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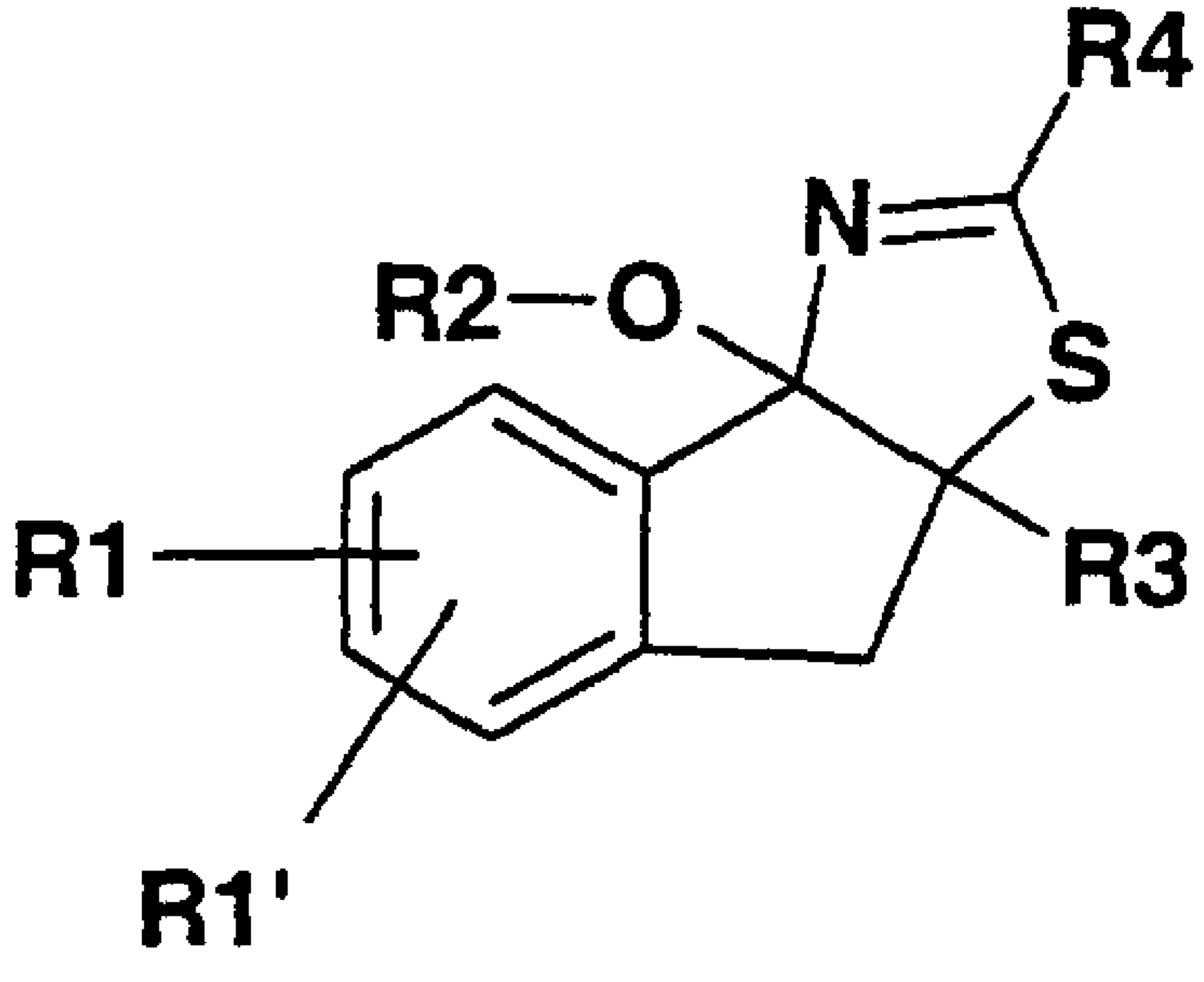
(54) **Titre** : DERIVES DE 8,8A-DIHYDRO-3AH-INDENO[1,2-D]THIAZOLES SUBSTITUES A LA POSITION 8A, PROCEDES DE FABRICATION ET UTILISATION EN TANT QU'AGENTS PHARMACEUTIQUES PAR EX. EN TANT QU'ANOREXIGENES

(54) **Title**: 8,8A-DIHYDRO-INDENO[1,2-D]THIAZOLE DERIVATIVES, SUBSTITUTED IN POSITION 8A, A METHOD FOR THEIR PRODUCTION AND THEIR USE AS MEDICAMENTS, E.G. ANORECTIC AGENTS



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(57) **Abrégé/Abstract**:

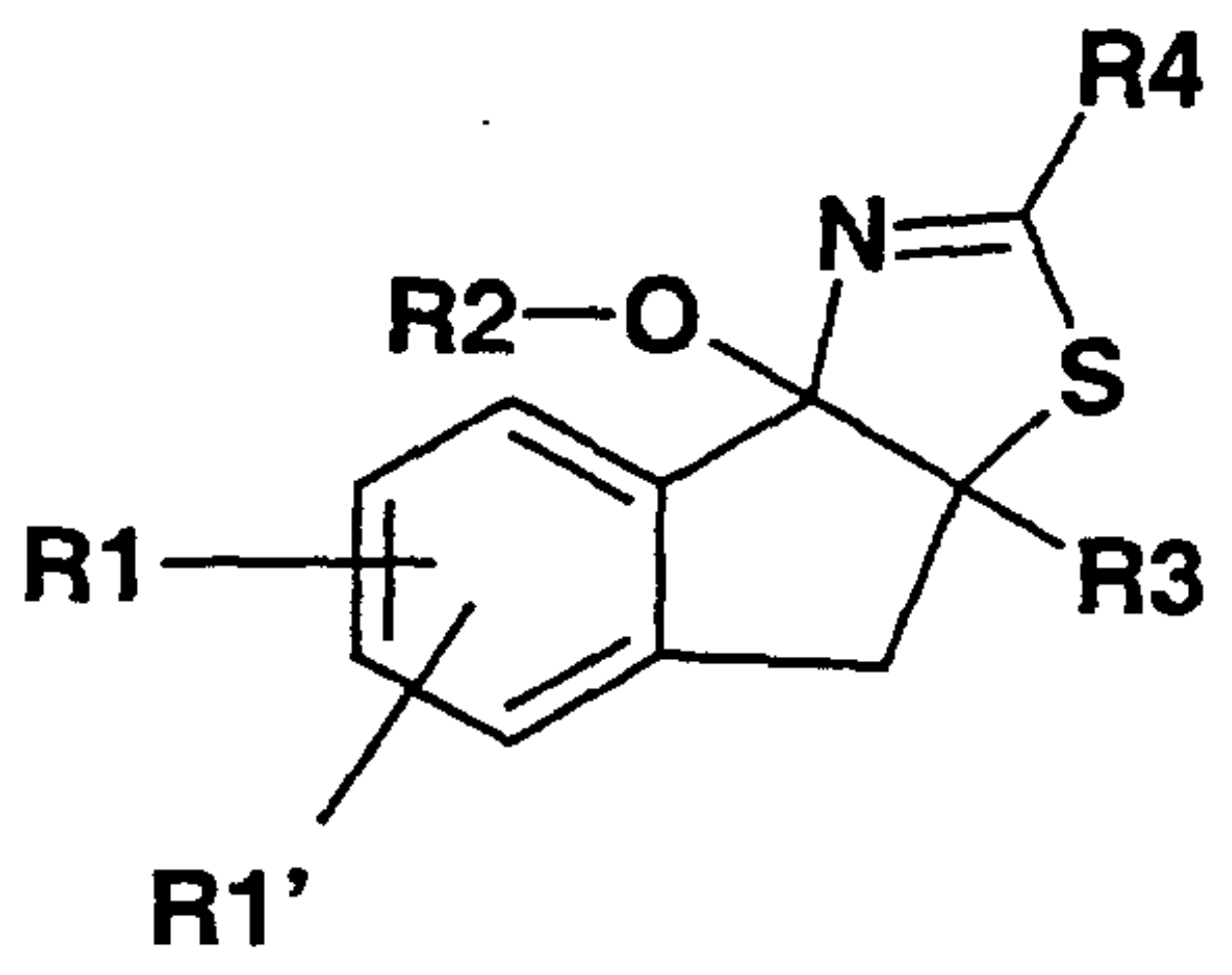
The invention relates to polycyclic dihydrothiazoles and to their physiologically compatible salts and physiologically functional derivatives. The invention relates to compounds of formula (I), wherein the groups have the given meanings, to their physiologically compatible salts and to a method for their production. The compounds are, for example, suitable for use as anorectic agents.

# Abstract

8,8a-Dihydroindeno[1,2-d]thiazole derivatives which are substituted in the 8a-position; processes for their preparation and their use as medicaments

The invention relates to polycyclic dihydrothiazoles and to their physiologically acceptable salts and physiologically functional derivatives.

Compounds of the formula I,



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in which the radicals are as defined above, and their physiologically acceptable salts and processes for their preparation are described. The compounds are suitable, for example, as anorectics.

Description

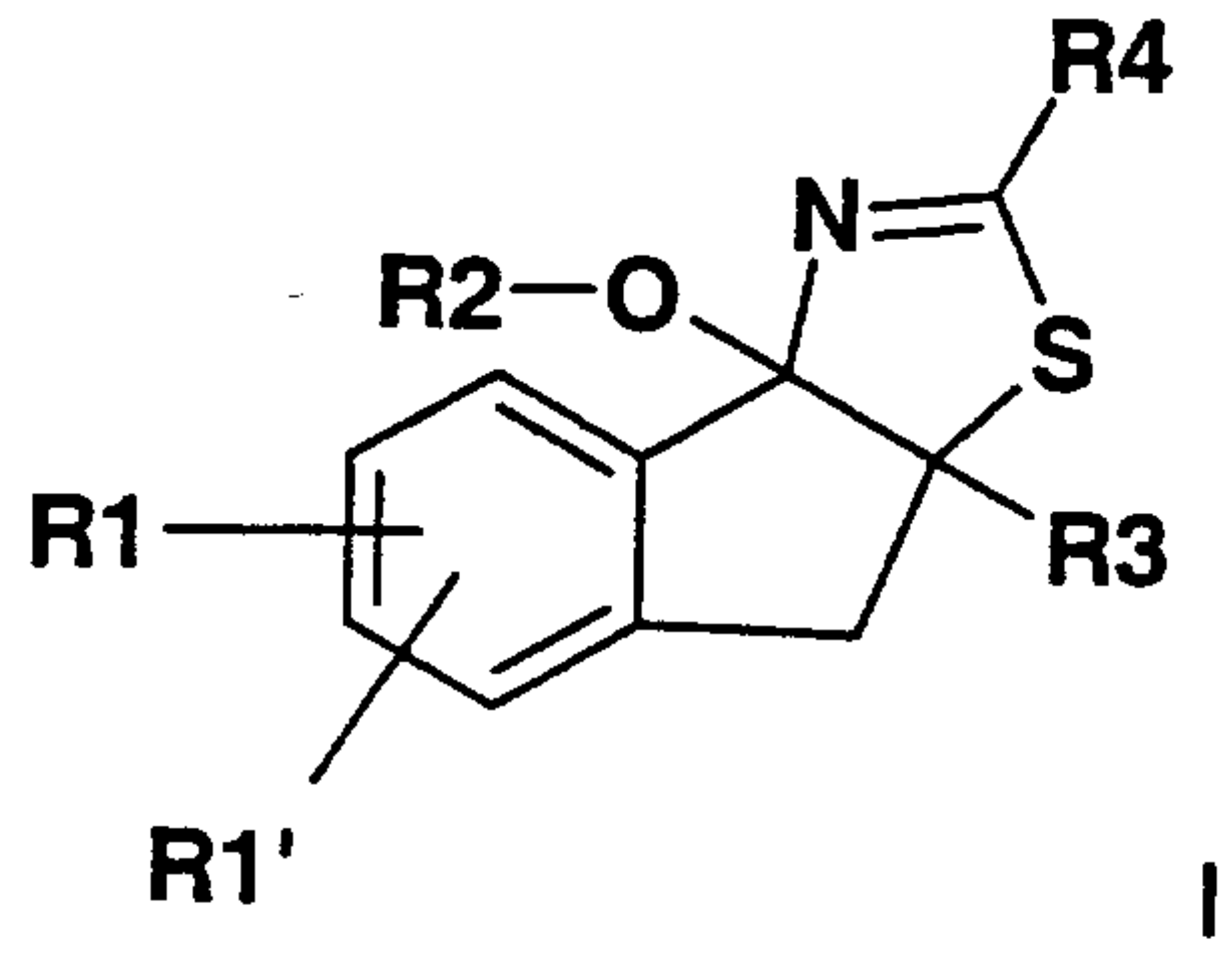
# 8,8a-DIHYDROINDENO[1,2-d]THIAZOLE DERIVATIVES WHICH ARE SUBSTITUTED IN THE 8a-POSITION; PROCESSES FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS, E.G. AS ANORECTICS

The invention relates to polycyclic dihydrothiazoles and to their physiologically acceptable salts and physiologically functional derivatives.

Thiazolidine derivatives having anorectic action have already been described in the prior art (Austrian Patent No. 365181).

The object of the invention was to provide further compounds having a therapeutically useful anorectic action.

Accordingly, the invention relates to compounds of the formula I,



I

in which

| | |
|---|---|
| R1, R1' | independently of one another are H, F, Cl, Br, I, $CF_3$, $NO_2$, CN, 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 in the alkyl radicals one or more, or all hydrogens may be replaced by fluorine, or one hydrogen may be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph, $NH_2$, NH-CO-$CH_3$ or N($COOCH_2Ph$)$_2$; |

are $SO_2$-$NH_2$, $SO_2NH(C_1$-$C_6)$-alkyl, $SO_2N[(C_1$-$C_6)$-alkyl$]_2$, S-$(C_1$-$C_6)$-alkyl, S-$(CH_2)_n$-phenyl, SO-$(C_1$-$C_6)$-alkyl, SO-$(CH_2)_n$-phenyl, $SO_2$-$(C_1$-$C_6)$-alkyl, $SO_2$-$(CH_2)_n$-phenyl, where n can be 0–6 and the phenyl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, $NO_2$, CN, $OCF_3$, O-$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkyl, $NH_2$;

are $NH_2$, NH-$(C_1$-$C_6)$-alkyl, $N[(C_1$-$C_6)$-alkyl$]_2$, $NH(C_1$-$C_7)$-acyl, phenyl, biphenylyl, O-$(CH_2)_n$-phenyl, where n can be 0–6, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-furanyl or 2- or 3-thienyl, where the phenyl, biphenylyl, naphthyl, pyridyl, furanyl or thienyl rings can in each case 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, $CONH_2$;

are 1,2,3-triazol-5-yl, where the triazole ring can be substituted in the 1-, 2- or 3-position by methyl or benzyl;

are tetrazol-5-yl, where the tetrazole ring can be substituted in the 1- or 2-position by methyl or benzyl;

R2 is H, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, C(O)-$(C_1$-$C_6)$-alkyl, C(O)-$(C_3$-$C_6)$-cycloalkyl, C(O)-$(CH_2)_n$-phenyl, C(O)-$(CH_2)_n$-thienyl, C(O)-$(CH_2)_n$-pyridyl, C(O)-$(CH_2)_n$-furyl, where n can be 0-5 and in which phenyl, thienyl, pyridyl and furyl can in each case be substituted up to two times by Cl, F, CN, $CF_3$, $(C_1$-$C_3)$-alkyl, OH, O-$(C_1$-$C_6)$-alkyl;

R3 is Cl, Br, $CH_2$-$COO(C_1$-$C_6)$-alkyl, $CH_2$-COOH, $CH_2$-$CONH_2$;

R4 is $(C_1$-$C_8)$-alkyl, $(C_3$-$C_7)$-cycloalkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, $(C_4$-$C_7)$-cycloalkenyl, where in the alkyl radicals one or more, or all hydrogens can be replaced by fluorine or one hydrogen can be replaced by OH, $OC(O)CH_3$, OC(O)H, O-$CH_2$-Ph or O-$(C_1$-$C_4)$-alkyl;

is $(CH_2)_n$-pyrrolidin-1-yl, $(CH_2)_n$-piperidin-1-yl, $(CH_2)_n$-morpholin-4-yl, $(CH_2)_n$-piperazin-1-yl, $(CH_2)_n$-N-4-methylpiperazin-1-yl, $(CH_2)_n$-N-4-benzylpiperazin-1-yl, $(CH_2)_n$-phthalimidoyl, where n can be 1-6;

is $(CH_2)_n$-aryl, where n can be 0–6 and aryl is phenyl, biphenylyl, 1- or 2-naphthyl, 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- or 5-isoxazolyl, 2- or 3-pyrrolyl, 2- or 3-pyridazinyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 2-(1,3,5-triazinyl), 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-methylimidazol-2-, -4- or -5-yl, and the aryl radical or heteroaryl radical can be substituted up to two times 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, $(CH_2)_n$-$SO_2$-$(C_1$-$C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, $(CH_2)_n$-$SO_2$-N(=CH-N$(CH_3)_2$), where n can be 0-6; $(C_1$-$C_6)$-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, NH-$SO_2$-$(C_1$-$C_6)$-alkyl, NH-$SO_2$-phenyl, where the phenyl ring can be substituted up to two times by F, Cl, CN, OH, $(C_1$-$C_6)$-alkyl, O-$(C_1$-$C_6)$-alkyl, $CF_3$, COOH, COO$(C_1$-$C_6)$-alkyl or $CONH_2$;

is pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, $(CH_2)_n$-phenyl, O-$(CH_2)_n$-phenyl, S-$(CH_2)_n$-phenyl, $SO_2$-$(CH_2)_n$-phenyl, where n can be 0-3;

is $(CH_2)_n$-A-R8, where n can be 1-6;

A is O, NH, N-$(C_1$-$C_6)$-alkyl, NCHO, N(CO-$CH_3$), S, SO, $SO_2$;

R8 is $(C_1$-$C_8)$-alkyl, $(C_3$-$C_8)$-cycloalkyl, where in the alkyl radicals one or more hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph or O-$(C_1$-$C_4)$-alkyl;

is $(CH_2)_m$-aryl, where m can be 0-6 and aryl can be phenyl, thienyl or pyridyl and the aryl moiety can be substituted up to two times 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, $(CH_2)_n$ -$SO_2$-$(C_1$-$C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, $(CH_2)_n$-$SO_2$-N(=CH-N$(CH_3)_2$), $(CH_2)_n$-$SO_2$-NH$(C_1$-$C_8)$-alkyl, $(CH_2)_n$-$SO_2$-N[$(C_1$-$C_8)$-

alkyl]$_2$, $(CH_2)_n$-$SO_2$-NH($C_3$-$C_8$)-cycloalkyl, $(CH_2)_n$-$SO_2$-N[($C_3$-$C_8$)-cycloalkyl]$_2$, where n can be 0-6; ($C_1$-$C_6$)-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($C_1$-$C_6$)-alkyl, N[($C_1$-$C_6$)-alkyl]$_2$, NH-CO-($C_1$-$C_6$)-alkyl, NH-CO-phenyl, NH-$SO_2$-phenyl, where the phenyl ring can be substituted up to two times by F, Cl, CN, OH, ($C_1$-$C_6$)-alkyl, O-($C_1$-$C_6$)-alkyl, $CF_3$, COOH, COO($C_1$-$C_6$)-alkyl or $CONH_2$;
NH-$SO_2$-($C_1$-$C_8$)-alkyl, N($C_1$-$C_6$)-alkyl-$SO_2$-($C_1$-$C_8$)-alkyl, pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, $(CH_2)_p$-phenyl, O-$(CH_2)_p$-phenyl, S-$(CH_2)_p$-phenyl or $SO_2$-$(CH_2)_p$-phenyl, where p can be 0-3;

and their physiologically acceptable salts and physiologically functional derivatives.

Preference is given to compounds of the formula I in which

R1, R1' independently of one another are H, F, Cl, Br, I, $CF_3$, $NO_2$, CN, 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 in the alkyl radicals one or more, or all hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, $OC(O)CH_3$, OC(O)H, O-$CH_2$-Ph, $NH_2$, NH-CO-$CH_3$ or $N(COOCH_2Ph)_2$;
are $SO_2$-$NH_2$, $SO_2$NH($C_1$-$C_6$)-alkyl, $SO_2$N[($C_1$-$C_6$)-alkyl]$_2$, S-($C_1$-$C_6$)-alkyl, S-$(CH_2)_n$-phenyl, SO-($C_1$-$C_6$)-alkyl, SO-$(CH_2)_n$-phenyl, $SO_2$-($C_1$-$C_6$)-alkyl, $SO_2$-$(CH_2)_n$-phenyl, where n can be 0–6, and the phenyl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, $NO_2$, CN, $OCF_3$, O-($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)-alkyl, $NH_2$;

are $NH_2$, NH-($C_1$-$C_6$)-alkyl, N[($C_1$-$C_6$)-alkyl]$_2$, NH($C_1$-$C_7$)-acyl, phenyl, biphenylyl, O-$(CH_2)_n$-phenyl, where n can be 0–6, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-furanyl or 2- or 3-thienyl, where the phenyl, biphenylyl, naphthyl, pyridyl, furanyl or thienyl rings can in each case 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, $CONH_2$;

1,2,3-triazol-5-yl, where the triazole ring can be substituted in the 1-, 2- or 3-position by methyl or benzyl;

tetrazol-5-yl, where the tetrazole ring can be substituted in the 1- or 2-position by methyl or benzyl;

R2 is H, ($C_1$-$C_6$)-alkyl, ($C_3$-$C_6$)-cycloalkyl, ($CH_2$)$_n$-phenyl, ($CH_2$)$_n$-thienyl, ($CH_2$)$_n$-pyridyl, ($CH_2$)$_n$-furyl, C(O)-($C_1$-$C_6$)-alkyl, C(O)-($C_3$-$C_6$)-cycloalkyl, C(O)-($CH_2$)$_n$-phenyl, C(O)-($CH_2$)$_n$-thienyl, C(O)-($CH_2$)$_n$-pyridyl, C(O)-($CH_2$)$_n$-furyl, where n can be 0-5 and in which phenyl, thienyl, pyridyl and furyl can in each case be substituted up to two times by Cl, F, CN, $CF_3$, ($C_1$-$C_3$)-alkyl, OH, O-($C_1$-$C_6$)-alkyl;

R3 is Cl, Br, $CH_2$-COO($C_1$-$C_6$)-alkyl, $CH_2$-COOH, $CH_2$-$CONH_2$;

R4 is ($C_1$-$C_8$)-alkyl, ($C_3$-$C_7$)-cycloalkyl, ($C_2$-$C_6$)-alkenyl, ($C_2$-$C_6$)-alkynyl, ($C_4$-$C_7$)-cycloalkenyl, where in the alkyl radicals one or more, or all hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph or O-($C_1$-$C_4$)-alkyl;

is ($CH_2$)$_n$-pyrrolidin-1-yl, ($CH_2$)$_n$-piperidin-1-yl, ($CH_2$)$_n$-morpholin-4-yl, ($CH_2$)$_n$-piperazin-1-yl, ($CH_2$)$_n$-N-4-methylpiperazin-1-yl, ($CH_2$)$_n$-N-4-benzylpiperazin-1-yl, ($CH_2$)$_n$-phthalimidoyl, where n can be 1-6;

is ($CH_2$)$_n$-aryl, where n can be 0–6 and aryl can be phenyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl and the aryl radical or heteroaryl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-($C_1$-$C_6$)-alkyl, ($CH_2$)$_n$-$SO_2$-($C_1$-$C_6$)-alkyl, ($CH_2$)$_n$-$SO_2$-$NH_2$, ($CH_2$)$_n$-$SO_2$-N(=CH-N($CH_3$)$_2$), where n can be 0-6; NH-$SO_2$-($C_1$-$C_6$)-alkyl, NH-$SO_2$-phenyl, where the phenyl ring can be substituted up to

two times by F, Cl, CN, OH, $(C_1-C_6)$-alkyl, O-$(C_1-C_6)$-alkyl, $CF_3$, COOH, COO$(C_1-C_6)$-alkyl or $CONH_2$;
$(C_1-C_6)$-alkyl, COOH, COO$(C_1-C_6)$-alkyl or $CONH_2$;
is $(CH_2)_n$-A-R8, where n can be 1-6;

A is O, NH, $(C_1-C_6)$-alkyl, $SO_2$;

R8 is $(C_1-C_8)$-alkyl, $(C_3-C_8)$-cycloalkyl, where in the alkyl radicals one or more hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, $OC(O)CH_3$, OC(O)H, O-$CH_2$-Ph or O-$(C_1-C_4)$-alkyl;
is $(CH_2)_m$-aryl, where m can be 0-6 and aryl can be phenyl, thienyl or pyridyl, and the aryl moiety can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, $(CH_2)_n$-$SO_2$-N(=CH-N$(CH_3)_2$), where n can be 0-6;
NH-$SO_2$-$(C_1-C_6)$-alkyl, NH-$SO_2$-phenyl, where the phenyl ring can be substituted up to two times by F, Cl, CN, OH, $(C_1-C_6)$-alkyl, O-$(C_1-C_6)$-alkyl, $CF_3$, COOH, COO$(C_1-C_6)$-alkyl, $CONH_2$, where n can be 0-6;
COOH, COO$(C_1-C_6)$-alkyl, or $CONH_2$;

and their physiologically acceptable salts and physiologically functional derivatives.

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

R1, R1' independently of one another are H, F, Cl, Br, -OH, O-$(C_1-C_6)$-alkyl, $(C_1-C_6)$-alkyl, where in the alkyl radicals one hydrogen can be replaced by OH;

R2 is H, $(C_1-C_6)$-alkyl, C(O)-$(C_1-C_6)$-alkyl;

R3 is Cl, Br, $CH_2$-COO$(C_1-C_6)$-alkyl, $CH_2$-COOH, $CH_2$-$CONH_2$;

R4 is $(C_1-C_4)$-alkyl or $(C_3-C_6)$-cycloalkyl, where in the alkyl radicals one hydrogen can be replaced by OH;
$(CH_2)_n$-aryl, where n can be 0–6 and aryl can be phenyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, and the aryl radical or heteroaryl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-$(C_1-C_6)$-alkyl, $SO_2$-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, where n can be 0-6; $(C_1-C_6)$-alkyl, COOH, COO$(C_1-C_6)$-alkyl or $CONH_2$;

$(CH_2)_n$-A-R8, where n can be 1-6;

A is O, $SO_2$;

R8 is $(C_1-C_8)$-alkyl, $(C_3-C_8)$-cycloalkyl, where in the alkyl radicals one hydrogen can be replaced by OH;
$(CH_2)_m$-aryl, where m can be 0-6 and aryl can be phenyl or thienyl and the aryl moiety can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-$(C_1-C_6)$-alkyl, $SO_2$-$(C_1-C_6)$-alkyl, $SO_2$-$NH_2$, COOH, COO$(C_1-C_6)$-alkyl or $CONH_2$;

and their physiologically acceptable salts.

The invention relates to compounds of the formula I, in the form of their racemates, racemic mixtures and pure enantiomers, and to their diastereomers and mixtures thereof.
The alkyl, alkenyl and alkynyl radicals in the substituents R1, R1', R2, R3, R4, R8 and A can be either straight-chain or branched.

On account of their higher water solubility, pharmaceutically acceptable salts are particularly suitable for medicinal applications compared with the starting materials or base compounds. These salts must have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds according to the invention are salts of inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid, sulfonic acid and sulfuric acid, and of organic acids, such as, for example, acetic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, fumaric acid, gluconic acid, glycolic acid, isethionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methanesulfonic acid, succinic acid, p-toluenesulfonic acid, tartaric acid and trifluoroacetic acid. For medicinal purposes, the chlorine salt is particularly preferred. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium salts and potassium salts) and alkaline earth metal salts (such as magnesium salts and calcium salts).

Salts having a pharmaceutically unacceptable anion are likewise included in the scope of the invention as useful intermediates for the production or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in-vitro, applications.

The term “physiologically functional derivative” used here relates to any physiologically acceptable derivative of a compound of the formula I according to the invention, for example an ester, which on administration to a mammal, such as, for example, Man, is able (directly or indirectly) to form a compound of the formula I or an active metabolite thereof.

The physiologically functional derivatives also include prodrugs of the compounds according to the invention. Such prodrugs can be metabolized in vivo to a compound according to the invention. These prodrugs can themselves be active or inactive.

The compounds according to the invention can also be present in various polymorphic forms, for example as amorphous and crystalline polymorphic forms. All polymorphic forms of the compounds according to the invention are included in the scope of the invention and are a further aspect of the invention.

Hereinbelow, all references to “compound(s) according to formula (I)” refer to a compound/compounds of the formula (I) as described above, and to their salts, solvates and physiologically functional derivatives as described herein.

The amount of a compound according to formula (I) which is necessary in order to achieve the desired biological effect is dependent on a number of factors, for example the specific compound selected, the intended use, the manner of administration and the clinical condition of the patient. In general, the daily dose is in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day per kilogram of bodyweight, for example 3-10 mg/kg/day. An intravenous dose can be, for example, in the range from 0.3 mg to 1.0 mg/kg, which can be suitably administered as an infusion of 10 ng to 100 ng per kilogram per minute. Suitable infusion solutions for these purposes can contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg per milliliter. Individual doses can contain, for example, from 1 mg to 10 g of the active compound. Thus, ampoules for injections can contain, for example, from 1 mg to 100 mg, and orally administrable individual dose formulations, such as, for example, tablets or capsules, can contain, for example, from 1.0 to 1 000 mg, typically from 10 to 600 mg. In the case of pharmaceutically acceptable salts, the abovementioned weight details relate to the weight of the dihydrothiazolium ion derived from the salt. For the prophylaxis or therapy of the abovementioned conditions, the compounds according to formula (I) can be used themselves as the compound, but they are preferably present in the form of a pharmaceutical composition with a tolerable excipient. The excipient must of course be tolerable, in the sense that it is compatible with the other constituents of the composition and is not harmful to the patient’s health. The excipient can be a solid or a liquid or both and is preferably formulated with the compound as an individual dose, for example as a tablet which can contain from 0.05% to 95% by weight of the active compound. Further pharmaceutically active substances can also be present, including further compounds according to formula (I). The pharmaceutical compositions according to the invention can be prepared by one of the known pharmaceutical methods, which essentially consist in mixing the constituents with pharmacologically acceptable excipients and/or auxiliaries.

Pharmaceutical compositions according to the invention are those which are suitable for oral, rectal, topical, peroral (e.g. sublingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable manner of administration in each individual case is dependent on the nature and severity of the condition to be treated and on the nature of the compound according to formula (I) used in each case. Sugar-coated formulations and sugar-coated delayed release formulations are also included in the scope of the invention. Acid-resistant and enteric formulations are preferred. Suitable enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration can be present in separate units, such as, for example, capsules, cachets, lozenges or tablets which in each case contain a certain amount of the compound according to 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. As already mentioned, these compositions can be prepared by any suitable pharmaceutical method which includes a step in which the active compound and the excipient (which can consist of one or more additional constituents) are brought into contact. In general, the compositions are prepared by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid excipient, after which the product is shaped, if necessary. Thus a tablet, for example, can be prepared by pressing or shaping a powder or granules of the compound, if appropriate with one or more additional constituents. Pressed tablets can be prepared by tableting the compound in free-flowing form, such as, for example, in a powder or granules, if appropriate mixed with a binder, lubricant, inert diluent and/or one (a number of) surface-active/dispersing agent(s) in a suitable machine. Shaped tablets can be prepared by shaping the pulverulent compound, moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges which contain a compound according to formula

(I) with a flavoring, customarily sucrose and gum arabic or tragacanth, and pastilles which include the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

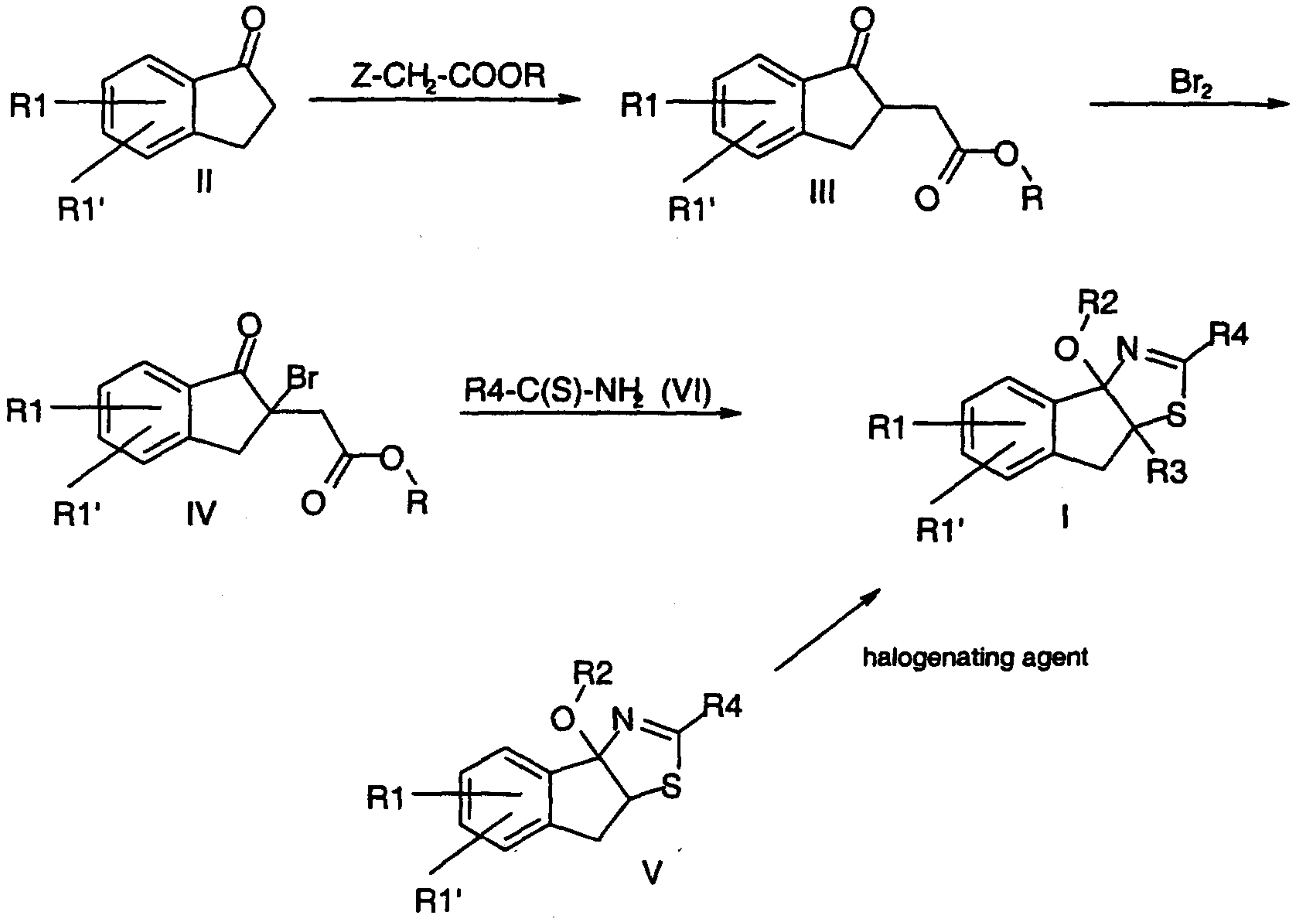
Suitable pharmaceutical compositions for parenteral administration preferably include sterile aqueous preparations of a compound according to formula (I), which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although the administration can also take place subcutaneously, intramuscularly or intradermally as an injection. These preparations can preferably be prepared by mixing the compound with water and rendering the obtained solution sterile and isotonic with the blood. Injectable compositions according to the invention in general contain from 0.1 to 5% by weight of the active compound.

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

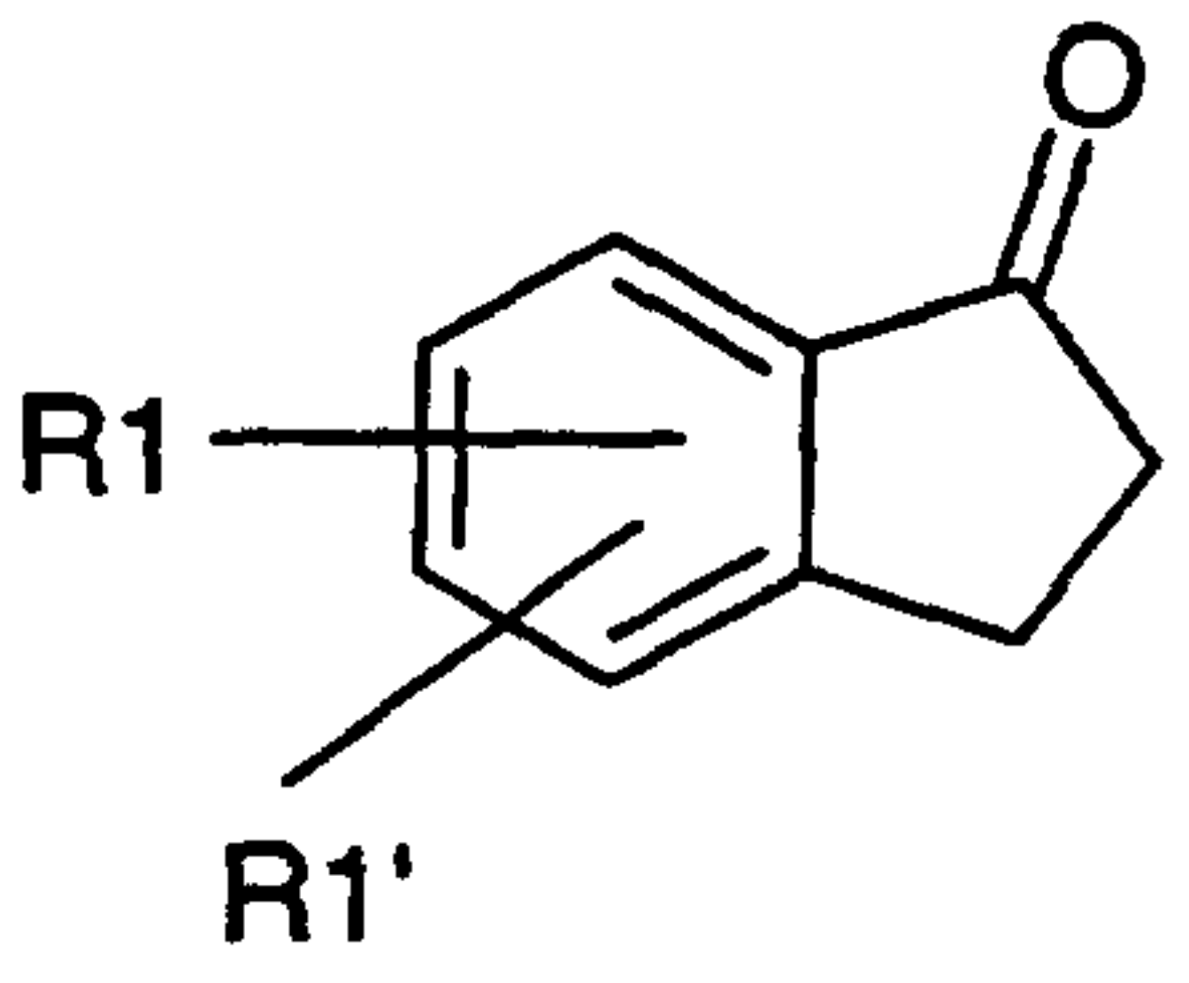
Suitable pharmaceutical compositions for topical application to the skin are preferably present as ointment, cream, lotion, paste, spray, aerosol or oil. Excipients which can be used are petroleum jelly, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The active compound is in general present in a concentration of from 0.1 to 15%, for example of from 0.5 to 2%, by weight of the composition.

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

The invention furthermore relates to a process for preparing the compounds of the formula I, which comprises obtaining the compounds of the formula I in such a way that the procedure is according to the following reaction scheme:



To this end, compounds of the formula II,

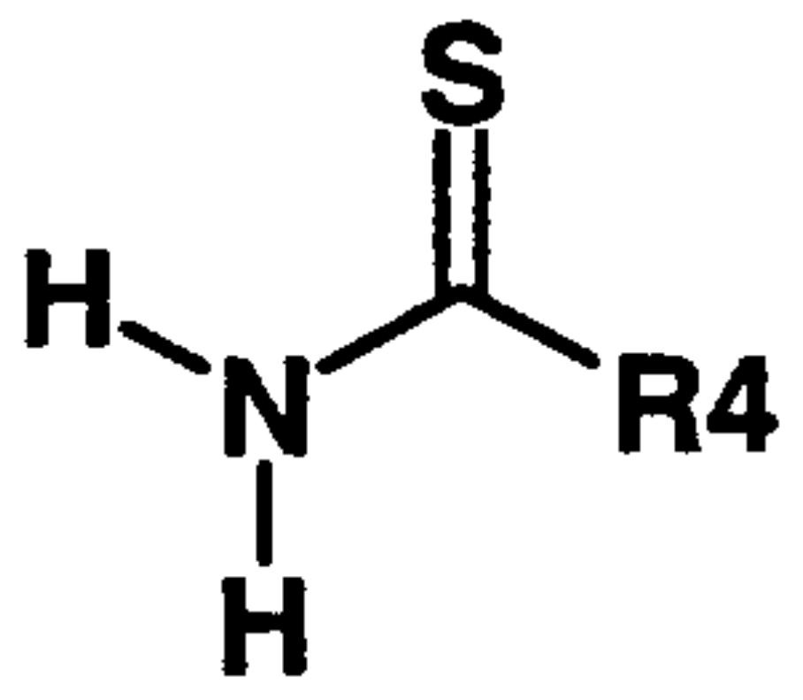


Formula II

in which R1 and R1' are as defined above, are reacted with a compound of the formula Z-$CH_2$-COOR, in which Z is, for example, halogen and R is, for example, methyl to give a compound of the formula III in which R3 is –$CH_2$-COOR.

The compounds of the formula III are reacted further with a halogen, for example bromine, to give compounds of the formula IV in which R1 and R1' are as defined above and R3 is, for example, –$CH_2$-COOR.

Compounds of the formula IV are then reacted with thioamides of the formula VI



VI

in which R4 is as defined above, to give compounds of the formula I. Compounds of the formula I in which R3 is chlorine or bromine can be prepared by reacting compounds of the formula V with a halogenating agent, such as, for example, N-chlorosuccinimide or N-bromosuccinimide.

The compounds of the formula I can also be present as salts with acids. Suitable inorganic acids are, for example:
Hydrohalic acids, such as hydrochloric acid and hydrobromic acid, and also sulfuric acid, phosphoric acid and amidosulfonic acid.

Organic acids which may be mentioned are, for example: formic acid, acetic acid, benzoic acid, p-toluenesulfonic acid, benzenesulfonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, citric acid, L-ascorbic acid, salicylic acid, isethionic acid, methanesulfonic acid, trifluoromethanesulfonic acid, 1,2-benzisothiazol-3(2H)-one, 6-methyl-1,2,3-oxathiazin-4(3H)-one 2,2-dioxide.

The procedure described above is advantageously carried out such that the compounds IV are reacted with the thioamides VI in a molar ratio of from 1:1 to 1:1.5. The reaction is advantageously carried out in an inert solvent, for example in polar organic solvents, such as dimethylformamide, dimethylacetamide, N-methyl-2-pyrrolidone, dioxane, tetrahydrofuran, acetonitrile, nitromethane or diethylene glycol dimethyl ether. Particularly advantageous solvents, however, have proved to be methyl acetate and ethyl acetate, short-chain alcohols, such as methanol, ethanol, propanol, isopropanol, and lower dialkyl ketones, such as, for example, acetone, butan-2-one or hexan-2-one. Mixtures of the reaction media mentioned can also be used; and mixtures of the solvents mentioned with solvents which, taken per se, are less suitable, such as, for example, mixtures of methanol with benzene, ethanol with toluene, methanol with diethyl ether or with tert-butyl methyl ether, ethanol with carbon tetrachloride, acetone with chloroform, dichloromethane or 1,2-dichloroethane, can also be used, where the more polar solvent in each case should expediently be used in an excess. The reactants can be suspended or dissolved in the respective reaction medium. In principle, the reactants can also be reacted in the absence of a solvent, in particular if the respective thioamide has a melting point which is as low as possible. The reaction proceeds in an only slightly exothermic manner and can be carried out between −10°C and 150°C, preferably between 30°C and 100°C. A temperature range between 50°C and 90°C has generally been found to be particularly favorable.

The reaction time is largely dependent on the reaction temperature and is between 2 minutes and 3 days at relatively high and relatively low temperatures, respectively. In the favorable temperature range, the reaction time is generally between 5 minutes and 48 hours.

In the course of the reaction, the compounds I frequently form a poorly soluble deposit in the form of their acid addition salts, expediently a suitable precipitating agent is additionally subsequently added. Those used are, for example, hydrocarbons such as benzene, toluene, cyclohexane or heptane or carbon tetrachloride; in particular, alkyl acetates, such as ethyl acetate or n-butyl acetate, or dialkyl ethers, such as diethyl ether, diisopropyl ether, di-n-butyl ether or tert-butyl methyl ether prove particularly suitable. If the reaction mixture remains in solution after the end of the reaction, the salts of the compounds I can be precipitated using one of the precipitating agents mentioned, if appropriate after concentration of the reaction solution. Furthermore, the solution of the reaction mixture can also be advantageously filtered into the solution of one of the precipitating agents mentioned, with stirring. Since the reaction of the compounds IV with the thioamides VI proceeds almost quantitavely, the crude products obtained are mostly already analytically pure. Work-up of the reaction mixture can also be carried out such that the reaction mixture is rendered alkaline by addition of an organic base, such as, for example, triethylamine or diisobutylamine or ammonia or morpholine or piperidine or 1,8-diazabicyclo[5.4.0]undec-7-ene, and the crude reaction product is purified chromatographically, for example on a silica gel column, after concentration. Suitable eluents for this prove to be, for example, mixtures of ethyl acetate with methanol, mixtures of dichloromethane with methanol, mixtures of toluene with methanol or ethyl acetate or mixtures of ethyl acetate with hydrocarbons such as heptane. If the purification of the crude product is carried out in the manner last described, an acid addition product of the formula I can be obtained from the pure base of the formula I thus obtained by dissolving or suspending the base in an organic protic solvent, such as methanol, ethanol, propanol or isopropanol, or in an organic aprotic solvent, such as ethyl acetate, diethyl ether, diisiopropyl ether, tert-butyl methyl ether, dioxane, tetrahydrofuran, acetone or butan-2-one, and then treating this mixture with an at least equimolar amount of an inorganic acid such as, for example, hydrochloric acid, dissolved in an inert solvent such as, for example, diethyl ether or ethanol, or another of the inorganic or organic acids mentioned further above.

The compounds of the formula I can be recrystallized from an inert suitable solvent such as, for example, acetone, butan-2-one, acetonitrile or nitromethane. However, particularly advantageous is reprecipitation from a solvent such as, for example, dimethylformamide, dimethylacetamide, nitromethane, acetonitrile, preferably methanol or ethanol.

The reaction of the compounds of the formula IV with the thioamides of the formula VI can also be carried out such that an at least equimolar amount of a base, such as, for example, triethylamine, is added to the reaction mixture and the resulting compounds I are then optionally converted into their acid addition products.

By treatment with bases, the acid addition products I can be converted into the compounds of the formula I (free base). Suitable bases are, for example, solutions of inorganic hydroxides, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide or barium hydroxide, carbonates or hydrogen carbonates, such as sodium carbonate or potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate, ammonia and amines, such as triethylamine, diisopropylamine, dicyclohexylamine, piperidine, morpholine, methyldicyclohexylamine.

Thioamides of the formula VI are either commercially available or can be obtained, for example, by reaction of the corresponding carboxamide V with phosphorus pentasulfide in pyridine (R. N. Hurd, G. Delameter, Chem. Rev. 61, 45 (1961)), or with Lawesson's reagent in toluene, pyridine, hexamethylphosphoric triamide [Scheibye, Pedersen and Lawesson: Bull. Soc. Chim. Belges 87, 229 (1978)], preferably in a mixture of tetrahydrofuran with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone or 1,3-dimethyl-2-imidazolidinone. Hydroxyl, amino or additional carbonyl functions are in this case expediently protected using a removable protective function, such as, for example, a benzyl, tert-butyloxycarbonyl or benzyloxycarbonyl radical, or converted into an optionally cyclic acetal. Methods for this are described, for example, in Th. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, Second Edition, 1991, John Wiley & Sons, New York.

Thioamides of the formula VI can also be obtained by reacting nitriles of the formula VII

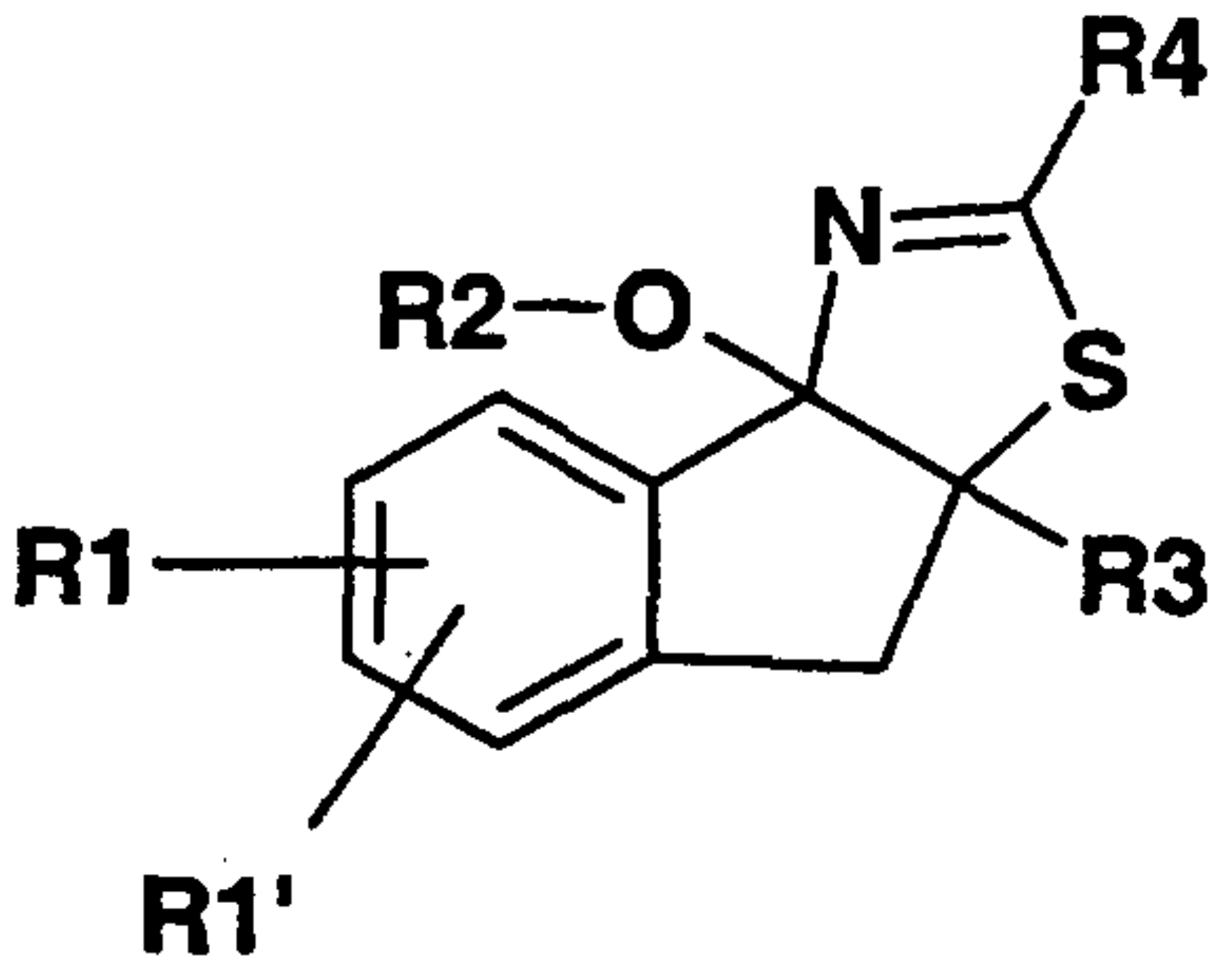
$$N\equiv C-R4$$

Formula VII

with hydrogen sulfide (Houben-Weyl IX, 762) or thioacetamide (E. C. Taylor, J. A. Zoltewicz, J. Am. Chem. Soc. 82, 2656 (1960)) or O,O-diethyl dithiophosphoric acid. The reactions with hydrogen sulfide are preferably carried out in an organic solvent, such as methanol or ethanol, those with thioacetamide in a solvent such as dimethylformamide with addition of hydrochloric acid, and those with O,O-diethyl dithiophosphoric acid in a solvent such as ethyl acetate under acidic, e.g. HCl, conditions at room temperature or with warming.

The examples given below serve to illustrate the invention, but without restricting it. The measured melting or decomposition points (m.p.) were not corrected and are generally dependent on the heating rate.

Table 1: Examples



Formula I

| Example | R1; R1' | R2 | R3 | R4 | Salt | m.p. [°C] |
|---|---|---|---|---|---|---|
| 1 | 6-Cl; H | H | Br | Phenyl | - | 148 |
| 2 | 6-Cl; H | H | Cl | Phenyl | - | 88 |

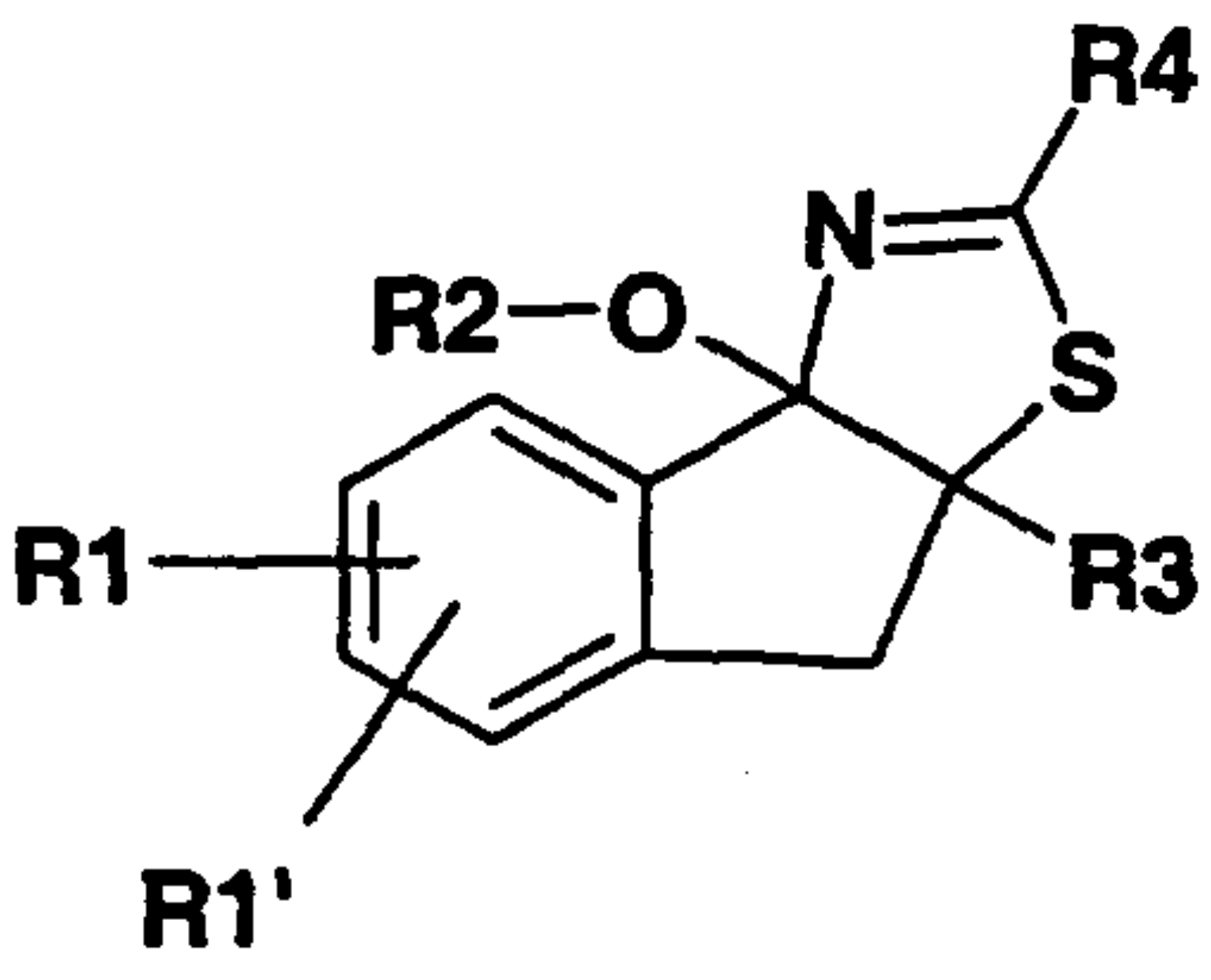
The compounds of the formula I are distinguished by favorable effects on lipid metabolism; in particular, they are suitable as anorectics. The compounds can be employed on their own or in combination with other anorectically active compounds. Such further anorectically active compounds are mentioned, for example, in the Rote Liste, chapter 01 under slimming preparations/anorectics. The compounds are suitable for the prophylaxis and in particular for the treatment of obesity. The compounds are furthermore suitable for the prophylaxis and in particular for the treatment of type II diabetes.

The efficacy of the compounds was tested as follows:

Biological test model:

The anorectic action was tested on female NMRI mice. After withdrawal of feed for 24 hours, the test preparation was administered via a stomach tube. Kept individually and with free access to drinking water, the animals were offered evaporated milk 30 minutes after the administration of the preparation. The consumption of evaporated milk was determined half-hourly for 7 hours and the general condition of the animals was observed. The measured milk consumption was compared with that of untreated control animals.

Table 2: Anorectic action, measured as reduction of the cumulated milk consumption of treated animals compared to untreated animals.

| Compound/Example  Formula I | Oral dose [mg/kg] | Number of animals / cumulated milk consumption of the treated animals N / [ml] | Number of animals / cumulated milk consumption of the untreated control animals N / [ml] | Reduction of the cumulated milk consumption in % of the control |
|---|---|---|---|---|
| | | | | |
| Example 1 | 50 | 5 / 0.64 | 5 / 3.50 | 82 |

It can be inferred from the table that the compounds of the formula I exhibit very good anorectic action.

The preparation of some examples is described in detail below; the other compounds of the formula I were obtained in a similar manner:

Example 1 (Compound 1):

8a-Bromo-6-chloro-2-phenyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

a) 2-Bromo-5-chloroindan-1-one:

At room temperature, 10 g (0.06 mol) of 5-chloroindan-1-one are dissolved with stirring in 120 ml of glacial acetic acid. 0.05 ml of a 48% strength solution of HBr in water and then 3.074 ml (0.06 mol) of bromine, dissolved in 25 ml of glacial acetic acid, are added dropwise. After 2 h of stirring at room temperature, the reaction has ended (TLC). The solution of the crude product is slowly added dropwise with stirring to 300 ml of ice-water. The precipitated crude product is filtered off with suction and washed thoroughly with water. The moist residue is removed from the filter using ethyl acetate, and the phases of the filtrate are separated. The organic phase is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is dissolved in 120 ml of hot n-heptane; the hot solution is filtered through a pleated filter and the solution is then left to crystallize at 0°C. The crystallized product is filtered off with suction and dried under reduced pressure.

M.p.: 94-96°C

b) 6-Chloro-2-phenyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

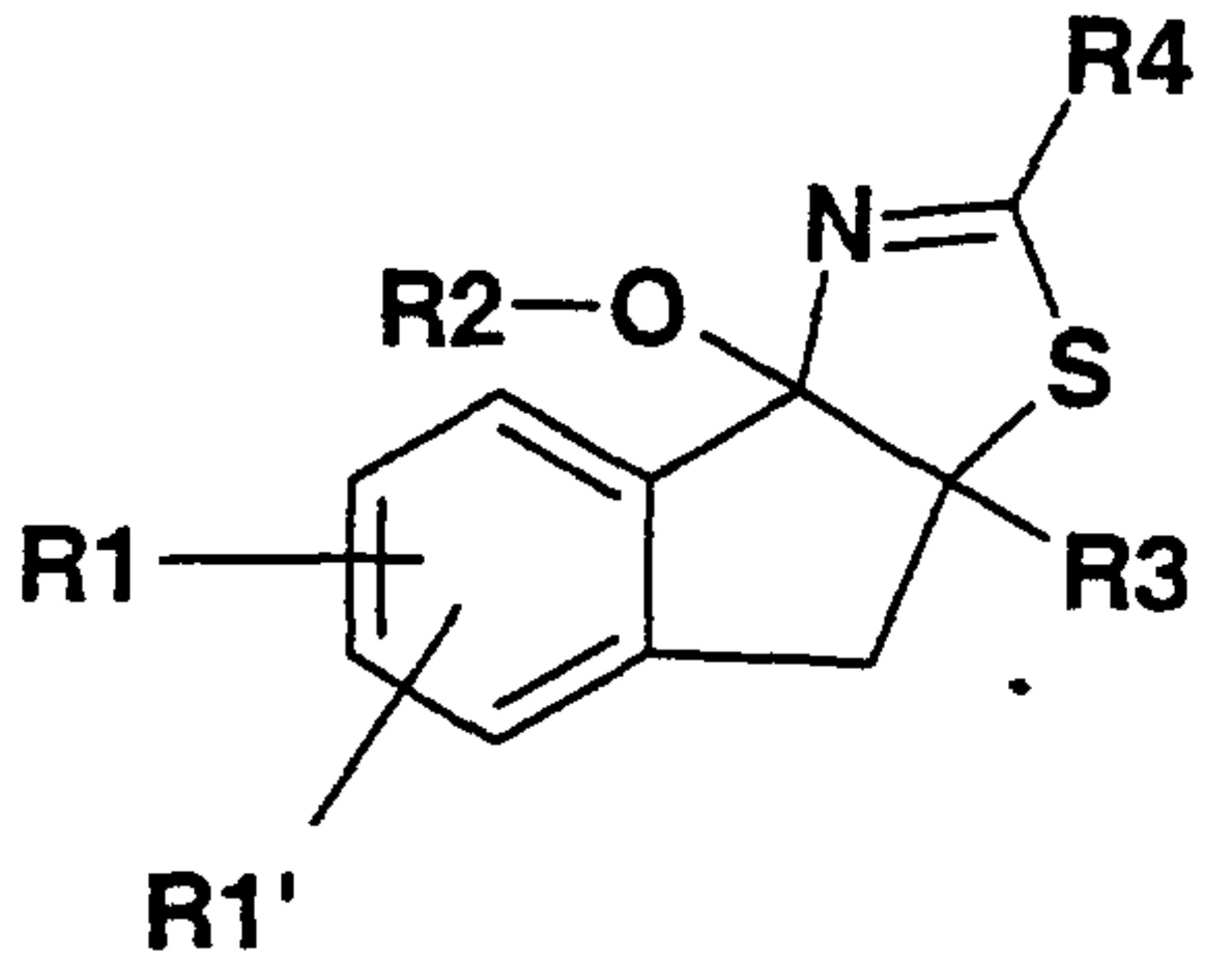
At room temperature, 1.0 g of 2-bromo-5-chloroindan-1-one is dissolved in 20 ml of dry acetone and admixed with 620 mg of thiobenzamide. The mixture is stirred at room temperature for 6 h, the crystallized hydrobromide of the product is filtered off with suction and the residue is washed with acetone and dried under reduced pressure. The free base is obtained by introducing the salt into a mixture of 30 ml of ethyl acetate and 20 ml of saturated sodium bicarbonate solution and stirring for 20 min. The organic phase is separated off, washed with saturated sodium chloride solution and dried over magnesium sulfate. The mixture is filtered and the filtrate is concentrated under reduced pressure. This gives 6-chloro-2-phenyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol of melting point 164-165°C.

c) 8a-Bromo-6-chloro-2-phenyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

1.51 g of the compound of Example 1b and 0.89 g of N-bromosuccinimide are dissolved in 20 ml of carbon tetrachloride and admixed with 50 mg of benzoyl peroxide, and the mixture is stirred under reflux for 3 h. The cooled reaction solution is extracted twice with 20 ml of water and the organic phase is dried over magnesium sulfate, filtered and concentrated under reduced pressure. Chromatographic purification on silica gel using the mobile phase dichloromethane gives 8a-bromo-6-chloro-2-phenyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol of melting point 148°C.

Patent claims:

1. A compound of the formula I,



I

in which

R1, R1' independently of one another are H, F, Cl, Br, I, $CF_3$, $NO_2$, CN, 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 in the alkyl radicals one or more, or all hydrogens may be replaced by fluorine, or one hydrogen may be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph, $NH_2$, NH-CO-$CH_3$ or N($COOCH_2Ph$)$_2$;

are $SO_2$-$NH_2$, $SO_2NH$($C_1$-$C_6$)-alkyl, $SO_2N$[($C_1$-$C_6$)-alkyl]$_2$, S-($C_1$-$C_6$)-alkyl, S-($CH_2$)$_n$-phenyl, SO-($C_1$-$C_6$)-alkyl, SO-($CH_2$)$_n$-phenyl, $SO_2$-($C_1$-$C_6$)-alkyl, $SO_2$-($CH_2$)$_n$-phenyl, where n can be 0–6 and the phenyl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, $NO_2$, CN, $OCF_3$, O-($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)-alkyl, $NH_2$;

are $NH_2$, NH-($C_1$-$C_6$)-alkyl, N[($C_1$-$C_6$)-alkyl]$_2$, NH($C_1$-$C_7$)-acyl, phenyl, biphenylyl, O-($CH_2$)$_n$-phenyl, where n can be 0–6, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-furanyl or 2- or 3-thienyl, where the phenyl, biphenylyl, naphthyl, pyridyl, furanyl or thienyl rings can in each case 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, $CONH_2$;

are 1,2,3-triazol-5-yl, where the triazole ring can be substituted in the 1-, 2- or 3-position by methyl or benzyl;

are tetrazol-5-yl, where the tetrazole ring can be substituted in the 1- or 2-position by methyl or benzyl;

R2 is H, $(C_1-C_6)$-alkyl, $(C_3-C_6)$-cycloalkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, C(O)-$(C_1-C_6)$-alkyl, C(O)-$(C_3-C_6)$-cycloalkyl, C(O)-$(CH_2)_n$-phenyl, C(O)-$(CH_2)_n$-thienyl, C(O)-$(CH_2)_n$-pyridyl, C(O)-$(CH_2)_n$-furyl, where n can be 0-5 and in which phenyl, thienyl, pyridyl and furyl can in each case be substituted up to two times by Cl, F, CN, $CF_3$, $(C_1-C_3)$-alkyl, OH, O-$(C_1-C_6)$-alkyl;

R3 is Cl, Br, $CH_2$-COO$(C_1-C_6)$-alkyl, $CH_2$-COOH, $CH_2$-$CONH_2$;

R4 is $(C_1-C_8)$-alkyl, $(C_3-C_7)$-cycloalkyl, $(C_2-C_6)$-alkenyl, $(C_2-C_6)$-alkynyl, $(C_4-C_7)$-cycloalkenyl, where in the alkyl radicals one or more, or all hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph or O-$(C_1-C_4)$-alkyl;
is $(CH_2)_n$-pyrrolidin-1-yl, $(CH_2)_n$-piperidin-1-yl, $(CH_2)_n$-morpholin-4-yl, $(CH_2)_n$-piperazin-1-yl, $(CH_2)_n$-N-4-methylpiperazin-1-yl, $(CH_2)_n$-N-4-benzylpiperazin-1-yl, $(CH_2)_n$-phthalimidoyl, where n can be 1-6;
is $(CH_2)_n$-aryl, where n can be 0–6 and aryl is phenyl, biphenylyl, 1- or 2-naphthyl, 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- or 5-isoxazolyl, 2- or 3-pyrrolyl, 2- or 3-pyridazinyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, 2-(1,3,5-triazinyl), 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-methylimidazol-2-, -4- or -5-yl, and the aryl radical or heteroaryl radical can be substituted up to two times 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, $(CH_2)_n$-$SO_2$-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, $(CH_2)_n$-$SO_2$-N(=CH-N$(CH_3)_2$), where n can be 0-6; $(C_1-C_6)$-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, NH-$SO_2$-$(C_1-C_6)$-alkyl, NH-$SO_2$-phenyl,

where the phenyl ring can be substituted up to two times by F, Cl, CN, OH, $(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl, $CF_3$, COOH, COO$(C_1\text{-}C_6)$-alkyl or $CONH_2$;

is pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, $(CH_2)_n$-phenyl, O-$(CH_2)_n$-phenyl, S-$(CH_2)_n$-phenyl, $SO_2$-$(CH_2)_n$-phenyl, where n can be 0-3;

is $(CH_2)_n$-A-R8, where n can be 1-6;

A is O, NH, N-$(C_1\text{-}C_6)$-alkyl, NCHO, N(CO-$CH_3$), S, SO, $SO_2$;

R8 is $(C_1\text{-}C_8)$-alkyl, $(C_3\text{-}C_8)$-cycloalkyl, where in the alkyl radicals one or more hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph or O-$(C_1\text{-}C_4)$-alkyl;

is $(CH_2)_m$-aryl, where m can be 0-6 and aryl can be phenyl, thienyl or pyridyl and the aryl moiety can be substituted up to two times by F, Cl, Br, OH, $CF_3$, $NO_2$, CN, $OCF_3$, O-$(C_1\text{-}C_6)$-alkyl, S-$(C_1\text{-}C_6)$-alkyl, SO-$(C_1\text{-}C_6)$-alkyl, $(CH_2)_n$ -$SO_2$-$(C_1\text{-}C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, $(CH_2)_n$-$SO_2$-N(=CH-N$(CH_3)_2$), $(CH_2)_n$-$SO_2$-NH$(C_1\text{-}C_8)$-alkyl, $(CH_2)_n$-$SO_2$-N[$(C_1\text{-}C_8)$-alkyl]$_2$, $(CH_2)_n$-$SO_2$-NH$(C_3\text{-}C_8)$-cycloalkyl, $(CH_2)_n$-$SO_2$-N[$(C_3\text{-}C_8)$-cycloalkyl]$_2$, where n can be 0-6; $(C_1\text{-}C_6)$-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[$(C_1\text{-}C_6)$-alkyl]$_2$, CONH$(C_3\text{-}C_6)$-cycloalkyl, $NH_2$, NH$(C_1\text{-}C_6)$-alkyl, N[$(C_1\text{-}C_6)$-alkyl]$_2$, NH-CO-$(C_1\text{-}C_6)$-alkyl, NH-CO-phenyl, NH-$SO_2$-phenyl, where the phenyl ring can be substituted up to two times by F, Cl, CN, OH, $(C_1\text{-}C_6)$-alkyl, O-$(C_1\text{-}C_6)$-alkyl, $CF_3$, COOH, COO$(C_1\text{-}C_6)$-alkyl or $CONH_2$;

NH-$SO_2$-$(C_1\text{-}C_8)$-alkyl, N$(C_1\text{-}C_6)$-alkyl-$SO_2$-$(C_1\text{-}C_8)$-alkyl, pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, $(CH_2)_p$-phenyl, O-$(CH_2)_p$-phenyl, S-$(CH_2)_p$-phenyl or $SO_2$-$(CH_2)_p$-phenyl, where p can be 0-3;

and its physiologically acceptable salts and physiologically functional derivatives.

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

R1, R1' independently of one another are H, F, Cl, Br, I, $CF_3$, $NO_2$, CN, 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 in the alkyl radicals one or more, or all hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph, $NH_2$, NH-CO-$CH_3$ or N($COOCH_2Ph$)$_2$;

are $SO_2$-$NH_2$, $SO_2NH$($C_1$-$C_6$)-alkyl, $SO_2N$[($C_1$-$C_6$)-alkyl]$_2$, S-($C_1$-$C_6$)-alkyl, S-($CH_2$)$_n$-phenyl, SO-($C_1$-$C_6$)-alkyl, SO-($CH_2$)$_n$-phenyl, $SO_2$-($C_1$-$C_6$)-alkyl, $SO_2$-($CH_2$)$_n$-phenyl, where n can be 0–6, and the phenyl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, $NO_2$, CN, $OCF_3$, O-($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)-alkyl, $NH_2$;

are $NH_2$, NH-($C_1$-$C_6$)-alkyl, N[($C_1$-$C_6$)-alkyl]$_2$, NH($C_1$-$C_7$)-acyl, phenyl, biphenylyl, O-($CH_2$)$_n$-phenyl, where n can be 0–6, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-furanyl or 2- or 3-thienyl, where the phenyl, biphenylyl, naphthyl, pyridyl, furanyl or thienyl rings can in each case 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, $CONH_2$;

1,2,3-triazol-5-yl, where the triazole ring can be substituted in the 1-, 2- or 3-position by methyl or benzyl;

tetrazol-5-yl, where the tetrazole ring can be substituted in the 1- or 2-position by methyl or benzyl;

R2 is H, ($C_1$-$C_6$)-alkyl, ($C_3$-$C_6$)-cycloalkyl, ($CH_2$)$_n$-phenyl, ($CH_2$)$_n$-thienyl, ($CH_2$)$_n$-pyridyl, ($CH_2$)$_n$-furyl, C(O)-($C_1$-$C_6$)-alkyl, C(O)-($C_3$-$C_6$)-cycloalkyl, C(O)-($CH_2$)$_n$-phenyl, C(O)-($CH_2$)$_n$-thienyl, C(O)-($CH_2$)$_n$-pyridyl, C(O)-($CH_2$)$_n$-furyl, where n can be 0-5 and in which phenyl, thienyl, pyridyl and furyl can in each case be substituted up to two times by Cl, F, CN, $CF_3$, $(C_1-C_3)$-alkyl, OH, O-$(C_1-C_6)$-alkyl;

R3 is Cl, Br, $CH_2$-COO$(C_1-C_6)$-alkyl, $CH_2$-COOH, $CH_2$-$CONH_2$;

R4 is $(C_1-C_8)$-alkyl, $(C_3-C_7)$-cycloalkyl, $(C_2-C_6)$-alkenyl, $(C_2-C_6)$-alkynyl, $(C_4-C_7)$-cycloalkenyl, where in the alkyl radicals one or more, or all hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph or O-$(C_1-C_4)$-alkyl;
is $(CH_2)_n$-pyrrolidin-1-yl, $(CH_2)_n$-piperidin-1-yl, $(CH_2)_n$-morpholin-4-yl, $(CH_2)_n$-piperazin-1-yl, $(CH_2)_n$-N-4-methylpiperazin-1-yl, $(CH_2)_n$-N-4-benzylpiperazin-1-yl, $(CH_2)_n$-phthalimidoyl, where n can be 1-6;
is $(CH_2)_n$-aryl, where n can be 0–6 and aryl can be phenyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl and the aryl radical or heteroaryl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, $(CH_2)_n$-$SO_2$-N(=CH-N$(CH_3)_2$), where n can be 0-6; NH-$SO_2$-$(C_1-C_6)$-alkyl, NH-$SO_2$-phenyl, where the phenyl ring can be substituted up to two times by F, Cl, CN, OH, $(C_1-C_6)$-alkyl, O-$(C_1-C_6)$-alkyl, $CF_3$, COOH, COO$(C_1-C_6)$-alkyl or $CONH_2$;
$(C_1-C_6)$-alkyl, COOH, COO$(C_1-C_6)$-alkyl or $CONH_2$;
is $(CH_2)_n$-A-R8, where n can be 1-6;

A is O, NH, $(C_1-C_6)$-alkyl, $SO_2$;

R8 is $(C_1-C_8)$-alkyl, $(C_3-C_8)$-cycloalkyl, where in the alkyl radicals one or more hydrogens can be replaced by fluorine, or one hydrogen can be replaced by OH, OC(O)$CH_3$, OC(O)H, O-$CH_2$-Ph or O-$(C_1-C_4)$-alkyl;
is $(CH_2)_m$-aryl, where m can be 0-6 and aryl can be phenyl, thienyl or pyridyl, and the aryl moiety can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$(C_1-C_6)$-alkyl, $(CH_2)_n$-$SO_2$-$NH_2$, $(CH_2)_n$-$SO_2$-N(=CH-N$(CH_3)_2$), where n can be 0-6;

NH-$SO_2$-($C_1$-$C_6$)-alkyl, NH-$SO_2$-phenyl, where the phenyl ring can be substituted up to two times by F, Cl, CN, OH, ($C_1$-$C_6$)-alkyl, O-($C_1$-$C_6$)-alkyl, $CF_3$, COOH, COO($C_1$-$C_6$)-alkyl, $CONH_2$, where n can be 0-6; COOH, COO($C_1$-$C_6$)-alkyl, or $CONH_2$;

and its physiologically acceptable salts and physiologically functional derivatives.

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

R1, R1' independently of one another are H, F, Cl, Br, -OH, O-($C_1$-$C_6$)-alkyl, ($C_1$-$C_6$)-alkyl, where in the alkyl radicals one hydrogen can be replaced by OH;

R2 is H, ($C_1$-$C_6$)-alkyl, C(O)-($C_1$-$C_6$)-alkyl;

R3 is Cl, Br, $CH_2$-COO($C_1$-$C_6$)-alkyl, $CH_2$-COOH, $CH_2$-$CONH_2$;

R4 is ($C_1$-$C_4$)-alkyl or ($C_3$-$C_6$)-cycloalkyl, where in the alkyl radicals one hydrogen can be replaced by OH;
($CH_2$)$_n$-aryl, where n can be 0–6 and aryl can be phenyl, 1- or 2-naphthyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, and the aryl radical or heteroaryl radical can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-($C_1$-$C_6$)-alkyl, $SO_2$-($C_1$-$C_6$)-alkyl, ($CH_2$)$_n$-$SO_2$-$NH_2$, where n can be 0-6; ($C_1$-$C_6$)-alkyl, COOH, COO($C_1$-$C_6$)-alkyl or $CONH_2$;

($CH_2$)$_n$-A-R8, where n can be 1-6;

A is O, $SO_2$;

R8 is ($C_1$-$C_8$)-alkyl, ($C_3$-$C_8$)-cycloalkyl, where in the alkyl radicals one hydrogen can be replaced by OH;

$(CH_2)_m$-aryl, where m can be 0-6 and aryl can be phenyl or thienyl and the aryl moiety can be substituted up to two times by F, Cl, Br, OH, $CF_3$, O-($C_1$-$C_6$)-alkyl, $SO_2$-($C_1$-$C_6$)-alkyl, $SO_2$-$NH_2$, COOH, COO($C_1$-$C_6$)-alkyl or $CONH_2$;

and its physiologically acceptable salts.

4. A medicament, comprising one or more compounds as claimed in one or more of claims 1 to 3.

5. A medicament, comprising one or more compounds as claimed in one or more of claims 1 to 3 and one or more anorectics.

6. A compound as claimed in one or more of claims 1 to 3 for use as a medicament for the prophylaxis or treatment of obesity.

7. A compound as claimed in one or more of claims 1 to 3 for use as a medicament for the prophylaxis or treatment of type II diabetes.

8. A compound as claimed in one or more of claims 1 to 3 in combination with at least one further anorectic for use as a medicament for the prophylaxis or treatment of obesity.

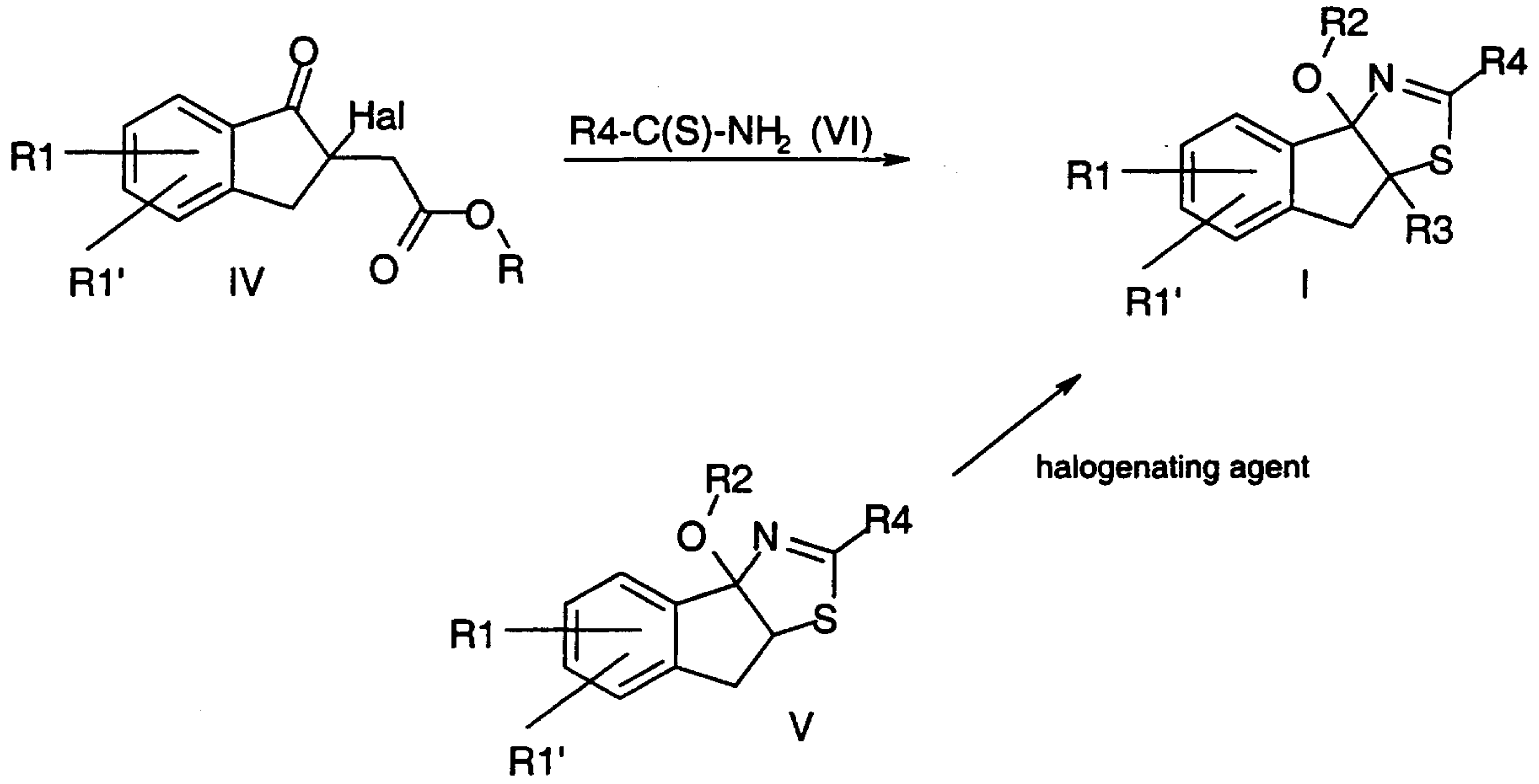
9. A compound as claimed in one or more of claims 1 to 3 in combination with at least one further anorectic for use as a medicament for the prophylaxis or treatment of type II diabetes.

10. A process for preparing a medicament comprising one or more of the compounds as claimed in one or more of claims 1 to 3, which comprises mixing the active compound with a pharmaceutically suitable excipient and bringing this mixture into a form suitable for administration.

11. The use of the compounds as claimed in one or more of claims 1 to 3 for preparing a medicament for the prophylaxis or treatment of obesity.

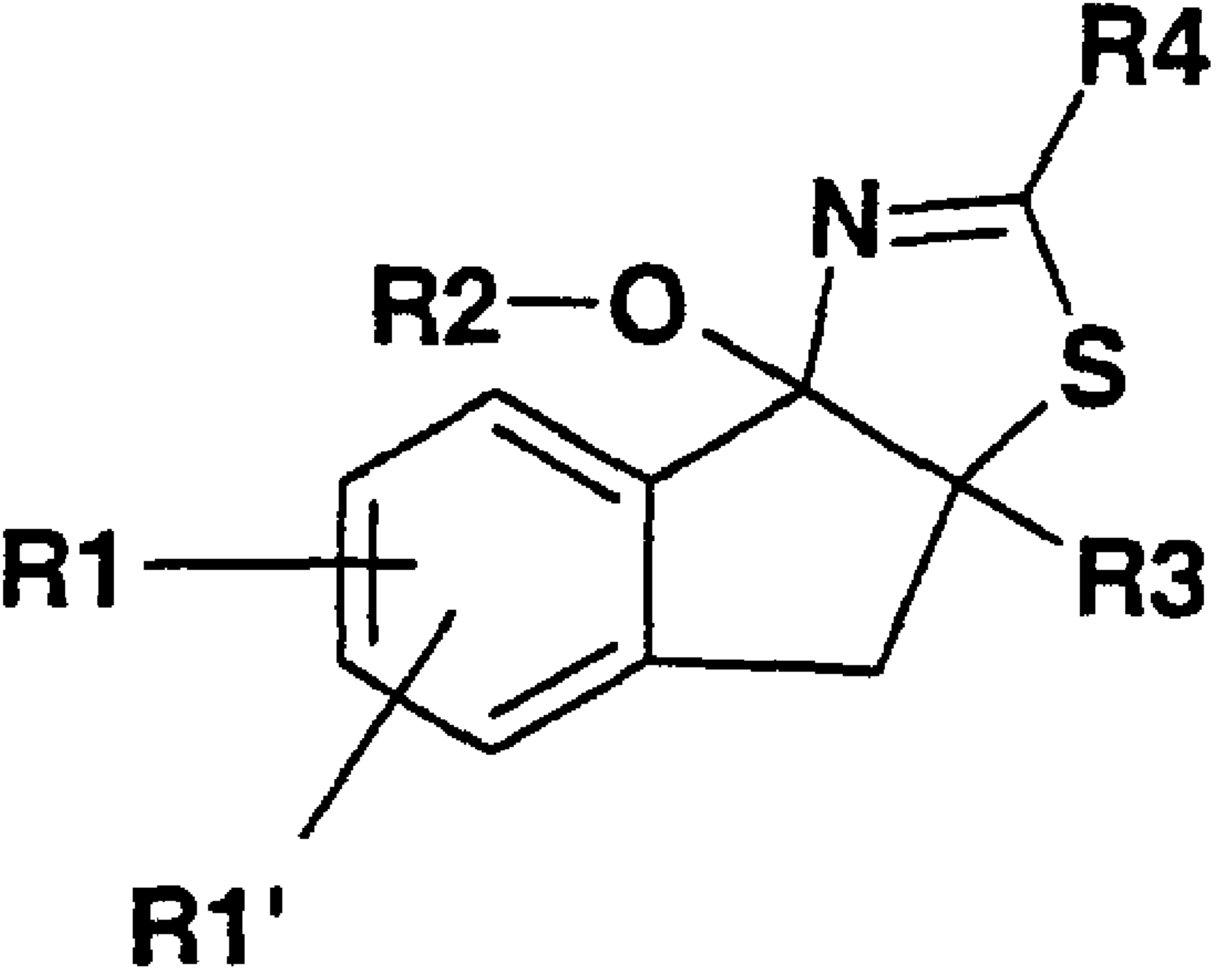
12. The use of the compounds as claimed in one or more of claims 1 to 3 for preparing a medicament for the prophylaxis or treatment of type II diabetes.

13. A process for preparing compounds as claimed in one or more of claims 1 to 3, which comprises reacting, according to the equation below,



either a compound of the formula IV in which R1 and R1' are as defined for formula I and Hal is a halogen atom and R is an alkyl radical, with a compound VI in which R4 is as defined for formula I, or a compound V in which R1, R1', R2 and

R4 are as defined for formula I, with a halogenating agent, such as, for example, N-chlorosuccinimide or N-bromosuccinimide, to give compounds of the formula I.



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