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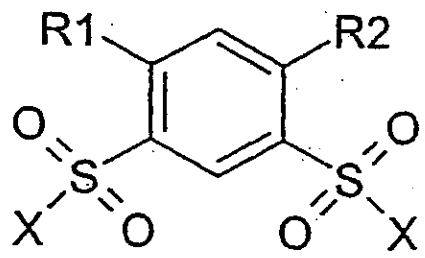
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(54) Title: USE OF BIS-SULFONAMIDES FOR PRODUCING MEDICAMENTS USED FOR PREVENTING OR TREATING HYPERLIPIDAEMIA

(54) Bezeichnung: VERWENDUNG VON BISSULFONAMIDEN ZUR HERSTELLUNG VON MEDIKAMENTEN ZUR PROPHYLAXE ODER BEHANDLUNG VON HYPERLIPIDÄMIE



(I)

(57) Abstract: The invention relates to the use of bis-sulfonamides, and of their physiologically compatible salts and physiologically functional derivatives for producing medicaments used for preventing or treating hyperlipidaemia. The invention involves the use of compounds of formula (I), wherein the radicals have the cited meanings, and the use of their physiologically compatible salts and physiologically functional derivatives for producing a medicament used for preventing or treating hyperlipidaemia or arteriosclerosis.

(57) Zusammenfassung: Die Erfindung betrifft die Verwendung von Bissulfonamiden sowie derer physiologisch verträglichen Salze und physiologisch funktionellen Derivate zur Herstellung von Medikamenten zur Prophylaxe oder Behandlung von Hyperlipidämie. Es wird die Verwendung der Verbindungen der Formel (I), worin die Reste die angegebenen Bedeutungen haben, sowie derer physiologisch verträglichen Salze und physiologisch funktionellen Derivate zur Herstellung eines Medikaments zur Prophylaxe oder Behandlung von Hyperlipidämie oder von Arteriosklerose beschrieben.

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Description

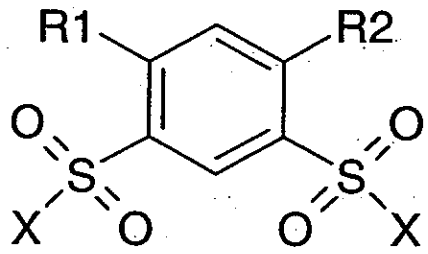
The use of bissulfonamides for producing medicines for the prophylaxis or treatment of hyperlipidemia.

The invention relates to the use of bissulfonamides and their physiologically tolerated salts and physiologically functional derivatives for producing medicines for the prevention and treatment of hyperlipidemia and arteriosclerotic disorders.

US 3,876,632 describes bissulfonamides as antihypertensives.

The invention was based on the object of providing compounds which display a therapeutically utilizable hypolipidemic effect.

The invention therefore relates to the use of compounds of the formula I



I

in which

X, R1, R2 are, independently of one another, NR6R7, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyridine, it being possible for each of the rings to be substituted by phenyl, (C_1-C_6)-alkyl-phenyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-OH, O-phenyl, S-phenyl, (CO)-(C_1-C_6)-alkyl, (CO)-phenyl, where the phenyl substituent is unsubstituted or up to disubstituted by F, Cl, Br, OH, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, COOH, COO(C_1-C_6)alkyl, COO(C_3-C_6)cycloalkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CON[(C_1-C_6)alkyl]$_2$,

$CONH(C_3\text{-}C_6)$cycloalkyl, NH_2, NH-CO-$(C_1\text{-}C_6)$-alkyl, NH-CO-phenyl;

R6 and R7 are, independently of one another, H, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, CO-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-NH-C(O)-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-NH-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-N-$[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_1\text{-}C_6)$-alkyl-O-phenyl, CHO, CO-phenyl,

$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, biphenylyl, 1- or 2-naphthyl, 1- or 2-tetrahydrofuranyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 1-pyrazolyl, 3-, 4- or 5-isoxazolyl, $(C_3\text{-}C_6)$-cycloalkyl, piperidinyl, pyrrolidinyl, 2- or 3-pyrrolyl, 2- or 3-pyridazinyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 2-(1,3,5-triazinyl), 2-, 3- or 4-morpholinyl, 2- or 5-benzimidazolyl, 2-benzothiazolyl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, tetrazol-5-yl, indol-3-yl, indol-5-yl or N-methyl-imidazol-2-, -4- or -5-yl, and Ar may be substituted up to twice by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-CH_2-O, O-$(C_1\text{-}C_6)$-alkyl, S-$(C_1\text{-}C_6)$-alkyl, SO-$(C_1\text{-}C_6)$-alkyl, SO_2-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, COOH, $COO(C_1\text{-}C_6)$alkyl, $COO(C_3\text{-}C_6)$cycloalkyl, $CONH_2$, $CONH(C_1\text{-}C_6)$alkyl, $CON[(C_1\text{-}C_6)\text{alkyl}]_2$, $CONH(C_3\text{-}C_6)$cycloalkyl, NH_2, NH-CO-$(C_1\text{-}C_6)$-alkyl, NH-CO-phenyl, pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl, $(CH_2)_n$-phenyl, O-$(CH_2)_n$-phenyl, S-$(CH_2)_n$-phenyl, SO_2-$(CH_2)_n$-phenyl, where n = 0-3;

and of their physiologically tolerated salts and physiologically functional derivatives for producing a medicine for the prevention and treatment of hyperlipidemia.

It is preferred to use compounds of the formula I in which one or more radical(s) has or have the following meaning:

R1 NR6R7, pyrrolidine, piperidine, piperazine, tetrahydropyridine, it being possible for each of the rings to be substituted by

phenyl, (C_1-C_6)-alkyl-phenyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-OH, O-phenyl, S-phenyl, (CO)-(C_1-C_6)-alkyl, (CO)-phenyl, where the phenyl substituent is unsubstituted or up to disubstituted by F, Cl, Br, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, COOH, COO(C_1-C_6)-alkyl, COO(C_3-C_6)cycloalkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CON[(C_1-C_6)alkyl]$_2$, NH_2, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl;

R6, R7 independently of one another H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-C(O)-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-[(C_1-C_6)-alkyl]$_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, biphenylyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 3- or 5-isoxazolyl, (C_3-C_6)-cycloalkyl, piperidinyl, pyrrolidinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 4-morpholinyl, 2- or 5-benzimidazolyl, 2-benzothiazolyl or indol-3-yl, indol-5-yl, and Ar may be up to disubstituted by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, COOH, COO(C_1-C_6)alkyl, COO(C_3-C_6)cycloalkyl, $CONH_2$, CONH(C_1-C_6)alkyl, NH_2, NH-CO-phenyl, $(CH_2)_n$-phenyl, O-$(CH_2)_n$-phenyl, S-$(CH_2)_n$-phenyl, where n = 0-3;

R2 NR8R9, piperazine, it being possible for piperazine to be substituted by (C_1-C_6)-alkyl-phenyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-OH, O-phenyl, S-phenyl, (CO)-(C_1-C_6)-alkyl, (CO)-phenyl;

R8, R9 independently of one another H, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-[(C_1-C_6)-alkyl]$_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 2-, 3- or 4-pyridyl, piperidinyl, pyrrolidinyl, morpholinyl;

X NR10R11, pyrrolidine, piperidine, piperazine, morpholine, it being possible for each of the rings to be substituted by phenyl,

$(C_1$-$C_6)$alkyl-phenyl, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-OH, O-phenyl, S-phenyl, (CO)-$(C_1$-$C_6)$-alkyl, (CO)-phenyl, where the phenyl substituent is unsubstituted or up to disubstituted by F, Cl, Br, CF_3, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, COOH, COO$(C_1$-$C_6)$-alkyl, COO$(C_3$-$C_6)$cycloalkyl, $CONH_2$, CONH$(C_1$-$C_6)$alkyl, CON[$(C_1$-$C_6)$alkyl]$_2$, NH_2, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl;

R10, R11 independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, CO-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-NH-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-N-[$(C_1$-$C_6)$-alkyl]$_2$, CO-phenyl, $(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, biphenylyl, 1- or 2-naphthyl, 1- or 2-tetrahydrofuranyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 3- or 5-isoxazolyl, piperidinyl, pyrrolidinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 4-morpholinyl, 2-benzothiazolyl, and Ar may be disubstituted by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, S-$(C_1$-$C_6)$-alkyl, SO-$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $CONH_2$, CONH$(C_1$-$C_6)$alkyl, CON[$(C_1$-$C_6)$alkyl]$_2$, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl, $(CH_2)_n$-phenyl where n = 0-3;

and their physiologically tolerated salts and physiologically functional derivatives for producing a medicine for the prevention and treatment of hyperlipidemia.

It is particularly preferred to use compounds of the formula I in which one or more radical(s) has or have the following meaning:

R1 NR6R7, piperidine, piperazine, tetrahydropyridine, it being possible for each of the rings to be substituted by phenyl, $(C_1$-$C_6)$-alkyl-phenyl;

R6, R7 independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $(C_1$-$C_6)$-alkyl-NH-C(O)-

$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-NH-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-N-$[(C_1$-$C_6)$-alkyl$]_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, $(C_3$-$C_6)$-cycloalkyl, piperidinyl, pyrrolidinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 4-morpholinyl, and Ar may be up to disubstituted by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, NH_2;

R2 NR8R9, piperazine, it being possible for piperazine to be substituted by $(C_1$-$C_6)$-alkyl;

R8, R9 independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, CO-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-NH-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-N-$[(C_1$-$C_6)$-alkyl$]_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 2-, 3- or 4-pyridyl, piperidinyl, pyrrolidinyl, morpholinyl;

X NR10R11, pyrrolidine, piperidine, morpholine, it being possible for each of the rings to be substituted by phenyl, $(C_1$-$C_6)$-alkyl-phenyl;

R10, R11 independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $(C_1$-$C_6)$-alkyl-NH-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-N-$[(C_1$-$C_6)$-alkyl$]_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar equals phenyl, 2- or 3-thienyl;

and their physiologically tolerated salts for producing a medicine for the prevention and treatment of hyperlipidemia.

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

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

Pharmaceutically acceptable salts are particularly suitable for medical applications because their solubility in water is higher than the initial or

basic compounds. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of compounds of the formula I are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric, metaphosphoric, nitric, sulfonic and sulfuric acids, and organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic, tartaric and trifluoroacetic acids. The chloride salt and the tartaric acid salt are particularly preferably used for medical purposes. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

Salts with a pharmaceutically unacceptable anion likewise fall within the scope of the invention as useful intermediates for preparing or purifying pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound according to the invention, for example an ester, which is able on administration to a mammal such as, for example, a human to form (directly or indirectly) such a compound or an active metabolite thereof.

A further aspect of this invention is the use of prodrugs of compounds of the formula I. Such prodrugs can be metabolized in vivo to a compound of the formula I. These prodrugs may themselves be active or not.

The compounds of the formula I may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the formula I lie within the scope of the invention and are a further aspect of the invention.

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

The amount of a compound of formula (I) which is 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. In general, the daily dose is in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day 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 most suitably be administered as infusion of from 10 ng to 100 ng per kilogram and per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg, per milliliter. Single doses may contain, for example, from 1 mg to 10 g of the active ingredient. It is thus possible for ampoules for injections to contain, for example, from 1 mg to 100 mg, and single-dose formulations which can be administered orally, such as, for example, tablets or capsules, to contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. In the case of pharmaceutically acceptable salts, the aforementioned weight data are based on the weight of the salt of the compound of formula (I). For the prophylaxis or therapy of the abovementioned conditions, the compounds of formula (I) can 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 hazardous for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as single dose, for example as tablet which may contain from 0.05% to 95% by weight of the active ingredient. Further pharmaceutically active substances may likewise be present, including other compounds of formula (I). The pharmaceutical compositions according to 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 according to 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 in each individual case depends 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 lie within the scope of the invention. Formulations resistant to acid and gastric fluid are preferred. Suitable coatings resistant to gastric fluid 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 contain 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. In general, the compositions are 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 tabletting the compound in free-flowing form, such as, for example, a powder or granules, where appropriate mixed with a binder, lubricant, inert diluent and/or a (plurality of) 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 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 arabric.

Suitable pharmaceutical compositions 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 solution sterile and isotonic with blood. Injectable compositions according to the invention generally contain from 0.1 to 5% by weight of the active compound.

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

Suitable pharmaceutical compositions for topical application to the skin are preferably in the form of ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which can be 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%.

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

The following preparations serve to illustrate the invention without restricting it, however.

Example A

Soft gelatin capsules containing 100 mg of active ingredient per capsule:

	per capsule
Active ingredient	100 mg
Triclyceride mixture fractionated from coconut fat	400 mg
Capsule contents	500 mg

Example B

Emulsion containing 60 mg of active ingredient per 5 ml:

	per 100 ml emulsion
Active ingredient	1.2 g
Neutral oil	q.s.
Sodium carboxymethylcellulose	0.6 g
Polyoxyethylene stearate	q.s.
Glycerol, pure	0.2 to 2.0 g
Flavoring	q.s.
Water (deionized or distilled)	ad 100 ml

Example C

Rectal pharmaceutical form containing 40 mg of active ingredient per suppository:

	per suppository
Active ingredient	40 mg
Suppository base	ad 2 g

Example D

Tablets containing 40 mg of active ingredient per tablet:

	per tablet
Active ingredient	40 mg
Lactose	600 mg
Corn starch	300 mg
Soluble starch	20 mg
Magnesium stearate	40 mg

1000 mg

Example E

Coated tablets containing 50 mg of active ingredient per coated tablet:

	per coated tablet
Active ingredient	50 mg
Corn starch	100 mg
Lactose	60 mg
Sec. calcium phosphate	30 mg
Soluble starch	5 mg
Magnesium stearate	10 mg
Colloidal silica	5 mg
	260 mg

Example F

The following formulas are suitable for producing the contents of hard gelatin capsules:

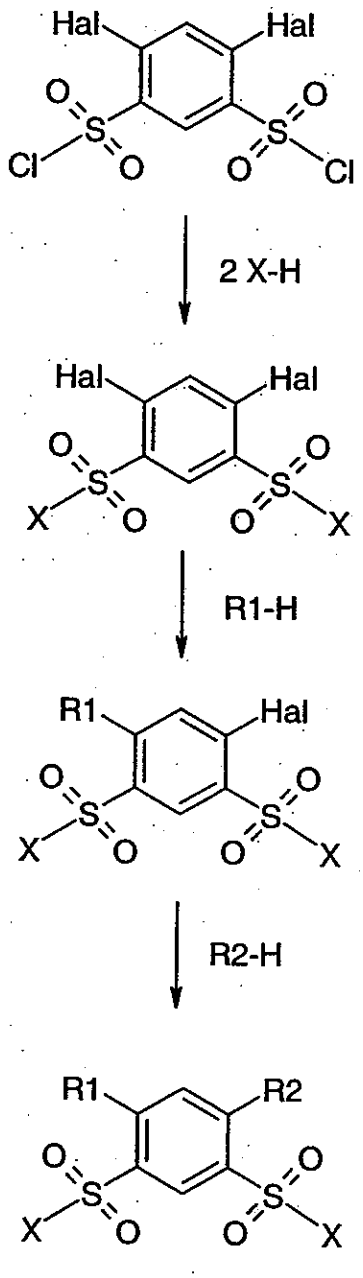
a)	Active ingredient	100 mg
	Corn starch	300 mg
		400 mg
b)	Active ingredient	140 mg
	Lactose	180 mg
	Corn starch	180 mg
		500 mg

Example G

Drops can be produced in accordance with the following formula (100 mg of active ingredient in 1 ml = 20 drops):

Active ingredient	10 g
Methyl benzoate	0.07 g
Ethyl benzoate	0.03 g
Ethanol 96% pure	5 ml
Demineralized water	ad 100 ml

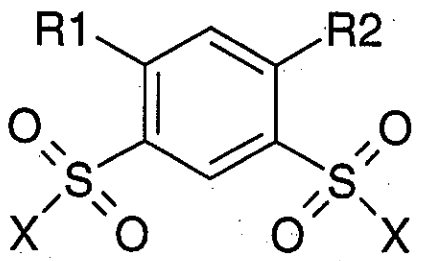
The invention also relates to a process for preparing the compounds of the formula I, which comprises preparing compounds of the formula I as shown in the following reaction diagram:



Hal = Halogen

The examples detailed below served to illustrate the invention without restricting it, however. The stated decomposition points are not corrected and generally depend on the heating rate.

Table 1: Example



formula I

Ex.	R1	R2	X	Molecular formula	MW	MS ($M+H^+$)	Mp (°C)
1	4-N(CH_3)-piperazin-1-yl	4-N(CH_3)-piperazin-1-yl	NH-cyclohexyl	C28 H48 N6 O4 S2	596.9	597.3	232.5
2	NH-benzyl	4-N(CH_3)-piperazin-1-yl	NH-cyclohexyl	C30 H45 N5 O4 S2	603.8	604.3	194
3	4-N(CH_3)-piperazin-1-yl	4-N(CH_3)-piperazin-1-yl	N$(CH)_3$-benzyl	C32 H44 N6 O4 S2	640.9	641.3	124
4	NH-benzyl	4-N(CH_3)-piperazin-1-yl	NH-phenyl	C30 H33 N5 O4 S2	591.8	592.3	211
5	NH-benzyl	4-N(CH_3)-piperazin-1-yl	pyrrolidin-1-yl	C26 H37 N5 O4 S2	547.7	548.3	173
6	4-N(CH_3)-piperazin-1-yl	4-N(CH_3)-piperazin-1-yl	NH-phenyl	C30 H40 N6 O4 S2	612.8	613.3	189
7	4-N(CH_3)-piperazin-1-yl	4-N(CH_3)-piperazin-1-yl	N(CH_3)-phenyl	C30 H40 N6 O4 S2	612.8	613.3	175

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8	4-N(CH_3)-piperazin-1-yl	4-N(CH_3)-piperazin-1-yl	piperidin-1-yl	C26 H44 N6 O4 S2	568.8	569.3	202.5
9	NH-benzyl	4-N(CH_3)-piperazin-1-yl	N$(CH)_3$-phenyl	C32 H37 N5 O4 S2	619.8	620.2	149
10	NH-CH_2-pyrid-2-yl	4-N(CH_3)-piperazin-1-yl	N$(CH)_3$-phenyl	C31 H36 N6 O4 S2	620.8	621.3	155.5
11	NH-CH_2-(3,4-methylenedioxyphenyl)	4-N(CH_3)-piperazin-1-yl	pyrrolidin-1-yl	C27 H37 N5 O6 S2	591.8	591.3	118 (decomp.)
12	NH-benzyl	4-N(CH_3)-piperazin-1-yl	NH-CH_2-$CH(CH_3)_2$	C26 H41 N5 O4 S2	551.8	552.3	169
13	NH-CH_2-cyclohexyl	4-N(CH_3)-piperazin-1-yl	morpholin-4-yl	C26 H43 N5 O6 S2	585.8	586.3	249
14	NH-CH_2-tetrahydrofuran-2-yl	4-N(CH_3)-piperazin-1-yl	N$(CH)_3$-phenyl	C30 H39 N5 O5 S2	613.8	614.3	147.5
15	NH-propyl-phenyl	4-N(CH_3)-piperazin-1-yl	morpholin-4-yl	C28 H41 N5 O6 S2	607.8	608.3	167
16	NH-benzyl	4-N(CH_3)-piperazin-1-yl	N$(ethyl)_2$	C26 H41 N5 O4 S2	551.8		89
17	NH-propyl-phenyl	4-N(CH_3)-piperazin-1-yl	piperidin-1-yl	C30 H45 N5 O4	603.8		134
18	NH-propyl-phenyl	4-N(CH_3)-piperazin-1-yl	NH-benzyl	C34 H41 N5 O4 S2	647.9		152
19	NH-CH_2-cyclohexyl	4-N(CH_3)-piperazin-1-yl	N$(ethyl)_2$	C26 H47 N5 O4	557.8		109
20	NH-propyl-phenyl	4-N(CH_3)-piperazin-1-yl	N$(ethyl)_2$	S2C28 H45 N5 O4 S2	579.8	580.3	Oil
21	NH-ethyl-phenyl	4-N(CH_3)-piperazin-1-yl	piperidin-1-yl	C29 H43 N5 O4 S2	589.8	590.3	70
22	NH-ethyl-phenyl	4-N(CH_3)-piperazin-1-yl	N$(ethyl)_2$	C27 H43 N5 O4 S2	565.8		Oil
23	NH-ethyl-phenyl	4-N(CH_3)-piperazin-1-yl	N$(CH)_3$-phenyl	C33 H39 N5 O4 S2	633.8	634.3	168

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24	NH-CH_2-cyclohexyl	4-N(CH_3)-piperazin-1-yl	N$(CH)_3$-phenyl	C32 H43 N5 O4 S2	625.9		174
25	NH-propyl-phenyl	4-N(CH_3)-piperazin-1-yl	N$(CH)_3$-phenyl	C34 H41 N5 O4 S2	647.9		132
26	NH-propyl-phenyl	4-N(CH_3)-piperazin-1-yl	Pyrrolidin-1-yl	C28 H41 N5 O4 S2	575.8		160
27	NH-propyl-phenyl	4-N(CH_3)-piperazin-1-yl	N(CH_3)-benzyl	C36 H45 N5 O4 S2	675.9		113
28	NH-ethyl-phenyl	4-N(CH_3)-piperazin-1-yl	N-morpholinyl	C27 H39 N5 O6 S2	593.8	594.3	181
29	NH-ethyl-N-$(Et)_2$	4-N(CH_3)-piperazin-1-yl	NH-CH_2-$CH(CH_3)_2$	C25 H48 N6 O4 S2	560.8	561.3	158
30	NH-CH_2-pyrid-3-yl	NH-ethyl-N$(CH_3)_2$	N(CH_3)-benzyl	C32 H40 N6 O4 S2	636.8	637.3	
31	NH-ethyl-N$(ethyl)_2$	NH-ethyl-N$(CH_3)_2$	N(CH_3)-benzyl	C32 H48 N6 O4 S2	644.9	645.3	
32	NH-propyl-O-CH_3	NH-ethyl-N$(CH_3)_2$	N(CH_3)-benzyl	C30 H43 N5 O5 S2	617.8	618.3	
33	NH-ethyl-N-morpholin-4-yl	NH-ethyl-N-pyrrolidin-1-yl	N(CH_3)-benzyl	C34 H48 N6 O5 S2	684.9	685.3	
34	NH-ethyl-N-pyrrolindin-1-yl	NH-ethyl-NH-acetyl	N(CH_3)-benzyl	C32 H44 N6 O5 S2	656.9	657.3	
35	NH-propyl-O-CH_3	NH-ethyl-N-pyrrolidin-1-yl	N(CH_3)-benzyl	C32 H45 N5 O5 S2	643.9	644.3	
36	N-piperidinyl	N(ethyl)-ethyl-N$(CH_3)_2$	N(CH_3)-benzyl	C33 H47 N5 O4 S2	641.9	642.3	
37	NH-ethyl-N-morpholin-4-yl	NH-ethyl-N-pyrrolidin-1-yl	N$(CH)_3$-phenyl	C30 H42 N6 O5 S2	630.8	631.3	
38	NH-benzyl	NH-ethyl-N$(CH_3)_2$	N$(CH)_3$-phenyl	C31 H37 N5 O4 S2	607.8	608.2	
39	NH-ethyl-N$(ethyl)_2$	NH-ethyl-N$(CH_3)_2$	N$(CH)_3$-phenyl	C30 H44 N6 O4 S2	616.8	617.3	
40	NH-propyl-O-CH_3	NH-ethyl-N-pyrrolidin-1-yl	N$(CH)_3$-phenyl	C30 H41 N5 O5 S2	615.8	616.3	

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41	N-piperidinyl	N(ethyl)-ethyl-$N(CH_3)_2$	$N(CH)_3$-phenyl	C31 H43 N5 O4 S2	613.8	614.3	
42	NH-ethyl-N-pyrrolidin-1-yl	NH-ethyl-N-pyrrolidin-1-yl	$N(CH)_3$-phenyl	C32 H46 N6 O4 S2	642.9	643.3	
43	NH-benzyl	NH-ethyl-N-pyrrolidin-1-yl	$N(CH)_3$-phenyl	C33 H39 N5 O4 S2	633.8	634.3	
44	N-piperidinyl	NH-ethyl-N-pyrrolidin-1-yl	$N(CH)_3$-phenyl	C31 H41 N5 O4 S2	611.8	612.3	
45	NH-ethyl-morpholin-4-yl	NH-ethyl-N-pyrrolidin-1-yl	$N(CH)_3$-phenyl	C32 H44 N6 O5 S2	656.9	657.3	
46	NH-CH_2-pyrid-2-yl	piperazin-1-yl	$N(CH)_3$-phenyl	C30 H34 N6 O4 S2	606.8	607.3	89
47	NH-CH_2-cyclohexyl	4-$N(CH_3)$-piperazin-1-yl	NH-piperidin-4-yl-(1-N-ethyl-phenyl)	C44 H65 N7 O4 S2	820.2		175
48	NH-benzyl	4-$N(CH_3)$-piperazin-1-yl	NH-piperidin-4-yl-(1-N-ethyl-phenyl)	C44 H59 N7 O4 S2	814.1		111 (decomp.)
49	NH-ethyl-phenyl	4-$N(CH_3)$-piperazin-1-yl	NH-piperidin-4-yl-(1-N-ethyl-phenyl)	C45 H61 N7 O4 S2	828.2		84 (decomp.)
50	NH-propyl-phenyl	4-$N(CH_3)$-piperazin-1-yl	NH-piperidin-4-yl-(1-N-ethyl-phenyl)	C46 H63 N7 O4 S2	842.2		118
51	Piperidin-1-yl	N(ethyl)-ethyl-$N(CH_3)_2$	NH-ethyl-$N(ethyl)_2$	C29 H57 N7 O4 S2	631.9	632.4	

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52	NH-ethyl-phenyl	NH-CH(CH_3)-propyl-N(ethyl)$_2$	piperidin-1-yl	C33 H53 N5 O4 S2	647.9	648.4	
53	NH-ethyl-thien-2-yl	piperazin-1-yl-4-ethyl-OH	piperidin-1-yl	C28 H43 N5 O5 S3	625.9	626.3	
54	NH-ethyl-thien-2-yl	NH-CH(CH_3)-(CH_2)$_3$-N(ethyl)$_2$	piperidin-1-yl	C31 H51 N5 O4 S3	654.0	654.3	
55	NH-ethyl-N(CH_3)$_2$	NH-ethyl-N(ethyl)$_2$	NH-phenyl	C28 H40 N6 O4 S2	588.8	589.3	
56	NH-ethyl-phenyl	NH-ethyl-N(CH_3)$_2$	NH-ethyl-N(ethyl)$_2$	C30 H53 N7 O4 S2	639.9	640.4	
57	N(ethyl)-ethyl-N(CH_3)$_2$	4-N(CH_3)-piperazin-1-yl	NH-ethyl-thien-2-yl	C29 H44 N6 O4 S4	668.2	669.2	
58	NH-benzyl	N-ethyl-N-pyrrolidinyl	N(ethyl)-ethyl-N(CH_3)$_2$	C31 H53 N7 O4 S2	651.9	652.3	
59	N(CH_3)-benzyl	NH-ethyl-N-pyrrolidinyl	N(ethyl)-ethyl-N(CH_3)$_2$	C32 H55 N7 O4 S2	666.0	666.3	
60	NH-benzyl	4-N(CH_3)-piperazin-1-yl	N(ethyl)-ethyl-N(CH_3)$_2$	C30 H51 N7 O4 S2	637.9	638.3	
61	N(CH_3)-benzyl	4-N(CH_3)-piperazin-1-yl	N(ethyl)-ethyl-N(CH_3)$_2$	C31 H53 N7 O4 S2	651.9	652.3	
62	NH-ethyl-phenyl	NH-ethyl-N-pyrrolidinyl	N(ethyl)-ethyl-N(CH_3)$_2$	C32 H55 N7 O4 S2	666.0	666.3	

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63	$N(CH_3)$-benzyl	NH-ethyl-N-pyrrolidinyl	$NH-CH_2$-cyclopropyl	C28 H41 N5 O4 S2	575.8	576.3	
64	piperazin-1-yl-4-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C32 H50 N6 O4 S2	646.9	647.3	116 - 118
65	NH-piperidin-4-yl-N-benzyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C34 H54 N6 O4 S2	675.0	675.4	
66	NH-ethyl-phenyl-3,4-$(OCH_3)_2$	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C32 H51 N5 O6 S2	665.9	666.3	
67	NH-ethyl-phenyl-4-Cl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C30 H46 Cl N5 O4 S2	640.3	640.3	
68	NH-ethyl-phenyl-4-NH_2	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C30 H48 N6 O4 S2	620.9	621.3	
69	NH-propyl-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C31 H49 N5 O4 S2	619.9	620.3	
70	NH-butyl-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C32 H51 N5 O4 S2	633.9	634.3	
71	$N(CH_3)$-ethyl-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C31 H49 N5 O4 S2	619.9	620.3	
72	Piperazin-1-yl-4-ethyl-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C34 H54 N6 O4 S2	675.0	675.4	
73	$NH-CH_2$-3,5-$(CH_3)_2$-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C31 H49 N5 O4 S2	619.9	620.3	
74	NH-ethyl-3-CF_3-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C31 H46 F3 N5 O4 S2	673.9	674.3	
76	NH-ethyl-O-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C30 H47 N5 O5 S2	621.9	622.3	
77	NH-ethyl-3,4-Cl_2-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	piperidin-1-yl	C30 H45 Cl2 N5 O4 S2	674.8	674.2	
78	piperazin-1-yl-4-phenyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C32 H48 N6 O4 S2	644.9	645.3	
79	piperidin-1-yl-4-phenyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C33 H49 N5 O4 S2	643.9	644.3	

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80	piperidin-1-yl-4-benzyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C34 H51 N5 O4 S2	657.9	658.3	
81	NH-ethyl-3,4(OCH_3)$_2$-phenyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C32 H49 N5 O6 S2	663.9	664.3	
82	NH-propyl-phenyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C31 H47 N5 O4 S2	617.9	618.3	
83	NH-butyl-phenyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C32 H49 N5 O4 S2	631.9	632.3	
84	Piperazin-1-yl-4-ethyl-phenyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C34 H52 N6 O4 S2	673.0	673.4	
85	NH-CH_2-(3-Cl-phenyl)	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C29 H42 Cl N5 O4 S2	624.3	624.2	
87	NH-ethyl-O-phenyl	NH-ethyl-N-pyrrolidinyl	piperidin-1-yl	C30 H45 N5 O5 S2	619.8	620.3	
88	Piperazin-1-yl-4-CH_3	NH-ethyl-N(ethyl)$_2$	NH-phenyl	C29 H40 N6 O4 S2	600.8	601.3	
89	N(CH_3)-benzyl	NH-ethyl-N(CH_3)$_2$	NH-ethyl-N(ethyl)$_2$	C30 H53 N7 O4 S2	639.9	640.4	
90	N(CH_3)-benzyl	piperazin-1-yl-4-CH_3	NH-ethyl-N(ethyl)$_2$	C31 H53 N7 O4 S2	651.9	652.4	
91	piperazin-1-yl-4-phenyl	NH-ethyl-N(CH_3)$_2$	piperidin-1-yl	C30 H46 N6 O4 S2	618.9	619.3	
92	piperidin-1-yl-4-phenyl	NH-ethyl-N(CH_3)$_2$	piperidin-1-yl	C31 H47 N5 O4 S2	617.9	618.3	
93	piperidin-1-yl-4-benzyl	NH-ethyl-pyrrolidinyl	NH-(CH_2)$_3$-O-CH_3	C32 H51 N5 O6 S2	665.9	666.3	
94	NH-ethyl-3,4-(OCH_3)$_2$-phenyl	N(ethyl)-ethyl-N(CH_3)$_2$	NH-ethyl-thien-2-yl	C34 H47 N5 O6 S4	750.0	750.2	

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95	piperidin-1-yl-4-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	NH-ethyl-thien-2-yl	C35 H47 N5 O4 S4	730.1	730.3	
96	piperazin-1-yl-4-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	NH-ethyl-thien-2-yl	C34 H46 N6 O4 S4	731.0	731.3	
97	NH-CH_2-naphth-1-yl	NH-ethyl-N-pyrrolidinyl	NH-ethyl-thien-2-yl	C35 H41 N5 O4 S4	724.0	724.2	
98	piperazin-1-yl-4-phenyl	N(ethyl)-ethyl-$N(CH_3)_2$	NH-propyl-O-CH_3	C30 H50 N6 O6 S2	654.9	655.3	
99	NH-(4-t-butyl)-benzyl	NH-ethyl-N-pyrrolidinyl	NH-ethyl-thien-2-yl	C35 H47 N5 O4 S4	730.1	730.3	
100	NH-(3,4-Cl_2)-benzyl	NH-ethyl-$N(CH_3)_2$	Piperidin-1-yl	C27 H39 Cl2 N5 O4 S2	632.7	632.2	
101	NH-(3-Cl)-benzyl	NH-ethyl-$N(CH_3)_2$	Piperidin-1-yl	C27 H40 Cl N5 O4 S2	598.2	598.2	
102	NH-(4-t-butyl)-benzyl	NH-ethyl-$N(CH_3)_2$	Piperidin-1-yl	C31 H49 N5 O4 S2	619.9	620.3	
103	NH-ethyl-O-phenyl	NH-ethyl-$N(CH_3)_2$	Piperidin-1-yl	C28 H43 N5 O5 S2	593.8	594.3	
104	piperazin-1-yl-4-phenyl	NH-ethyl-N-pyrrolidinyl	NH-$(CH_2)_3$-O-CH_3	C30 H48 N6 O6 S2	652.9	653.3	
105	NH-(4-t-butyl)-benzyl	NH-ethyl-N-pyrrolidinyl	NH-$(CH_2)_3$-O-CH_3	C31 H51 N5 O6 S2	653.9	654.3	
106	piperazin-1-yl-4-phenyl	NH-ethyl-$N(CH_3)_2$	NH-$(CH_2)_3$-O-CH_3	C28 H46 N6 O6 S2	626.8	627.3	

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107	NH-(4-t-butyl)-benzyl	NH-ethyl-$N(CH_3)_2$	NH-$(CH_2)_3$-O-CH_3	C29 H49 N5 O6 S2	627.9	628.3	
108	piperazin-1-yl-4-phenyl	4-$N(CH_3)$-piperazin-1-yl	NH-$(CH_2)_3$-O-CH_3	C29 H46 N6 O6 S2	638.9	639.3	
109	NH-(4-t-butyl)-benzyl	4-$N(CH_3)$-piperazin-1-yl	NH-$(CH_2)_3$-O-CH_3	C30 H49 N5 O6 S2	639.9	640.3	
110	1,2,5,6-tetrahydropyridin-1-yl-(4-phenyl)	4-$N(CH_3)$-piperazin-1-yl	$N(CH_3)$-phenyl	C36 H41 N5 O4 S2	671.9	672.3	

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The compounds of the formula I are distinguished by beneficial effects on lipid metabolism, and they are suitable in particular as hypolipidemics. The compounds can be employed alone or in combination with other lipid-lowering agents. Such other lipid-lowering agents are mentioned, for example, in the Rote Liste, chapter 58. The compounds are suitable for the prophylaxis and, in particular, for the treatment of hyperlipidemia.

Arteriosclerosis is a complex disorder of the metabolic and circulatory systems. Elevated plasma LDL cholesterol is one of the main risk parameters for this disorder. In humans, LDL cholesterol is mostly removed from the blood circulation via the LDL receptor in the liver. A reduction in the plasma LDL cholesterol reduces the risk of arteriosclerosis and thus also the overall mortality. The compounds according to the invention are thus also suitable for the prophylaxis and for the treatment of arteriosclerotic disorders.

The activity of the compounds was tested as follows:

1) In vitro determination of LDL receptor induction using the luciferase assay

LDL-receptor induction is determined using the luciferase assay as follows: for this purpose a regulatory DNA fragment (4kb) of the human LDL receptor gene which contains the complete promoter region is coupled to the firefly luciferase reporter gene and stably transfixed into a Hep-G2 cell line. Cells from this line were seeded out on collagen-coated 96-well plates in MEM (minimum essential medium). After 24 hours in culture, the test substances, dissolved in DMSO, were added in final concentrations of 10 nM to 10 μM (final DMSO concentration = 2%). The substances were incubated for 12-18 hours overnight (4 wells/conc. in each case), then D-luciferin was added as substrate for the luciferase, and the luminescence was measured. The measured luminescence as a percentage of the control (control = 100%) incubated only with DMSO indicates the extent of the relative LDL receptor induction (Table 2).

Further details of the method are described in: Current Protocols in Molecular Biology, F.M. Ausubel, R. Brent, R.E.Kingston, D.D. Moore, J.G.Seidman, J.A.Smith and Kevin Struhl editors, J.Wiley and Sons Inc., U.S.A.

Table 2: LDL receptor induction by selected examples as % of the control

Example	LDL receptor induction (% of control)
1	195 % (1.5 μM)
2	227 % (4 μM); 155 % (1.5 μM)
3	414 % (1.5 μM), 184 % (0.15 μM)
5	240 % (4 μM)
6	299 % (4 μM)
8	190 % (4 μM)
9	402 % (1.5 μM), 244 % (0.15 μM)
10	270 % (4 μM), 144 % (0.15 μM)
12	244 % (1.5 μM)
15	243 % (1.5 μM), 137 % (0.15 μM)
16	214 % (1.5 μM)
25	189 % (1.5 μM), 168 % (0.15 %)
26	206 % (1.5 μM), 146 % (0.15 μM)
46	223 % (1.5 μM), 152 % (0.15 μM)
58	219 % (4 μM);196 % (1.5 μM)
61	190 % (4 μM)
65	314 % (4 μM), 292 % (1.5 μM), 177 % (0.15 μM)
70	238 % (4 μM), 194 % (0.15 μM)
84	223 % (4 μM), 199 % (1.5 μM)
92	233 % (4 μM), 213 % (1.5 μM)
93	337 % (4 μM), 293 % (1.5 μM), 213 % (0.15 μM)
94	321 % (4 μM), 194 % (1.5 μM)
95	301 % (4 μM), 267 % (1.5 μM), 198 % (0.15 μM)
96	326 % (4 μM), 278 % (1.5 μM), 138 % (0.15 μM)
98	285 % (4 μM), 249 (1.5 μM)
99	322 % (4 μM), 247 % (1.5 μM)
102	298 % (4 μM), 239 % (1.5 μM)
108	249 % (4 μM), 191 % (1.5 μM)

2) In vivo determination of reduction in LDL cholesterol in the hamster; cholesterol-lowering effect of LDL receptor inducers in hyperlipemic hamsters

In this animal experiment, the effect of LDL receptor inducers after bolus administration to hamsters on a lipid-rich diet was investigated.

The experimental animals used were male Syrian hamsters (Charles River) with an average body weight of 100 - 120 g at the start of adaption.
The animals were divided into groups (n = 6) on the basis of the body weight. Severe hyperlipidemia was induced by feeding with a diet supplemented with 15% butter and 3% cholesterol. The treatment started after preliminary feeding for 2 weeks. The test substances were administered orally by gavage once a day over a period of 10 days. The plasma lipid level was analyzed after 10 days.

Table 3 shows the relative changes in the lipid level in % compared with placebo-treated control animals.

Table 3

Relative change in the plasma lipid level in hyperlipemic hamsters after oral treatment for ten days [%]				
Group	Treatment (Exp. No./dose)	Total cholesterol	LDL cholesterol	Triglycerides
1	Control I	-	-	-
2	95 20 mg/kg p.o.	- 45	- 44	- 61
3	95 40 mg/kg p.o.	- 50	- 49	- 73
4	98 20 mg/kg p.o.	-23	- 26	- 27
5	98 40 mg/kg p.o.	-46	- 44	- 68

The good lipid-lowering effect of the compounds according to the invention is evident from the marked reduction in total cholesterol, LDL cholesterol and triglycerides.

For detailed illustration of the preparation, one example (No. 64) is described precisely below.

Example:

N-Ethyl-N',N'-dimethyl-N-[5-(4-phenyl-piperazin-1-yl)-2,4-bis-(piperidine-1-sulfonyl)-phenyl]ethane-1,2-diamine (Table 1, Example 64)

2.63 g (5.1 mmol) of N-[5-chloro-2,4-bis-(piperidine-1-sulfonyl)-phenyl]-N-ethyl-N',N'-dimethylethane-1,2-diamine, prepared as described below, are dissolved in 12 ml of 4-phenylpiperazine, and the reaction mixture is stirred at 90°C for 9 hours. Workup entails extraction with ethyl acetate/water, drying of the combined organic phases over sodium sulfate, and removing the extractant under reduced pressure in a rotary evaporator. This is followed by purification by chromatography on silica gel (40 - 63 µ, Merck Darmstadt; mobile phase dichloromethane / methanol = 20 / 1).

The reaction product, yield 1.43 g (44%), crystallizes from a diisopropyl ether/n-pentane solvent mixture in the form of pale yellow crystals of melting point 116 to 118°C .

C32 H50 N6 O4 S2 (646.9); mass spectrum 647.3 ($M+H^+$)

Synthesis of N-[5-chloro-2,4-bis-(piperidine-1-sulfonyl)-phenyl]-N-ethyl-N',N'-dimethylethane-1,2-diamine

11.2 g (25.3 mmol) of 4,6-dichloro-N,N-dipiperidylbenzene-1,3-disulfonamide (prepared as described below) are dissolved in 100 ml of ethanol, and 4.26 g of N,N-dimethyl-N'-ethylenediamine are added. The reaction mixture is heated to reflux in the solvent for 12 hours. It is then poured into 500 ml of ice-water and extracted three times with 100 ml of ethyl acetate each time. The organic phases are combined and dried with sodium sulfate, and the extract is removed under reduced pressure in a rotary evaporator, and then the product is purified by chromatography on silica gel (40 - 63 µ, Merck Darmstadt; mobile phase dichloromethane/ ethylacetate = 20 : 1).

Removal of the solvent results in 6.8 g of N-[5-chloro-2,4-bis-(piperidine-1-sulfonyl)-phenyl]-N-ethyl-N',N'-dimethylethane-1,2-diamine,

yield 52% of theory, colorless oil.

$C_{22}H_{37}ClN_4O_4S_2$ (521.1), mass spectrum 521.2 $(M+H^+)$

Synthesis of 4,6-dichloro-N,N-dipiperidylbenzene-1,3-disulfonamide

20 g (58 mmol) of 4,6-dichlorobenzene-1,3-disulfonyl dichloride (prepared as described below) are dissolved in 175 ml of absolute tetrahydrofuran and, while cooling at 0°C in ice, a mixture of 12.65 ml of piperidine, 16.1 ml of triethylamine and 10 ml of tetrahydrofuran is added dropwise. The reaction temperature must not increase above room temperature during this. The mixture is then stirred at room temperature for one hour and filtered to remove the precipitate which has formed. The mother liquor is dried with sodium sulfate and concentrated under reduced pressure, and the product is purified by chromatography on silica gel (40 - 63 µ, Merck Darmstadt) with n-heptane : ethyl acetate = 1:2 as mobile phase.

18.2 g (71.1% of theory) of 4,6-dichloro-N,N-dipiperidylbenzene-1,3-disulfonamide of melting point 170°C are obtained.

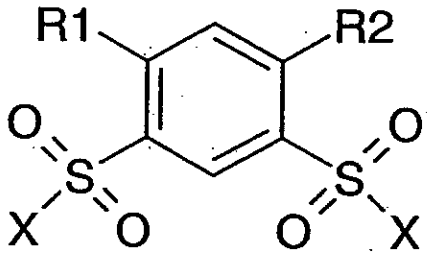
Synthesis of 4,6-dichlorobenzene-1,3-disulfonyl dichloride

80 g (0.54 mol) of 1,3-dichlorobenzene are dissolved in 645 g of chlorosulfonic acid and stirred at 125°C for 5 hours. The mixture is then stirred at 23°C for 8 hours. Then 145.6 ml of thionyl chloride are added with cooling, and the mixture is stirred at 80°C for 2 hours. The reaction mixture is then hydrolyzed by dropwise addition of 42 ml of water cautiously and with efficient cooling. The reaction solution is then added dropwise at 0°C to about 3.5 l of ice/water mixture. This precipitates the reaction product as a colorless solid, which is then filtered off.

After drying, 179.2 g of 4,6-dichlorobenzene-1,3-disulfonyl dichloride (95% of theory) of melting point 104°C are obtained; the product melts with decomposition.

Claims:

1. The use of compounds of formula I,



wherein the meanings are

R1 NR6R7, piperidine, piperazine, tetrahydropyridine, it being possible for each of the rings to be substituted by phenyl, (C_1-C_6)-alkyl-phenyl;

R6, R7 independently of one another H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl-NH-C(O)-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-[(C_1-C_6)-alkyl]$_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, (C_3-C_6)-cycloalkyl, piperidinyl, pyrrolidinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 4-morpholinyl, and Ar may be up to disubstituted by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, NH_2;

R2 NR8R9, piperazine, it being possible for piperazine to be substituted by (C_1-C_6)-alkyl;

R8, R9 independently of one another H, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-[(C_1-C_6)-alkyl]$_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 2-, 3- or 4-pyridyl, piperidinyl, pyrrolidinyl, morpholinyl;

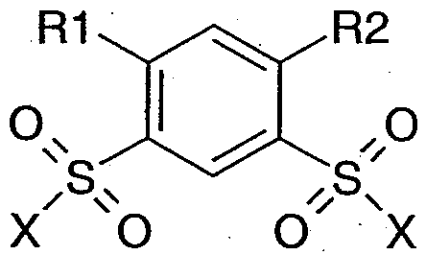
X NR10R11, pyrrolidine, piperidine, morpholine, it being possible for each of the rings to be substituted by phenyl, (C_1-C_6)-alkyl-phenyl;

R10, R11 independently of one another H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-[(C_1-C_6)-alkyl]$_2$, $(CH_2)_n$-Ar, where n can be 0 – 6, and Ar equals phenyl, 2- or 3-thienyl;

and of their physiologically tolerated salts for producing a medicine for the prevention and treatment of hyperlipidemia.

2. The use of the compounds as claimed in claim 1 in combination with one or more lipid-lowering agents for producing a medicine for the prophylaxis or treatment of hyperlipidemia.

3. The use of compounds of formula I



in which

X, R1, R2 are, independently of one another, NR6R7, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyridine, it being possible for each of the rings to be substituted by phenyl, (C_1-C_6)-alkyl-phenyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-OH, O-phenyl, S-phenyl, (CO)-(C_1-C_6)-alkyl, (CO)-phenyl, where the phenyl substituent is unsubstituted or up to disubstituted by F, Cl, Br, OH, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, COOH, COO(C_1-C_6)alkyl, COO(C_3-C_6)cycloalkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CON[(C_1-C_6)alkyl]$_2$,

$CONH(C_3-C_6)$cycloalkyl, NH_2, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl;

R6 and R7 are, independently of one another, H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, O-(C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-C(O)-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-$[(C_1-C_6)$-alkyl$]_2$, (C_1-C_6)-alkyl-O-phenyl, CHO, CO-phenyl,

$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, biphenylyl, 1- or 2-naphthyl, 1- or 2-tetrahydrofuranyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 1-pyrazolyl, 3-, 4- or 5-isoxazolyl, (C_3-C_6)-cycloalkyl, piperidinyl, pyrrolidinyl, 2- or 3-pyrrolyl, 2- or 3-pyridazinyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 2-(1,3,5-triazinyl), 2-, 3- or 4-morpholinyl, 2- or 5-benzimidazolyl, 2-benzothiazolyl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, tetrazol-5-yl, indol-3-yl, indol-5-yl or N-methyl-imidazol-2-, -4- or -5-yl, and Ar may be substituted up to twice by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-CH_2-O, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, COOH, COO(C_1-C_6)alkyl, COO(C_3-C_6)cycloalkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CON$[(C_1-C_6)$alkyl$]_2$, CONH(C_3-C_6)cycloalkyl, NH_2, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl, pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl, $(CH_2)_n$-phenyl, O-$(CH_2)_n$-phenyl, S-$(CH_2)_n$-phenyl, SO_2-$(CH_2)_n$-phenyl, where n = 0-3;

and of their physiologically tolerated salts and physiologically functional derivatives for producing a medicine for the prevention and treatment of arteriosclerosis.

4. The use of compounds of formula I as claimed in claim 3 , wherein the meanings are

R1 NR6R7, pyrrolidine, piperidine, piperazine, tetrahydropyridine, it being possible for each of the rings to be substituted by

phenyl, (C_1-C_6)-alkyl-phenyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-OH, O-phenyl, S-phenyl, (CO)-(C_1-C_6)-alkyl, (CO)-phenyl, where the phenyl substituent is unsubstituted or up to disubstituted by F, Cl, Br, CF_3, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, COOH, COO(C_1-C_6)-alkyl, COO(C_3-C_6)cycloalkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CON[(C_1-C_6)alkyl]$_2$, NH_2, NH-CO-(C_1-C_6)-alkyl, NH-CO-phenyl;

R6, R7 independently of one another H, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-O-(C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-C(O)-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-[(C_1-C_6)-alkyl]$_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, biphenylyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 3- or 5-isoxazolyl, (C_3-C_6)-cycloalkyl, piperidinyl, pyrrolidinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 4-morpholinyl, 2- or 5-benzimidazolyl, 2-benzothiazolyl or indol-3-yl, indol-5-yl, and Ar may be up to disubstituted by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-(C_1-C_6)-alkyl, S-(C_1-C_6)-alkyl, SO-(C_1-C_6)-alkyl, SO_2-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, COOH, COO(C_1-C_6)alkyl, COO(C_3-C_6)cycloalkyl, $CONH_2$, CONH(C_1-C_6)alkyl, NH_2, NH-CO-phenyl, $(CH_2)_n$-phenyl, O-$(CH_2)_n$-phenyl, S-$(CH_2)_n$-phenyl, where n = 0-3;

R2 NR8R9, piperazine, it being possible for piperazine to be substituted by (C_1-C_6)-alkyl-phenyl, (C_1-C_6)-alkyl, (C_1-C_6)-alkyl-OH, O-phenyl, S-phenyl, (CO)-(C_1-C_6)-alkyl, (CO)-phenyl;

R8, R9 independently of one another H, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-NH-(C_1-C_6)-alkyl, (C_1-C_6)-alkyl-N-[(C_1-C_6)-alkyl]$_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 2-, 3- or 4-pyridyl, piperidinyl, pyrrolidinyl, morpholinyl;

X NR10R11, pyrrolidine, piperidine, piperazine, morpholine, it being possible for each of the rings to be substituted by phenyl,

$(C_1$-$C_6)$alkyl-phenyl, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-OH, O-phenyl, S-phenyl, (CO)-$(C_1$-$C_6)$-alkyl, (CO)-phenyl, where the phenyl substituent is unsubstituted or up to disubstituted by F, Cl, Br, CF_3, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, COOH, COO$(C_1$-$C_6)$-alkyl, COO$(C_3$-$C_6)$cycloalkyl, $CONH_2$, CONH$(C_1$-$C_6)$alkyl, CON[$(C_1$-$C_6)$alkyl]$_2$, NH_2, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl;

R10, R11 independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, CO-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-NH-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-N-[$(C_1$-$C_6)$-alkyl]$_2$, CO-phenyl, $(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, biphenylyl, 1- or 2-naphthyl, 1- or 2-tetrahydrofuranyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 3- or 5-isoxazolyl, piperidinyl, pyrrolidinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 4-morpholinyl, 2-benzothiazolyl, and Ar may be disubstituted by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1$-$C_6)$-alkyl, S-$(C_1$-$C_6)$-alkyl, SO-$(C_1$-$C_6)$-alkyl, SO_2-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $CONH_2$, CONH$(C_1$-$C_6)$alkyl, CON[$(C_1$-$C_6)$alkyl]$_2$, NH-CO-$(C_1$-$C_6)$-alkyl, NH-CO-phenyl, $(CH_2)_n$-phenyl, where n = 0-3;

and of their physiologically tolerated salts and physiologically functional derivatives for producing a medicine for the prevention and treatment of arteriosclerosis.

5. The use of compounds of formula I as claimed in claim 3 or 4 , wherein the meanings are

R1 NR6R7, piperidine, piperazine, tetrahydropyridine, it being possible for each of the rings to be substituted by phenyl, $(C_1$-$C_6)$-alkyl-phenyl;

R6, R7 independently of one another H, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl-O-$(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $(C_1$-$C_6)$-alkyl-NH-C(O)-

$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-NH-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-N-$[(C_1\text{-}C_6)\text{-alkyl}]_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, $(C_3\text{-}C_6)$-cycloalkyl, piperidinyl, pyrrolidinyl, 2-, 4- or 5-pyrimidinyl, 2-, 3- or 4-morpholinyl, and Ar may be up to disubstituted by F, Cl, Br, OH, CF_3, NO_2, CN, OCF_3, O-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, NH_2;

R2 NR8R9, piperazine, it being possible for piperazine to be substituted by $(C_1\text{-}C_6)$-alkyl;

R8, R9 independently of one another H, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, CO-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-NH-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-N-$[(C_1\text{-}C_6)\text{-alkyl}]_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar can be equal to phenyl, 2-, 3- or 4-pyridyl, piperidinyl, pyrrolidinyl, morpholinyl;

X NR10R11, pyrrolidine, piperidine, morpholine, it being possible for each of the rings to be substituted by phenyl, $(C_1\text{-}C_6)$-alkyl-phenyl;

R10, R11 independently of one another H, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, $(C_1\text{-}C_6)$-alkyl-NH-$(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl-N-$[(C_1\text{-}C_6)\text{-alkyl}]_2$,
$(CH_2)_n$-Ar, where n can be 0 – 6, and Ar equals phenyl, 2- or 3-thienyl;

and of their physiologically tolerated salts for producing a medicine for the prevention and treatment of arteriosclerosis.

6. The use of the compounds as claimed in one or more of claims 3 to 5 in combination with one or more lipid-lowering agents for producing a medicine for the prophylaxis or treatment of arteriosclerosis.

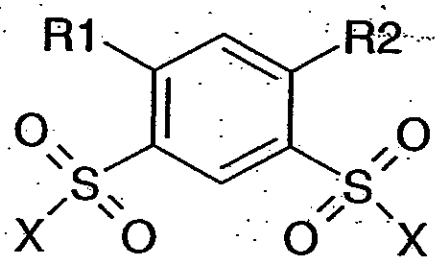
7. The use of the compounds as claimed in claim 1 in combination with one or more lipid-lowering agents for producing a medicine for the prophylaxis or treatment of hyperlipidemia.

Abstract

The use of bissulfonamides for producing medicines for the prophylaxis or treatment of hyperlipidemia.

The invention relates to the use of bissulfonamides and their physiologically tolerated salts and physiologically functional derivatives for producing medicines for the prophylaxis or treatment of hyperlipidemia.

The use of the compounds of formula I



I

in which the radicals have the stated meanings, and of their physiologically tolerated salts and physiologically functional derivatives for producing a medicine for the prophylaxis or treatment of hyperlipidemia or of arteriosclerosis is described.