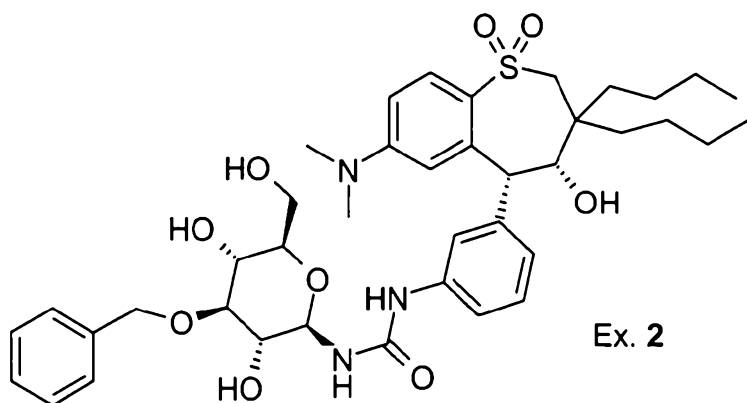
10 Synthesis of Example 1:



900 mg of triphosgene are dissolved in 10 ml of methylene chloride. A solution of

3.0 g (7.6 mmol) of amine **3** and 3 ml of N-ethylmorpholine in 20 ml of methylene chloride is added dropwise to the solution at room temperature over the course of 20 minutes. This is followed by stirring for 1 hour, and then a solution of 3.0 g (7.0 mmol) of aniline **4** (US 5,994,391), dissolved in 20 ml of methylene chloride, is slowly added dropwise. The reaction is complete (TLC check) after a further 30 minutes. Washing twice with sat. sodium chloride solution, filtering through silica gel and concentrating result in 7 g of crude product **5**. This is dissolved in 50 ml of methanol, and 2 ml of 1 M sodium methanolate/methanol solution are added. After 30 minutes, the reaction solution is neutralized with 4 ml of 0.5 M HCL/methanol solution and concentrated. The residue is purified by flash chromatography. Yield 4.72 g (93%) of Ex. 1 as colorless solid. TLC (methylene chloride/methanol/conc. ammonia 30/5/1). $R_f = 0.7$. $C_{38}H_{51}N_3O_9S$ (725.91). MS $(M + H)^+ = 726.38$.

Example 2



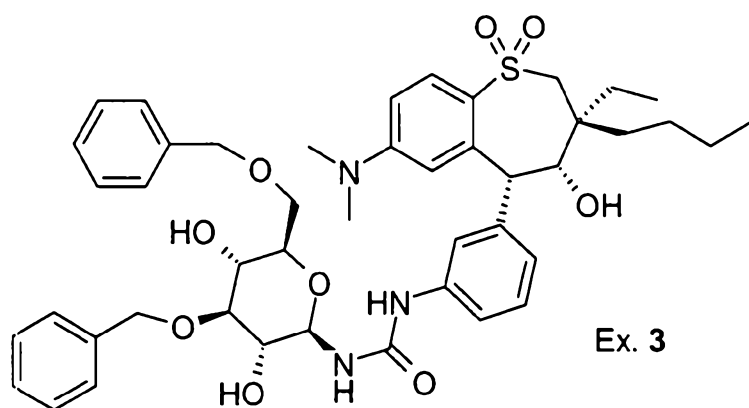
15

Example 2 is prepared starting from amines **3** and the di-n-butylaniline (US 5,994,391) with triphosgene in analogy to the synthesis of Example 1, and Ex. 2 is obtained in 90% yield as a colorless solid. TLC (methylene chloride/methanol/conc. ammonia 30/5/1). $R_f = 0.75$. $C_{40}H_{55}N_3O_9S$ (753.96). MS $(M + H)^+ = 754.38$.

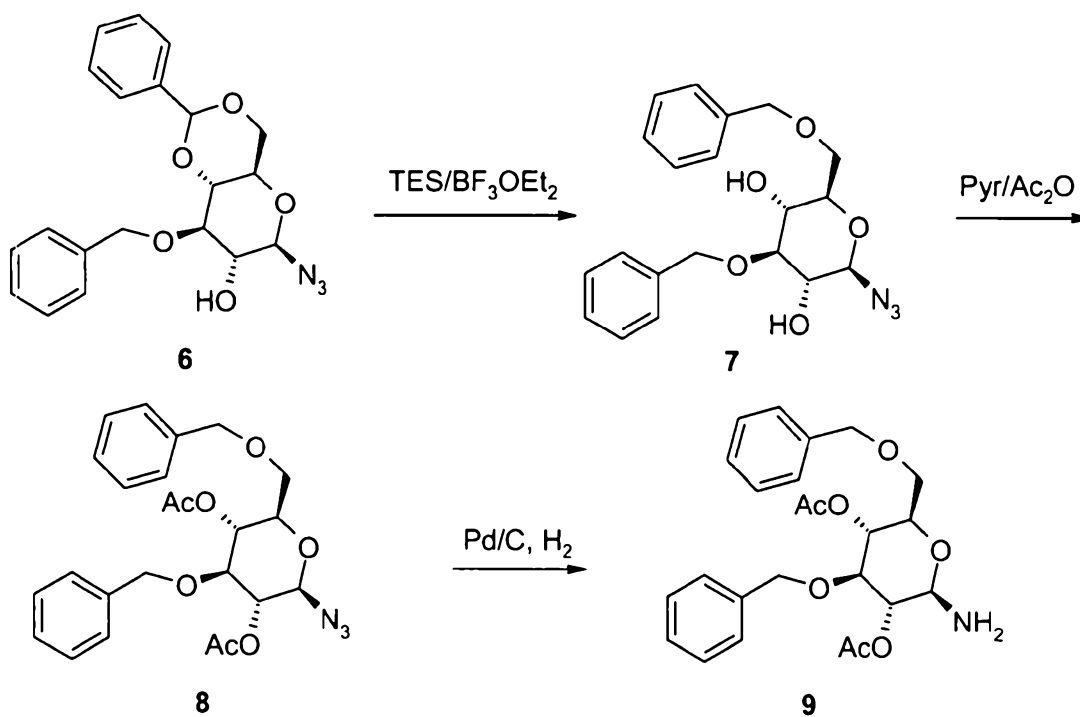
20

Example 3

46



Synthesis of the dibenzylglucos-1-amine building block 9:



1.36 g (3.55 mmol) of benzylidene derivative **6** (Tetrahedron Letters (1999), 40(3), 547-549) are dissolved in 35 ml of methylene chloride and 7 ml of triethylsilane (ABCR). After addition of 1 ml of boron trifluoride etherate, reaction is allowed to take place at room temperature for 30 minutes. The solution is then washed with saturated sodium bicarbonate solution, filtered through a little silica gel and concentrated. The residue is purified by flash chromatography (n-heptane/ethyl acetate) to result in 1.13 g (83% yield) of azide **7** as colorless oil, which solidifies on prolonged standing. TLC (n-heptane/ethyl acetate 1:1). $R_f = 0.4$. $C_{20}H_{23}N_3O_5$

(385.42). MS $(M+NH_4)^+ = 403.21$.

Synthesis of compound 8:

5 1.12 g (2.9 mmol) of diol **7** are dissolved in 15 ml of pyridine and 15 ml of acetic anhydride. The solution is heated at 50°C for 2 hours and then concentrated under high vacuum. The residue is purified by flash chromatography (n-heptane/ethyl acetate) to result in 1.2 g (88% yield) of azide **8** as colorless oil. TLC (n-heptane/ethyl acetate 2:1). $R_f = 0.5$. $C_{24}H_{27}N_3O_7$ (469.50). MS $(M+NH_4)^+ = 487.21$.

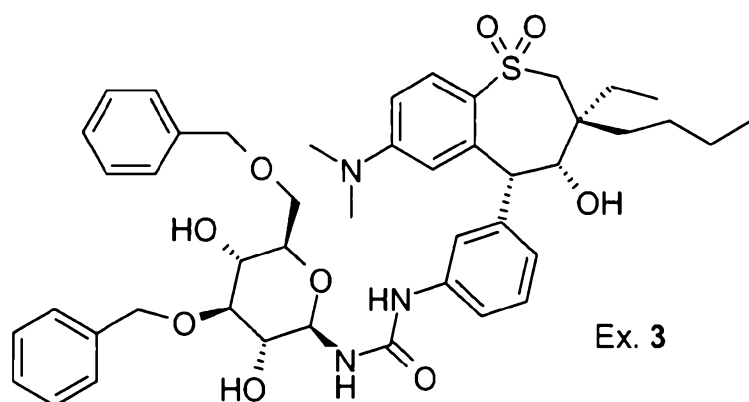
10

Synthesis of compound 9:

1.2 g (2.55 mmol) of azide **8** are dissolved in 30 ml of methylene chloride and 1 ml of triethylamine. Addition of 35 mg of 10% palladium on activated carbon is followed by hydrogenation under a pressure of 4 bar of hydrogen for 1 hour. The catalyst is removed on a little silica gel, and the silica gel is washed with ethyl acetate and concentrated. The residue is purified by flash chromatography (n-heptane/ethyl acetate) to result in 1.07 g (95% yield) of glucose-1-amine derivative **8** as colorless oil. TLC (ethyl acetate). $R_f = 0.2$. $C_{24}H_{29}NO_7$ (443.50). MS $(M+H)^+ = 444.32$.

20

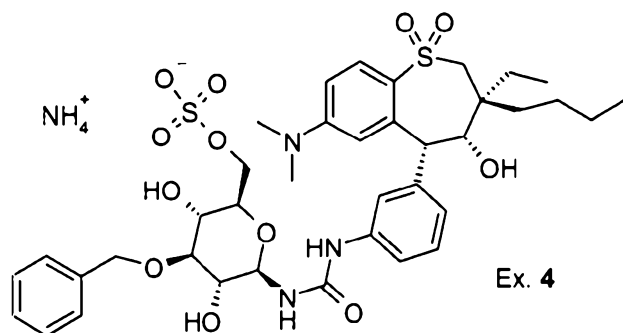
Example 3



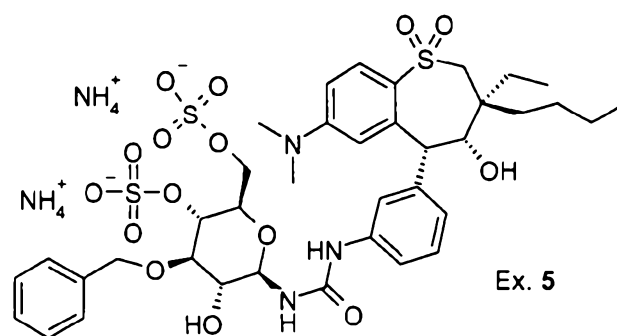
Example 3 is prepared starting from amines 9 and the aniline 4 (US 5.994.391) with
25 triphosgene in analogy to the synthesis of Example 1, and Ex. 3 is obtained in 80%
yield as a colorless solid. TLC (methylene chloride/methanol/conc. ammonia

100/7/1). $R_f = 0.5$. $C_{45}H_{57}N_3O_9S$ (816.03). MS $(M + H)^+ = 816.48$.

Example 4 and 5



Ex. 4



Ex. 5

50.0 g (68.9 mmol) of Example 1 are dissolved in 500 ml of pyridine and, after addition of 17 g of pyridine-sulfur trioxide complex, stirred at 60°C for 30 minutes. Addition of 400 ml of methanol is followed by concentration in a rotary evaporator. The residue is evaporated once more with 300 ml of methanol and then purified by flash chromatography. Yield 38.4 g (68%) Ex. 4 as ammonium salt. TLC (methylene chloride/methanol/conc. ammonia 30/5/1). $R_f = 0.4$. $C_{38}H_{51}N_3O_{12}S_2 \times NH_3$ (823.00). MS $(M + H)^+ = 804.21$.

As byproduct, 4.0 g (7%) of disulfate Example 5 are obtained as diammonium salt. TLC (methylene chloride/methanol/conc. ammonia 30/5/1). $R_f = 0.1$. $C_{38}H_{51}N_3O_{15}S_3 \times 2NH_3$ (920.09). MS $(M + H)^+ = 886.45$.

This disulfate can also be obtained as main product if twice the amount of sulfur trioxide complex is used.

Further prepared salts of Example 4.

Preparation of the potassium salt

8.3 g of Ex. 4 (ammonium salt) dissolved in 150 ml of methanol are, together with 200 g of potassium-laden Amberlit IR120, stirred vigorously at room temperature for one hour. The ion exchange resin is then separated off and washed twice with methanol. The solvent is evaporated, and 9 g of crude product are obtained. This is

dissolved in 40 ml of methanol and diluted with 150 ml of ethanol. 4.5 g of potassium salt Ex. 4 having a melting point of 220°C (with decomposition) crystallize out overnight at room temperature. By slow crystal growth from a solution of 2.5 of potassium salt Ex. 4 in 50 ml of methanol and 100 ml of ethanol (over 2 days), single
5 crystals are obtained, with the aid of which it was possible to confirm the structure and stereochemistry of Ex. 4 by single crystal X-ray structure.

Preparation of the zinc salt

10 1.1 g of Ex. 4 (ammonium salt) are dissolved in 11 ml of water (yellowish clear solution) and admixed with a solution of 120 mg of zinc chloride in 13 ml of water. The precipitate which separates out spontaneously is stirred for a further 2 hours at room temperature and then filtered off with suction. Crystalline zinc salt (977 mg
15 88%) Ex. 4 is obtained.

Preparation of the calcium salt

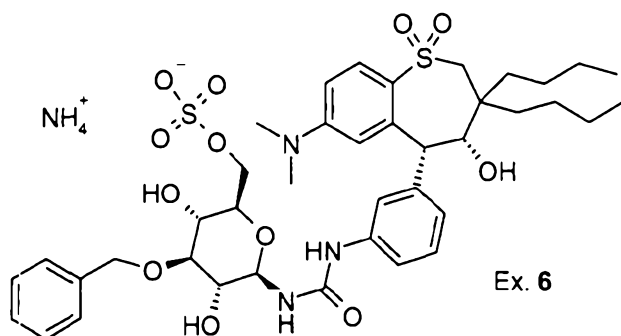
In analogy to the preparation of the zinc salt, a voluminous precipitate of the calcium salt is obtained after addition of a solution of 85 mg of calcium chloride in 13 ml of
20 water, which precipitate proves difficult to filter off with suction and is hygroscopic (937 mg, 85%).

Preparation of the magnesium salt

25 In analogy to the preparation of the zinc salt, a colorless precipitate of the magnesium salt is obtained after addition of a solution of 72 mg of magnesium chloride in 11 ml of water, which magnesium salt is hygroscopic (977 mg, 89%).

Example 6

30

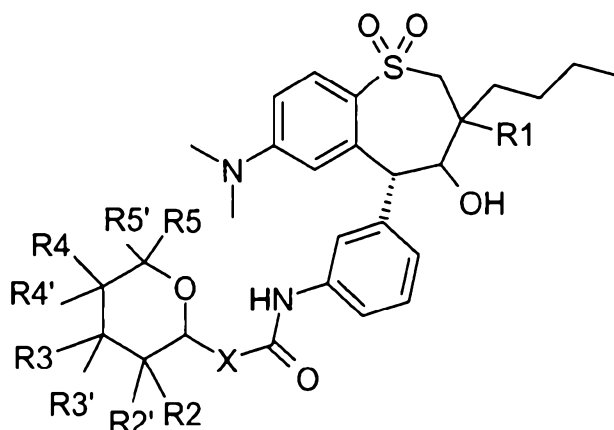


Example 6 is prepared starting from 105 mg of Example 2 in analogy to the synthesis described for Example 4, and 67 mg (65%) of ammonium salt of

5 Example 6 are obtained. TLC (methylene chloride/methanol/conc. ammonia 30/5/1). $R_f = 0.45$. $C_{40}H_{55}N_3O_{12}S_2 \times NH_3$ (851.06). MS $(M + H)^+ = 834.43$.

Claims:

1. A compound of the formula I,



I

in which the meanings are

X O, NH, CH₂ or a bond;

R₁ (C₁-C₆)-alkyl;

R₂, R_{2'}, R₃, R_{3'}, R₄, R_{4'}, R₅, R_{5'} independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R₆, O-S(O)_p-R₆, (C₁-C₆)-alkylene-S(O)_p-R₆, (C₁-C₆)-alkylene-O-S(O)_p-R₆, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine; phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

where always at least one of the radicals R₂, R_{2'}, R₃, R_{3'}, R₄, R_{4'}, R₅, R_{5'} has the meaning of -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

R₆ H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

5

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

10 p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

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

15

X O, NH, CH₂ or a bond;

R₁ (C₁-C₆)-alkyl;

20 R₂, R₂', R₃, R₃', R₄, R₄', R₅, R₅' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R₆, (C₁-C₆)-alkylene-S(O)_p-R₆, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may
25 be replaced by fluorine;
phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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,
30 COO-(C₁-C₆)-alkyl, CONH₂;

where always at least one of the radicals R₂, R₂', R₃, R₃', R₄, R₄', R₅, R₅' has the meaning of -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

R₆ H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

5

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

10 p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

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

X NH;

20 R₁ (C₁-C₆)-alkyl;

R₂, R₂', R₃, R₃', R₄, R₄', R₅, R₅' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R₆, (C₁-C₆)-alkylene-S(O)_p-R₆, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine;

25

phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

30

where always at least one of the radicals R2, R2', R3, R3', R4, R4', R5, R5' has the meaning of -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

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

X NH;

R1 (C₁-C₆)-alkyl;

R2, OH;

R2' H;

R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be

replaced by fluorine;

phenyl, $-(CH_2)$ -phenyl, $-(CH_2)_n$ -phenyl, O-phenyl, $O-(CH_2)_m$ -phenyl, $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$, SO_2-CH_3 , $COOH$, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

where always at least one of the radicals R_3 , R_3' , R_4 , R_4' , R_5 , R_5' has the meaning of $-O-(CH_2)_m$ -phenyl or $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$, SO_2-CH_3 , $COOH$, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

R_6 H, OH, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$;

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

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

X NH ;

R_1 (C_1-C_6) -alkyl;

R_2 , R_2' , R_3 , R_3' , R_4 , R_4' independently of one another H, Cl, Br, I, OH, $-(CH_2)-OH$, CF_3 , NO_2 , N_3 , CN, $S(O)_p-R_6$, $O-S(O)_p-R_6$, (C_1-C_6) -alkylene- $S(O)_p-R_6$, (C_1-C_6) -alkylene- $O-S(O)_p-R_6$, $COOH$, $COO(C_1-C_6)$ alkyl, $CONH_2$,

- CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine;
- 5 phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;
- 10 R5, R5' independently of one another H, -(CH₂)-OH, CF₃, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine;
- 15 phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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,
- 20 COO-(C₁-C₆)-alkyl, CONH₂;

where always at least one of the radicals R2, R2', R3, R3', R4, R4', R5, R5' has the meaning of -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

25

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

30 n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

5 6. A compound of the formula I as claimed in claim 5, in which the meanings are

X NH;

R1 (C₁-C₆)-alkyl;

10

R2, OH;

R2' H;

15 R3, R3', R4, R4' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all
20 hydrogen(s) in the alkyl radicals may be replaced by fluorine; phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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,
25 COO-(C₁-C₆)-alkyl, CONH₂;

R5, R5' independently of one another H, -(CH₂)-OH, CF₃, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂,
30 (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine; phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl,

-(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

5

where always at least one of the radicals R₃, R_{3'}, R₄, R_{4'}, R₅, R_{5'} has the meaning of -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

10

R₆ H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

15

m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

20 and the pharmaceutically acceptable salts thereof.

7. A compound of the formula I as claimed in claim 5 or 6, in which the meanings are

25 X NH;

R₁ (C₁-C₆)-alkyl;

R₂, OH;

30

R_{2'} H;

R₃, R_{3'}, R₄, R_{4'} independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂,

N_3 , CN, $S(O)_p-R_6$, $O-S(O)_p-R_6$, (C_1-C_6) -alkylene- $S(O)_p-R_6$, (C_1-C_6) -alkylene- $O-S(O)_p-R_6$, COOH, $COO(C_1-C_6)$ alkyl, $CONH_2$, $CONH(C_1-C_6)$ -alkyl, $CON[(C_1-C_6)alkyl]_2$, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, $O-(C_1-C_6)$ -alkyl, where one, more than one, or all hydrogen(s) in the

5

alkyl radicals may be replaced by fluorine;

phenyl, $-(CH_2)$ -phenyl, $-(CH_2)_n$ -phenyl, O-phenyl, $O-(CH_2)_m$ -phenyl, $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)alkyl)_2$, SO_2-CH_3 , COOH, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

10

R5, R5' independently of one another H, $-(CH_2)-OH$, CF_3 , $S(O)_p-R_6$, $O-S(O)_p-R_6$,

(C_1-C_6) -alkylene- $S(O)_p-R_6$, (C_1-C_6) -alkylene- $O-S(O)_p-R_6$, COOH, $COO(C_1-C_6)alkyl$, $CONH_2$, $CONH(C_1-C_6)alkyl$, $CON[(C_1-C_6)alkyl]_2$, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, $O-(C_1-C_6)$ -alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine;

15

phenyl, $-(CH_2)$ -phenyl, $-(CH_2)_n$ -phenyl, O-phenyl, $O-(CH_2)_m$ -phenyl, $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)alkyl)_2$, SO_2-CH_3 , COOH, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

20

where always at least one of the radicals R3, R3', R4, R4', R5, R5' has the meaning

of $O-(CH_2)_m$ -phenyl or $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)alkyl)_2$, SO_2-CH_3 , COOH, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

25

und where always at least one of the radicals R3, R3', R4, R4', R5, R5' has the meaning of $S(O)_p-R_6$, $O-S(O)_p-R_6$, (C_1-C_6) -alkylene- $S(O)_p-R_6$ or (C_1-C_6) -alkylene- $O-S(O)_p-R_6$;

30

R6 H, OH, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)alkyl)_2$;

n

2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

5

and the pharmaceutically acceptable salts thereof.

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

10 X NH;

R1 (C₁-C₆)-alkyl;

15 R2, R2', R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH,
 -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-
 S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)-alkyl,
 CONH₂, CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-
 alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or
 all hydrogen(s) in the alkyl radicals may be replaced by fluorine;
 20 phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl,
 -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one
 to 3 times 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, CONH₂;

25

where always at least one of the radicals R2, R2', R3, R3', R4, R4', R5, R5' has the
 meaning of S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6 or
 (C₁-C₆)-alkylene-O-S(O)_p-R6 and another has the meaning of
 -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may
 30 be substituted one to 3 times 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, CONH₂;

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

5 m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

10

9. A compound of the formula I as claimed in claim 8, in which the meanings are

X NH;

15 R1 (C₁-C₆)-alkyl;

R2, OH;

R2' H;

20

R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine; phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

30

where always at least one of the radicals R3, R3', R4, R4', R5, R5' has the meaning

of $(S(O)_p-R6$, $O-S(O)_p-R6$, (C_1-C_6) -alkylene- $S(O)_p-R6$ or (C_1-C_6) -alkylene- $O-S(O)_p-R6$ and another has the meaning of $-O-(CH_2)_m$ -phenyl or $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$, SO_2-CH_3 , $COOH$, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

R6 H, OH, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$;

10 n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

15

and the pharmaceutically acceptable salts thereof.

10. A compound of the formula I as claimed in claim 8 or 9, in which the meanings are

20

X NH ;

R1 (C_1-C_6) -alkyl;

25 R2, OH;

R2' H;

30

R3, R3', R4, R4', R5, R5' independently of one another H, Cl, Br, I, OH, $-(CH_2)-OH$, CF_3 , NO_2 , N_3 , CN, $S(O)_p-R6$, $O-S(O)_p-R6$, (C_1-C_6) -alkylene- $S(O)_p-R6$, (C_1-C_6) -alkylene- $O-S(O)_p-R6$, $COOH$, $COO(C_1-C_6)$ alkyl, $CONH_2$, $CONH(C_1-C_6)$ alkyl, $CON[(C_1-C_6)$ alkyl] $_2$, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, $O-(C_1-C_6)$ -alkyl, where one, more than one, or all

hydrogen(s) in the alkyl radicals may be replaced by fluorine; phenyl, $-(CH_2)$ -phenyl, $-(CH_2)_n$ -phenyl, O-phenyl, $O-(CH_2)_m$ -phenyl, $-(CH_2)-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$, SO_2-CH_3 , $COOH$, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

where always at least one of the radicals R_3 , R_3' , R_4 , R_4' , R_5 , R_5' has the meaning of (C_1-C_6) -alkylene- $O-S(O)_p-R_6$ and another has the meaning of $-O-(CH_2)_m$ -phenyl, where the phenyl ring may be substituted one to 3 times by F, Cl, Br, I, OH, CF_3 , NO_2 , CN, OCF_3 , $O-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$, SO_2-CH_3 , $COOH$, $COO-(C_1-C_6)$ -alkyl, $CONH_2$;

R_6 H, OH, (C_1-C_6) -alkyl, NH_2 , $NH(C_1-C_6)$ -alkyl, $N((C_1-C_6)$ -alkyl) $_2$;

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

11. A compound of the formula I as claimed in any one of claims 1 and 5 to 10, in which the meanings are

X NH ;

R_1 (C_1-C_6) -alkyl;

R_2 , OH;

R2' H;

R5' (C₁-C₆)-alkylene-O-S(O)₂-R6;

5

R3, R3', R4, R4', R5, independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R6, O-S(O)_p-R6, (C₁-C₆)-alkylene-S(O)_p-R6, (C₁-C₆)-alkylene-O-S(O)_p-R6, COOH, COO(C₁-C₆)alkyl, CONH₂, CONH(C₁-C₆)alkyl, CON[(C₁-C₆)alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine; phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

10

15

where always at least one of the radicals R3, R3', R4, R4', R5, R5' has the meaning of -O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

20

R6 H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

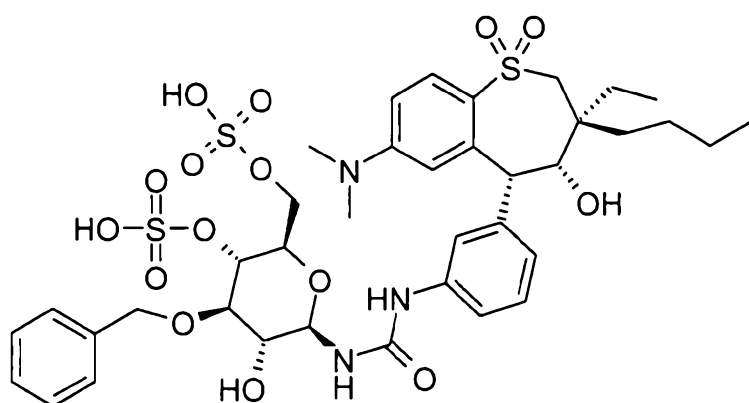
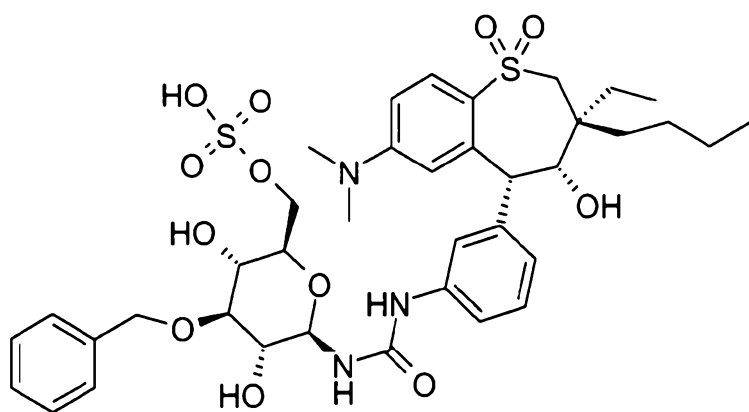
25

n 2, 3, 4, 5, 6;

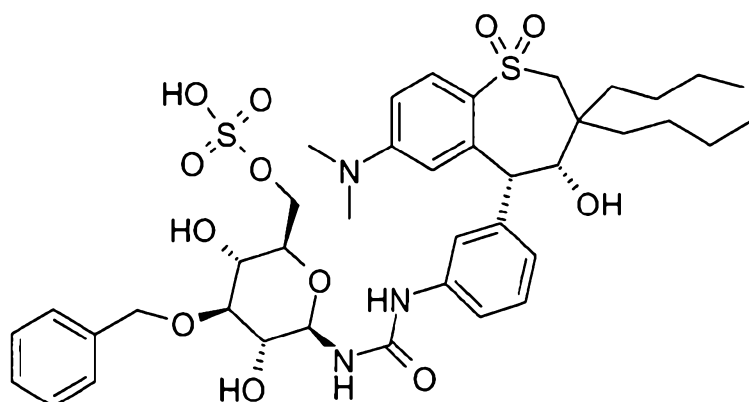
m 1, 2, 3, 4, 5, 6;

30 and the pharmaceutically acceptable salts thereof.

12. A compound of the formula



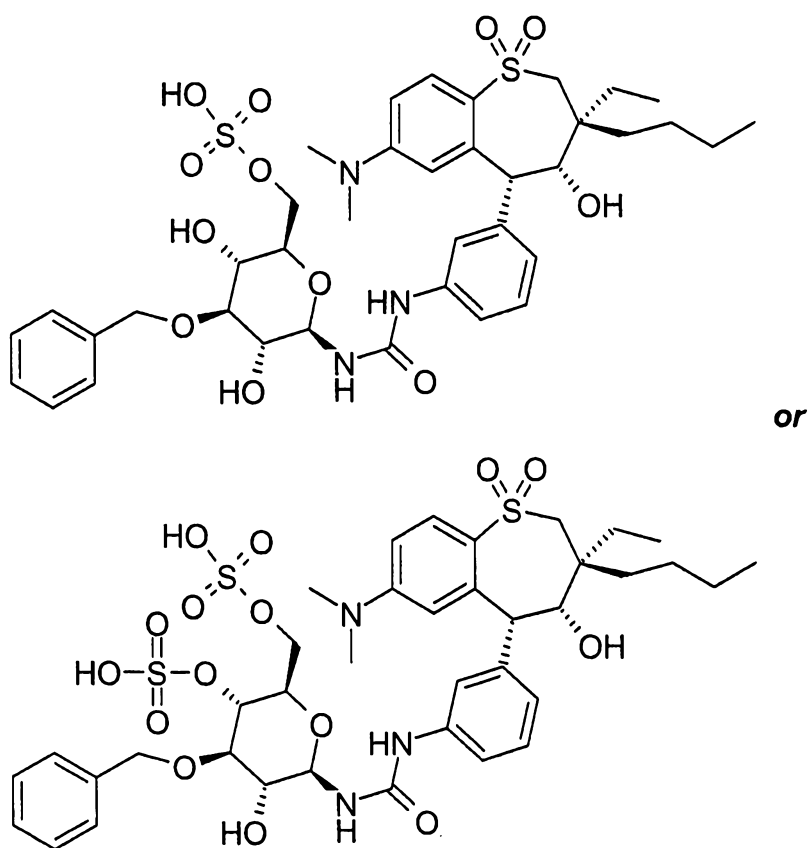
or



and the pharmaceutically acceptable salts thereof.

5

13. A compound of the formula



5 and the pharmaceutically acceptable salts thereof.

14. A compound as claimed in claim 12 or 13, wherein the pharmaceutically acceptable salt is an ammonium salt.

10 15. A compound as claimed in claim 12 or 13, wherein the pharmaceutically acceptable salt is an alkali metal or alkaline earth metal salt.

16. A compound as claimed in claim 12 or 13, wherein the pharmaceutically acceptable salt is a potassium salt.

15

17. A compound as claimed in claim 12 or 13, wherein the pharmaceutically acceptable salt is a zinc salt.

18. A compound of the formula I as claimed in any one of claims 1 to 17, for
20 use as a pharmaceutical.

19. A pharmaceutical comprising compounds of the formula I as claimed in any one of claims 1 to 17.
20. A pharmaceutical comprising compounds of the formula I as claimed in
5 any one of claims 1 to 17 and at least one further active ingredient.
21. A pharmaceutical as claimed in claim 20, which comprises as further active ingredient one or more compounds which normalize lipid metabolism.
- 10 22. A pharmaceutical as claimed in claim 21, which comprises as further active ingredient one or more antidiabetics, hypoglycemic active ingredients, HMGCoA reductase inhibitors, cholesterol absorption inhibitors, PPAR gamma agonists, PPAR alpha agonists, PPAR alpha/gamma agonists, PPAR delta agonists, fibrates, MTP inhibitors, bile acid absorption inhibitors, MTP inhibitors, CETP
15 inhibitors, polymeric bile acid adsorbents, LDL receptor inducers, ACAT inhibitors, antioxidants, lipoprotein lipase inhibitors, ATP-citrate lyase inhibitors, squalene synthetase inhibitors, lipoprotein(a) antagonists, HM74A receptor agonists, lipase inhibitors, insulins, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α -glucosidase inhibitors, active ingredients which act on the ATP-dependent
20 potassium channel of the beta cells, glycogen phosphorylase inhibitors, glucagon receptor antagonists, activators of glucokinase, inhibitors of gluconeogenesis, inhibitors of fructose-1,6-bisphosphatase, modulators of glucose transporter 4, inhibitors of glutamine-fructose-6-phosphate amidotransferase, inhibitors of dipeptidylpeptidase IV, inhibitors of 11-beta-hydroxysteroid dehydrogenase 1,
25 inhibitors of protein tyrosine phosphatase 1B, modulators of the sodium-dependent glucose transporter 1 or 2, modulators of GPR40, inhibitors of hormone-sensitive lipase, inhibitors of acetyl-CoA carboxylase, inhibitors of phosphoenolpyruvate carboxykinase, inhibitors of glycogen synthase kinase-3 beta, inhibitors of protein kinase C beta, endothelin-A receptor antagonists,
30 inhibitors of I kappaB kinase, modulators of the glucocorticoid receptor, CART agonists, NPY agonists, MC4 agonists, orexin agonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β 3 agonists, CB1 receptor antagonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin reuptake inhibitors, mixed serotonergic and noradrenergic
35 compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth

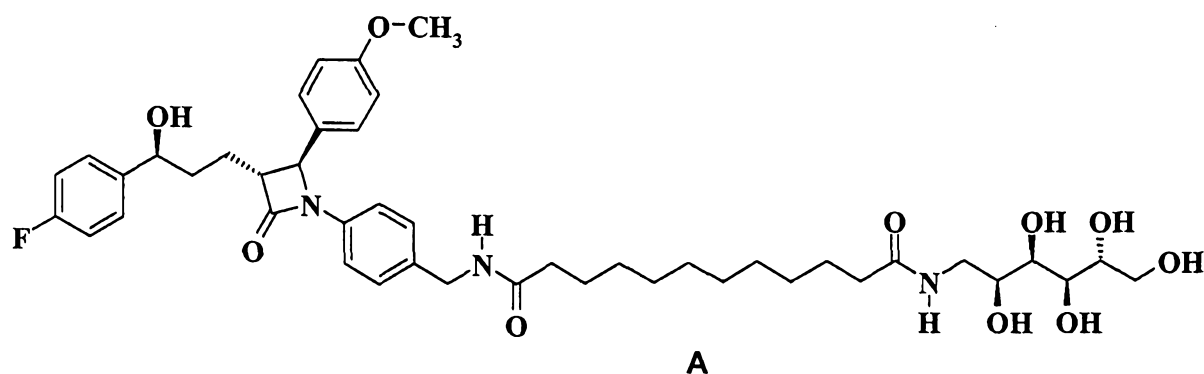
hormones, growth hormone-releasing compounds, TRH agonists, uncoupling protein 2 or 3 modulators, diphenylazetidinone derivatives, leptin agonists, DA agonists (bromocriptine, Doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR- β agonists or amphetamines.

5

23. A pharmaceutical as claimed in claim 22, which comprises as further active ingredient one or more HMGCoA reductase inhibitors from the group of simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin and rosuvastatin.

10

24. A pharmaceutical as claimed in claim 22, which comprises as further active ingredient ezetimibe or a compound of the formula A



15 or the salts or hydrates thereof.

25. A pharmaceutical as claimed in any one of claims 18, 19, 20, 21, 22, 23 or 24, which comprises as further excipient one or more metal salts.

20 26. A compound of the formula I as claimed in any one of claims 1 to 17 for use as a medicament for the treatment of lipid metabolism disorders.

25 27. A process for manufacturing a pharmaceutical comprising the compounds of the formula I as claimed in any one of claims 1 to 17, which comprises mixing the active ingredient with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.

28. The use of the compounds of the formula I as claimed in any one of claims 1 to 17 for the manufacture of a medicament for the treatment of hyperlipidemia.

29. The use of the compounds of the formula I as claimed in any one of claims 1 to 17 for the manufacture of a medicament for lowering the serum cholesterol level.

5

30. The use of the compounds of the formula I as claimed in any one of claims 1 to 17 for the manufacture of a medicament for the treatment of arteriosclerotic manifestations.

10

31. The use of the compounds of the formula I as claimed in any one of claims 1 to 17 for the manufacture of a medicament for the treatment of insulin resistance.

15

32. The use of the compounds of the formula I as claimed in any one of claims 1 to 17 for the manufacture of a medicament for the treatment of diabetes.

33. The use of the compounds of the formula I as claimed in any one of claims 1 to 17 for the manufacture of a medicament for the treatment of CNS disorders.

20

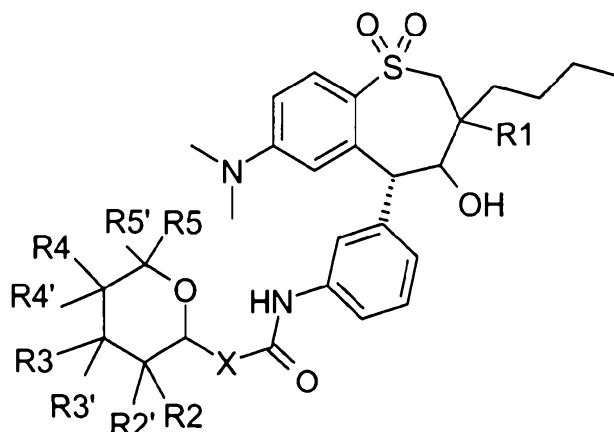
34. The use of the compounds as claimed in any one of claims 1 to 17 for the manufacture of a medicament for the treatment of schizophrenia.

35. The use of the compounds as claimed in any one of claims 1 to 17 for the manufacture of a medicament for the treatment of Alzheimer's.

25

36. A compound of the formula I,

70



I

in which the meanings are

5 X O, NH, CH₂ or a bond;

R₁ (C₁-C₆)-alkyl;

10 R₂, R₂', R₃, R₃', R₄, R₄', R₅, R₅' independently of one another H, Cl, Br, I, OH, -(CH₂)-OH, CF₃, NO₂, N₃, CN, S(O)_p-R₆, (C₁-C₆)-alkylene-S(O)_p-R₆, COOH, COO(C₁-C₆)-alkyl, CONH₂, CONH(C₁-C₆)-alkyl, CON[(C₁-C₆)-alkyl]₂, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, O-(C₁-C₆)-alkyl, where one, more than one, or all hydrogen(s) in the alkyl radicals may be replaced by fluorine;

15 phenyl, -(CH₂)-phenyl, -(CH₂)_n-phenyl, O-phenyl, O-(CH₂)_m-phenyl, -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

20 where always at least one of the radicals R₂, R₂', R₃, R₃', R₄, R₄', R₅, R₅' has the meaning of -O-(CH₂)_m-phenyl or -(CH₂)-O-(CH₂)_m-phenyl, where the phenyl ring may be substituted one to 3 times 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, CONH₂;

25

R₆ H, OH, (C₁-C₆)-alkyl, NH₂, NH(C₁-C₆)-alkyl, N((C₁-C₆)-alkyl)₂;

n 2, 3, 4, 5, 6;

m 1, 2, 3, 4, 5, 6;

5 p 0, 1, 2;

and the pharmaceutically acceptable salts thereof.

10 37. A compound of the formula I as claimed in claim 36 for use as pharmaceutical.

38. A pharmaceutical comprising compounds of the formula I as claimed in claim 36.

15 39. A pharmaceutical comprising compounds of the formula I as claimed in claim 36 and at least one further active ingredient.

40. A compound of the formula I substantially as hereinbefore described, with reference to the examples.

20

SANOFI-AVENTIS DEUTSCHLAND GMBH

WATERMARK PATENT & TRADE MARK ATTORNEYS

P31757AU00