Description

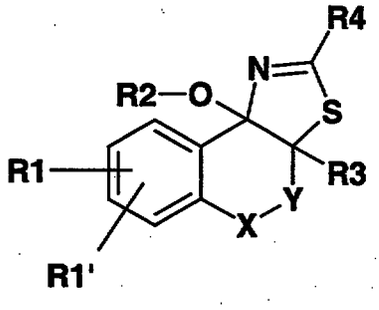
INDENO-, NAPHTHO- AND BENZOCYCLOHEPTADIHYDROTHIAZOLE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS ANORECTIC PHARMACEUTICALS

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

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

The invention is based on the object of making available further compounds which display a therapeutically utilizable anorectic action.

The invention therefore relates to compounds of the formula I



I

in which

Y is a direct bond, $-CH_2-$, $-CH_2-CH_2-$;

X is CH_2, $CH(CH_3)$, $CH(C_2H_5)$, $CH(C_3H_7)$, $CH(C_6H_5)$;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine, or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H, OCH_2Ph, NH_2,NH-CO-CH_3

or

$N(COOCH_2Ph)_2$;
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; NH_2, NH-$(C_1$-$C_6)$-alkyl, N$((C_1$-$C_6)$-alkyl$)_2$, NH$(C_1$-$C_7)$-acyl, phenyl, biphenyl, 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, biphenyl, naphthyl, pyridyl, furanyl or thienyl rings can each 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, furyl can each 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 H, $(C_1$-$C_6)$-alkyl, F, CN, N_3, O-$(C_1$-$C_6)$-alkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, where n can be 0 - 5 and in which phenyl, thienyl, pyridyl, furyl can each be substituted up to two times by Cl, F, CN, CF_3, $(C_1$-$C_3)$-alkyl, OH, O-$(C_1$-$C_6)$-alkyl; $(C_2$-$C_6)$-alkynyl, $(C_2$-$C_6)$-alkenyl, $C(O)OCH_3$, $C(O)OCH_2CH_3$, C(O)OH, $C(O)NH_2$, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $OC(O)CH_3$;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine or a hydrogen to be replaced by OH, $OC(O)CH_3$, $OC(O)H$,$O-CH_2-Ph$ or $O-(C_1-C_4)$-alkyl;

$(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, $CO-(C_1-C_6)$-alkyl, CHO or CO-phenyl, or -NR6R7 is a ring such as pyrrolidine, piperidine, morpholine, piperazine, N-4-methylpiperazin-1-yl, N-4-benzylpiperazin-1-yl, phthalimidoyl;

$(CH_2)_n$-aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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-methyl-imidazol-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, $SO_2-(C_1-C_6)$-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-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 = 0-3;

and their physiologically tolerable salts and physiologically functional derivatives.

Preferred compounds of the formula I are those in which one or more radicals has or have the following meaning:

Y is a direct bond;

X is CH_2;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine, or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H, $O-CH_2-Ph$, NH_2, $NH-CO-CH_3$ or $N(COOCH_2Ph)_2$;
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; NH_2, $NH-(C_1-C_6)$-alkyl, $N((C_1-C_6)-alkyl)_2$, $NH(C_1-C_7)$-acyl, phenyl, biphenyl, $O-(CH_2)_n$-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, biphenyl, naphthyl, pyridyl, furanyl or thienyl rings can each 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, furyl can each 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 H, (C_1-C_6)-alkyl, F, CN, N_3, O-(C_1-C_6)-alkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, where n can be 0-5 and in which phenyl, thienyl, pyridyl, furyl can each be substituted up to two times by Cl, F, CN, CF_3, (C_1-C_3)-alkyl, OH, O-(C_1-C_6)-alkyl; (C_2-C_6)-alkynyl, (C_2-C_6)-alkenyl, $C(O)OCH_3$, $C(O)OCH_2CH_3$, C(O)OH, $C(O)NH_2$, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $OC(O)CH_3$;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H,O-CH_2-Ph or O-(C_1-C_4)-alkyl;

$(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, CHO or CO-phenyl or -NR6R7 is a ring such as pyrrolidine, piperidine, morpholine, piperazine, N-4-methylpiperazin-1-yl, N-4-benzylpiperazin-1-yl, phthalimidoyl;

$(CH_2)_n$-aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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-methyl-imidazol-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, 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-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 = 0-3;

and their physiologically tolerable salts and physiologically functional derivatives.

Particularly preferred compounds of the formula I are those in which one or more radicals has or have the following meaning:

Y is a direct bond;

X is CH_2;

R1, R1' independently of one another are H, F, Cl, Br, I, CF3, NO_2, CN, COOH, $COO(C_1\text{-}C_6)$alkyl, $CONH_2$, $CONH(C_1\text{-}C_6)$alkyl, $CON[(C_1\text{-}C_6)alkyl]_2$, $(C_1\text{-}C_6)$-alkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $O\text{-}(C_1\text{-}C_6)$-alkyl, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine, or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H, $O\text{-}CH_2\text{-}Ph$, NH_2, NH-CO-CH_3 or $N(COOCH_2Ph)_2$;
$SO_2\text{-}NH_2$, $SO_2NH(C_1\text{-}C_6)$-alkyl, $SO_2N[(C_1\text{-}C_6)\text{-alkyl}]_2$, $S\text{-}(C_1\text{-}C_6)$-alkyl, $S\text{-}(CH_2)_n$-phenyl, $SO\text{-}(C_1\text{-}C_6)$-alkyl, $SO\text{-}(CH_2)_n$-phenyl, $SO_2\text{-}(C_1\text{-}C_6)$-alkyl, $SO_2\text{-}(CH_2)_n$-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, $O\text{-}(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, NH_2;

NH_2, $NH\text{-}(C_1\text{-}C_6)$-alkyl, $N((C_1\text{-}C_6)\text{-alkyl})_2$, $NH(C_1\text{-}C_7)$-acyl, phenyl, biphenyl, $O\text{-}(CH_2)_n$-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, biphenyl, naphthyl, pyridyl, furanyl or thienyl rings can each be substituted one to 3 times by F, Cl, Br, I, OH, CF_3, NO_2, CN, OCF_3, $O\text{-}(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl, NH_2, $NH(C_1\text{-}C_6)$-alkyl, $N((C_1\text{-}C_6)\text{-alkyl})_2$, $SO_2\text{-}CH_3$, COOH, $COO\text{-}(C_1\text{-}C_6)$-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, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, C(O)-$(C_1\text{-}C_6)$-alkyl, C(O)-$(C_3\text{-}C_6)$-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, furyl can each be substituted up to two times by Cl, F, CN, CF_3, $(C_1\text{-}C_3)$-alkyl, OH, O-$(C_1\text{-}C_6)$-alkyl;

R3 is H, F;

R4 is $(C_1\text{-}C_8)$-alkyl, $(C_3\text{-}C_7)$-cycloalkyl, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $(C_4\text{-}C_7)$-cycloalkenyl, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H,O-CH_2-Ph or O-$(C_1\text{-}C_4)$-alkyl;
$(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, CO-$(C_1\text{-}C_6)$-alkyl, CHO or CO-phenyl, or -NR6R7 is a ring such as pyrrolidine, piperidine, morpholine, piperazine, N4-methylpiperazin-1-yl, N4-benzylpiperazin-1-yl, phthalimidoyl;
$(CH_2)_n$-aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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-methyl-imidazol-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-$(C_1\text{-}C_6)$-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[$(C_1\text{-}C_6)$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-methylpiperazin-

1-yl, $(CH2)_n$-phenyl, O-$(CH_2)_n$ -phenyl, S-$(CH_2)_n$ -phenyl, SO_2-$(CH_2)_n$-phenyl, where n = 0-3;
and their physiologically tolerable salts.

Very particularly preferred compounds of the formula I are those in which one or more radicals has or have the following meaning:

Y is a direct bond;

X is CH_2;

R1, R1' independently of one another are H, F, Cl, Br, NO_2, CN, COOH, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, O-$(C_1$-$C_6)$-alkyl, OCF_3, OCH_2CF_3, phenyl, O-$(CH_2)_n$-phenyl, where n can be 0-6, 1- or 2-naphthyl, 2- or 3-thienyl, where the phenyl, naphthyl or thienyl rings can each 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;

R2 is H, $(C_1$-$C_6)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, $(CH_2)_n$-phenyl, where n can be 0-5;

R3 is H, F;

R4 is $(C_1$-$C_8)$-alkyl, $(C_3$-$C_7)$-cycloalkyl, $(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, $(C_1$-$C_6)$-alkyl, or –NR6R7 is a ring such as pyrrolidine, piperidine, morpholine, piperazine, N4-methylpiperazin-1-yl, N4-benzylpiperazin-1-yl, phthalimidoyl;
$(CH_2)_n$-Aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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-methyl-imidazol-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, pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methylpiperazin-1-yl;
and their physiologically tolerable salts.

Furthermore, very particularly preferred compounds of the formula I are those in which one or more radicals has or have the following meaning:

Y is a direct bond;
X is CH_2;
R1 is Cl;
R1' is H;
R2 is H;
R3 is H;
R4 is phenyl;
and their physiologically tolerable 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 and R4 can be either straight-chain or branched.

On account of their higher water solubility, pharmaceutically tolerable salts are particularly suitable for medicinal applications compared with the starting or base compounds. These salts must have a pharmaceutically tolerable anion or cation. Suitable pharmaceutically tolerable acid addition salts of the compounds according to the invention are salts of inorganic acids, such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic and sulfuric acid 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 acid. For medicinal purposes, the chlorine salt is particularly preferably used. Suitable pharmaceutically tolerable 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 nonpharmaceutically tolerable anion are likewise included in the scope of the invention as useful intermediates for the production or purification of pharmaceutically tolerable salts and/or for use in nontherapeutic, for example in-vitro, applications.

The expression "physiologically functional derivative" used here relates to any physiologically tolerable derivative of a compound of the formula I according to the invention, e.g. 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, e.g. 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.

Below, all references to "compound(s) (according to formula (I)" refer to compound(s) of the formula (I) as described above, and 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, e.g. 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 body weight, e.g. 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 1.0 to 1000 mg typically from 1 mg to 100 mg, and orally administrable individual dose formulations, such as, for example, tablets or capsules, can contain, for example, from 10 to 600 mg. In the case of pharmaceutically tolerable 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 as the compound itself, but they are preferably present in the form of a pharmaceutical composition with a tolerable vehicle. The vehicle 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 vehicle 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 tolerable 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 powder or granules; as a 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 vehicle (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 vehicle, after which the product, if necessary, is shaped. 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 tabletting the compound in free-flowing form, such as, for example, a powder or granules, if appropriate mixed with a binder, lubricant, inert diluent and/or one (a number of) surface-active/dispersing agents 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.

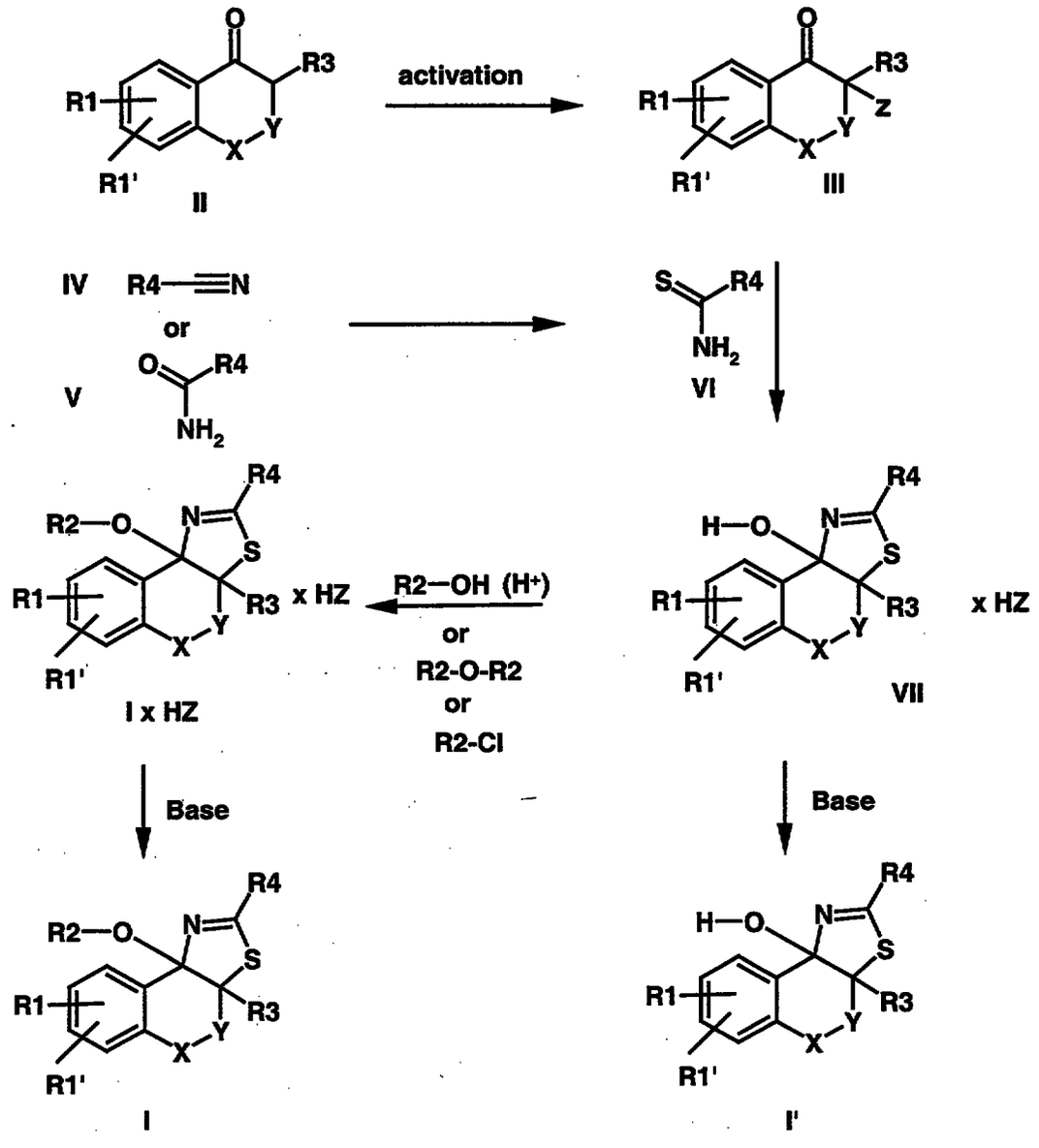
Suitable pharmaceutical compositions for rectal administration are preferably present as individual dose suppositories. These can be prepared

by mixing a compound according to formula (I) with one or more conventional solid vehicles, for example cocoa butter, and shaping the resulting mixture.

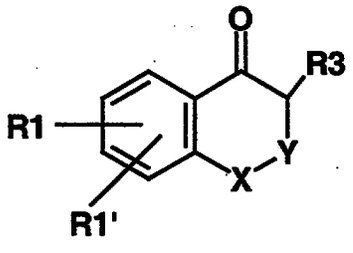
Suitable pharmaceutical compositions for topical application to the skin are preferably present as an ointment, cream, lotion, paste, spray, aerosol or oil. Vehicles which can be used are petroleum jelly, lanolin, polyethylene glycols, alcohols and combinations of two or more of these substances. The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

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 about 1% to 35%, preferably 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 the preparation of 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:



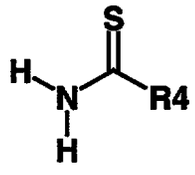
For this, compounds of the formula II



Formula II

in which R1, R1', R3 and X and Y have the meaning indicated, are activated and converted into a compound of the formula III, in which Z is the radical of an activated ester of an inorganic or organic acid.

The compounds of the formula III are reacted further with thioamides of the formula VI



VI

in which R4 has the meaning indicated, to give compounds of the formula VII or I', where, if appropriate, the compounds of the formula I' are converted into their acid addition salts of the formula VII using organic or inorganic acids or salts of the formula VII obtained are converted into the free basic compounds of the formula I' using organic or inorganic bases.

Suitable inorganic acids are, for example:
hydrohalic acids such as hydrochloric acid and hydrobromic acid, as well as 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-oxathiazine-4(3H)-one-2,2-dioxide.

The procedure described above is advantageously carried out such that the compounds III are reacted with the thioamides VI in the molar ratio from 1:1 to 1:1.5. The reaction is advantageously carried out in an inert solvent, e.g. 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, butane-2-one or hexane-2-one. Mixtures of the reaction media mentioned can also be used; and mixtures of the solvents mentioned can also be used 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 tetrachloromethane, acetone with chloroform, dichloromethane or 1,2-dichloroethane, where the more polar solvent in each case should expediently be used in an excess. The reaction components can be suspended or dissolved in the respective reaction medium. Fundamentally, the reaction components can also be reacted without 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 as a rule proves 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 in general between 5 minutes and 48 hours.

Frequently, the compounds VII separate in the form of their poorly soluble acid addition salts in the course of the reaction, expediently a suitable precipitating agent is additionally subsequently added. Those used are, for example, hydrocarbons such as benzene, toluene, cyclohexane or heptane or tetrachloromethane; 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 VII 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 III with the thioamides V proceeds virtually quantitatively, the crude products obtained are usually already analytically pure. The working-up of the reaction mixture can also be carried out such that the reaction mixture is rendered alkaline with 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, e.g. on a silica gel column, after

concentration. Suitable elution media 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 VII 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, diisopropyl 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, nitromethane. Particularly advantageous, however, 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 II 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 compounds I' thus obtained are then optionally converted into their acid addition products VII.

A possible radical of an activated ester Z in the compounds of the formula III is, for example: Cl, Br, I, O-C(O)-(C_6H_4)-4-NO_2, O-SO_2-CH_3, O-SO_2-CF_3, O-SO_2-(C_6H_4)-4-CH_3, O-SO_2-C_6H_4.

The acid addition products VII and I x HZ can be reacted to give the compounds of the formulae I and I' by treatment with bases. Possible bases are, for example, solutions of inorganic hydroxides, such as lithium, sodium, potassium, calcium or barium hydroxide, carbonates or hydrogencarbonates, such as sodium or potassium carbonate, sodium or potassium hydrogencarbonate, ammonia and amines, such as

triethylamine, diisopropylamine, dicyclohexylamine, piperidine, morpholine, methyldicyclohexylamine.

Thioamides of the formula VI are either commercially obtainable 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, hexamethylphosphoramide [Scheibye, Pedersen und 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 are also obtainable by reacting nitriles of the formula IV

Formula IV

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-diethyldithiophosphoric acid in a solvent such as ethyl acetate under acidic, e.g. HCl, conditions at room temperature or with warming.

The compounds of the formula I x HZ or I, where R2 is $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, and where n can be 0-5, can be obtained by either

aa) allowing the acid addition salts of the formula VII to react in a solvent of the formula R2-OH, where R2 has the meaning described above,

at a temperature from -20°C to 120°C, preferably at -5°C to 50°C, for 2 hours to 4 days, preferably 4 hours to 2 days,

or

ab) reacting the free bases of the formula I' in a solvent of the formula R2-OH, where R2 has the meaning described above, using equimolar, substoichiometric or catalytic, preferably catalytic, amounts of an inorganic or organic acid, such as are described further above, or with addition of an acidic ion exchanger at a temperature of -20°C to 120°C, preferably at -5°C to 50°C, for 2 hours to 4 days, preferably 4 hours to 2 days,

or

ac) carrying out the reactions as in aa) and ab) in an inert aprotic solvent such as dichloromethane, chloroform, 1,2-dichloroethane, heptane, benzene, toluene, acetonitrile, nitromethane, dioxane, tetrahydrofuran, ethylene glycol dimethyl ether, diethyl ether, diisopropyl ether, tert-butyl methyl ether, acetone, butan-2-one or lower alkyl acetates, such as, for example, ethyl acetate, by addition of 1 to 5, preferably 1.5-2, equivalents of a compound of the formula R2-OH

or

ad) converting compounds of the formula I' into their alkoxide in a polar aprotic solvent, such as, for example, tetrahydrofuran, dioxane, ethylene glycol dimethyl ether, nitromethane, acetonitrile or dimethylformamide, dimethylacetamide or N-methyl-2-pyrrolidone, with the aid of a base, such as, for example, sodium hydride, lithium diisopropylamide, KOH or potassium carbonate, and then allowing this to react with addition of an alkylating agent of the formula R2-W, where W = chlorine, bromine, iodine, O-C(O)-CH_3, O-C(O)-CF_3, O-C(O)-C_6H_4-4-NO_2, O-SO_2-CH_3, O-SO_2-CF_3, O-SO_2-C_6H_4-4-CH_3, O-SO_2-C_6H_4-4-NO_2, at –20 to 150°C, preferably at –15 to 50°C, for 10 minutes to 2 days, preferably for 20 minutes to 12 hours.

Compounds of the formula I x HZ or I where R2 = 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, can be obtained by either

ba) proceeding as described under aa)-ac), with the difference that instead of an alcohol R2-OH an acid R2-OH is employed, and 1 to 2 equivalents of the acid R2-OH, preferably 1.5 equivalents of the acid R2-OH, are employed and the addition of the acidic inorganic or organic catalyst described under aa)-ac) is dispensed with, but the acidic cation exchanger is advantageously employed

or

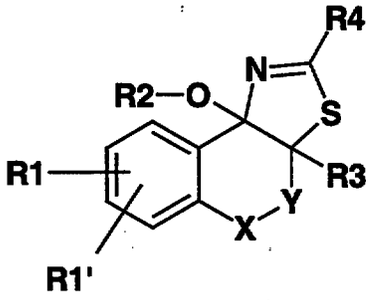
bb) reacting a compound of the formula VII or I' with an acid of the formula R2-OH in the sense of a Mitsunobu reaction (O. Mitsunobu, Synthesis 1981, 1) to give a compound of the formula I x HZ or I

or

bc) reacting a carbonyl chloride of the formula R2-Cl or a carboxylic anhydride of the formula R2-O-R2 with a compound of the formula I' in the sense of an esterification of an alcohol (Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag Stuttgart, Volume E5, pp. 656-715).

The examples listed below serve to illustrate the invention, but without restricting it. The measured fixed 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	Y	X	Salt	m.p. [°C]
A01	5-NO_2; H	H	H	CH_3	-	CH_2	-	210
A02	6-Cl; H	H	H	CH_3	-	CH_2	HCl	183
A03	5-SO_2-CH_3; H	H	H	CH_3	-	CH_2	HCl	741
A04	7-Cl; H	H	H	CH_3	-	CH_2	-	132
A05	5-Cl; H	H	H	CH_3	-	CH_2	-	210
A06	6-F; H	H	H	CH_3	-	CH_2	-	132
A07	6-(C_6H_5); H	H	H	CH_3	-	CH_2	HBr	275
A08	6-((C_6H_4)-3-CF_3); H	H	H	CH_3	-	CH_2	HBr	178
A09	6-(thien-3-yl); H	H	H	CH_3	-	CH_2	HBr	184
A10	6-((C_6H_4)-3-F); H	H	H	CH_3	-	CH_2	HBr	197
A11	6-CN; H	H	H	CH_3	-	CH_2	HBr	217
A12	6-((C_6H_4)-4-CH_3); H	H	H	CH_3	-	CH_2	HBr	194
A13	6-((C_6H_4)-4-CF_3); H	H	H	CH_3	-	CH_2	HBr	193
A14	6-((C_6H_3)-3,5-di-CF_3); H	H	H	CH_3	-	CH_2	HBr	262
A15	6-((C_6H_4)-3-Cl); H	H	H	CH_3	-	CH_2	HBr	184
A16	6-((C_6H_4)-3-OCF_3); H	H	H	CH_3	-	CH_2	HBr	212
A17	6-((C_6H_4)-4-Cl); H	H	H	CH_3	-	CH_2	HBr	190
A18	5-$C(CH_3)_3$; H	H	H	CH_3	-	CH_2	HBr	282
A19	6-((C_6H_4)-2-CF_3); H	H	H	CH_3	-	CH_2	HBr	200
A20	6-((C_6H_4)-3-OCH_3); H	H	H	CH_3	-	CH_2	HBr	169
A21	6-(naphth-1-yl); H	H	H	CH_3	-	CH_2	HBr	200
A22	7-((C_6H_4)-4-CF_3); H	H	H	CH_3	-	CH_2	HBr	213
A23	5-((C_6H_4)-4-CF_3); H	H	H	CH_3	-	CH_2	HBr	221

A24	6-OCF_3; H	H	H	CH_3	-	CH_2	HBr	219
A25	6-Cl; H	CH_2-CH_3	H	pyrid-3-yl	-	CH_2	-	89
A75	6-Cl; H	H	H	pyrid-3-yl	-	CH_2	-	134
A26	6-Cl; H	H	H	C_6H_5	-	CH_2	-	165
A27	6-Cl; H	CH_3	H	CH_3	-	CH_2	-	94
A28	6-((C_6H_4)-4-Cl); H	CH_3	H	CH_3	-	CH_2	-	129
A29	6-((C_6H_4)-3-Cl); H	CH_3	H	CH_3	-	CH_2	-	81
A30	6-Cl; H	H	H	C_6H_4-3-Cl	-	CH_2	HBr	207
A31	6-Cl; H	H	H	(C_6H_3)-2,4-di-Cl	-	CH_2	HBr	225
A32	6-Cl; H	H	H	(C_6H_4)-4-CF_3	-	CH_2	HBr	226
A33	6-Cl; H	H	H	C_6H_5	-	CH_2	HCl	155
A34	6-Cl; H	H	H	(C_6H_4)-4-O-pyrid-2-yl-5-CF3	-	CH_2	HBr	235
A35	6-Cl; H	H	H	(C_6H_4)-2-(pyrrol-1-yl)	-	CH_2	-	140
A36	6-Cl; H	H	H	(C_6H_4)-4-OCH_3	-	CH_2	-	144
A37	6-Cl; H	H	H	CH_2-CH_3	-	CH_2	HBr	230
A38	6-Cl; H	H	H	pyrid-4-yl	-	CH_2	-	158
A39	5-((C_6H_4)-4-CF_3); H	H	H	CH_3	-	CH_2	-	215
A40	6-Cl; H	H	H	cyclohexyl	-	CH_2	HBr	170
A41	6-Cl; H	H	H	(C_6H_4)-3-Cl-4-F	-	CH_2	HBr	255
A42	6-C≡CH; H	H	H	C_6H_5	-	CH_2	HBr	134
A43	6-CH_2-CH_3; H	H	H	C_6H_5	-	CH_2	HBr	119
A44	6-COOH; H	H	H	C_6H_5	-	CH_2	HBr	>300
A45	6-Cl; H	H	H	(C_6H_4)-4-Cl	-	CH_2	-	142
A46	6-Cl; H	H	H	thien-2-yl	-	CH_2	HBr	211
A47	6-O-CH2-CF_3; H	H	H	CH_3	-	CH_2	HBr	215
A48	6-O-CH2-CF_3; H	H	H	C_6H_5	-	CH_2	HBr	240
A49	6-O-((C_6H_4)-4-Cl); H	H	H	CH_3	-	CH_2	HBr	226

A50	6-O-((C_6H_4)-4-Cl); H	H	H	C_6H_5	-	CH_2	HBr	237
A51	6-O-((C_6H_4)-3- CH_3); H	H	H	CH_3	-	CH_2	HBr	267
A52	6-O-((C_6H_4)-3- CH_3); H	H	H	C_6H_5	-	CH_2	HBr	254
A53	6-Cl; H	H	H	(C_6H_4)-4-OCF_3	-	CH_2	-	178
A54	6-Cl; H	H	H	pyrid-2-yl	-	CH_2	-	130
A55	6-Cl; H	H	H	2-tert-Butyl-5-methyl-furan-4-yl	-	CH_2	-	243
A56	6-Cl; H	H	H	(C_6H_4)-3-O CH_3	-	CH_2	-	142
A57	6-Cl; H	H	H	(C_6H_4)-2-OC_2H_5	-	CH_2	-	140
A58	5-tBu; H	H	H	C_6H_5	-	CH_2	-	161
A59	5-tBu; H	H	H	(C_6H_4)-4-Cl	-	CH_2	-	133
A60	5-tBu; H	H	H	CH_2- CH_3	-	CH_2	-	128
A61	5-tBu; H	H	H	pyridin-4-yl	-	CH_2	-	132
A62	6-CN; H	H	H	pyridin-4-yl	-	CH_2	-	140
A63	6-CN; H	H	H	CH_2-CH_3	-	CH_2	-	196
A64	5-((C_6H_4)-4-CF_3); H	H	H	C_6H_5	-	CH_2	-	161
A 65	5-((C_6H_4)-4-CF_3); H	H	H	(C_6H_4)-4-Cl	-	CH_2	-	172
A66	5-((C_6H_4)-4-CF_3); H	H	H	pyridin-4-yl	-	CH_2	-	218
A67	5-((C_6H_4)-4-CF_3); H	H	H	CH_2- CH_3	-	CH_2	-	145
A68	6-OCF_3; H	H	H	pyridin-4-yl	-	CH_2	-	134
A69	6-OCF_3; H	H	H	CH_2- CH_3	-	CH_2	-	110
A70	6-C≡CH; H	H	H	C_6H_5	-	CH_2	-	118
A71	6-C≡CH; H	H	H	(C_6H_4)-4-Cl	-	CH_2	-	136
A72	6-C≡CH; H	H	H	pyridin-4-yl	-	CH_2	-	101
A73	6-C≡CH; H	H	H	CH_2-CH_3	-	CH_2	-	149
A74	H; H	H	H	CH_3	-	CH_2	HBr	273
A76	6-(thien-2-yl); H	H	H	C_6H_5	-	CH_2	-	157
A77	6-(thien-2-yl); H	H	H	(C_6H_4)-3-Cl	-	CH_2	-	138
A78	6-Cl; H	H	H	(C_6H_4)-2-Cl	-	CH_2	-	145
A79	6-(thien-2-yl); H	H	H	(C_6H_4)-2-Cl	-	CH_2	-	134

A80	6-(thien-2-yl); H	H	H	Pyridin-4-yl	-	CH_2	-	151
A81	5-(C_6H_3-3,5-di-Cl)	H	H	Pyridin-4-yl	-	CH_2	-	140
A82	5-(C_6H_3-3,5-di-Cl)	H	H	(C_6H_4)-3-Cl	-	CH_2	-	156
A83	5,6-di-CH_3; H	H	H	CH_3	-	CH_2	-	274
A84	5,6-di-CH_3; H	H	H	C_6H_5	-	CH_2	-	282
A85	6-Cl; H	H	H	CH_2-1H-indol-3-yl	-	CH_2	-	121
A86	6-Cl; H	H	H	CH_2-1H-indol-3-yl-5-OH	-	CH_2	-	260
A87	6-Cl; H	H	H	(C_6H_4)-2-OH	-	CH_2	-	146
A88	6-Cl; H	H	H	(C_6H_4)-4-OH	-	CH_2	-	220
A89	6-Cl; H	H	H	(C_6H_4)-3-OH	-	CH_2	-	119
A90	6-CN; H	H	H	CH_2-1H-indol-3-yl	-	CH_2	-	130 (dec.)
A91	6-C≡CH; H	H	H	CH_2-1H-indol-3-yl	-	CH_2	-	120 (dec.)
A92	6-(C_6H_4)-3-CF_3; H	H	H	CH_2-1H-indol-3-yl	-	CH_2	-	140 (dec.)

The compounds of the formula I are distinguished by favorable effects on the lipid metabolism; in particular, they are suitable as anorectics/slimming preparations. The compounds can be employed on their own or in combination with further slimming preparations (such as are described, for example, in Chapter D1 of the Roten Liste). 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.

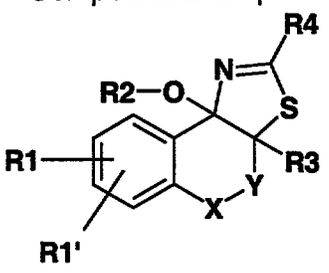
The efficacy of the compounds was tested as follows:

Biological test model:

The anorectic action was tested on male 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 giving 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 the untreated control animals.

Table 2: Anorectic action, measured as the reduction of the cumulated milk consumption of treated animals in comparison to the 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 animals N / [ml]	Reduction of the cumulated milk consumption in % of the control
Example A08	50	12 / 0.22	12 / 2.48	91
Example A14	50	5 / 0.8	5 / 3.92	80
Example A16	50	5 / 0.84	5 / 4.2	79
Example A22	50	5 / 1.58	5 / 5.42	71
Example A23	50	5 / 0.6	5 / 5.42	89
Example A75	25	5 / 2.30	5 / 4.02	43
Example A25	50	5 / 1.12	5 / 3.44	67
Example A26	50	5 / 0.2	5 / 4.02	95
Example A33	50	5 / 0.24	5 / 4.32	94
Example A27	50	5 / 1.14	5 / 4.50	75
Example A30	50	5 / 0.42	5 / 3.98	89
Example A31	50	5 / 0.2	5 / 3.98	95
Example A37	50	5 / 0.36	5 / 5.70	94
Example A38	50	5 / 0.28	5 / 4.12	93
Example A39	50	5 / 1.06	5 / 4.0	73
Example A40	50	5 / 0.62	4 / 3.53	82
Example A42	50	5 / 1.08	5 / 4.04	73
Example A45	50	5 / 0.34	5 / 4.38	92

Example A48	50	5 / 0.40	5 / 3.80	89
Example A49	50	5 / 0.74	5 / 3.30	78
Example A62	50	5 / 1.40	5 / 4.54	69
Example A70	50	5 / 1.06	5 / 4.82	78
Example A77	50	5 / 1.56	5 / 4.32	64

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

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

Example 1 (Compound A08):

2-Methyl-6-(3-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

a) 5-(3-Trifluoromethylphenyl)indan-1-one:

1.5 g of 5-bromoindan-1-one, 1.35 g of 3-(trifluoromethyl)phenylboronic acid and 1.5 g of sodium carbonate are suspended with stirring in a mixture of 50 ml of toluene with 10 ml of ethanol and 10 ml of water. Under a protective gas atmosphere (argon), 80 mg of palladium(II)acetate and 186 mg of triphenylphosphine are added and the mixture is stirred for 3 hours under reflux. The ethanol is removed from the cooled reaction mixture by distillation in vacuo, and the residue is treated with 20 ml of 0.5 N sodium hydroxide solution, stirred and filtered. The organic phase of the filtrate is washed a number of times with 20 ml of water in each case and finally with 20 ml of satd sodium chloride solution, dried over magnesium sulfate and concentrated. The residue is chromatographed on silica gel using n-heptane/ethyl acetate 3/1 and 5-(3-trifluoromethylphenyl)-indan-1-one of melting point 93°C is obtained.

b) 2-Bromo-5-(3-trifluoromethylphenyl)indan-1-one:

1.79 g of 5-(3-trifluoromethylphenyl)indan-1-one are dissolved in 10 ml of

glacial acetic acid. 5.5 µl of a 48% strength solution of hydrobromic acid in water are added and a solution of 0.362 ml of bromine in 5 ml of glacial acetic acid is then slowly added dropwise. The reaction mixture is stirred at room temperature for 3 hours and then poured into a mixture of 50 ml of water with 50 g of ice and 86 mg of sodium hydrogencarbonate. The aqueous suspension is extracted by shaking with 100 ml of dichloromethane, the organic phase is washed three times with 50 ml of water, dried over magnesium sulfate and concentrated, and the residue is chromatographed on silica gel using toluene/ethyl acetate 25/1. 2-Bromo-5-(3-trifluoromethylphenyl)indan-1-one of melting point 96°C is obtained. 2,2-Dibromo-5-(3-trifluoromethylphenyl)indan-1-one of melting point 210°C (dec.) is isolated as a by-product.

c) 2-Methyl-6-(3-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

213 mg of 2-bromo-5-(3-trifluoromethylphenyl)indan-1-one and 48.8 mg of thioacetamide are dissolved in 10 ml of dry acetone and the solution is stirred at 0°C for 8h. The precipitate is filtered off with suction, washed with acetone and dried in a high vacuum. 2-Methyl-6-(3-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide of melting point 245-250°C (dec.) is obtained.

Example 2 (Compound A14):

6-(3,5-Bistrifluoromethylphenyl)-2-methyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

a) 5-(3,5-Bistrifluoromethylphenyl)indan-1-one:

This compound is prepared analogously to the process described in Example 1a using 3,5-(bistrifluoromethyl)phenylboronic acid; melting point: 121°C.

b) 5-(3,5-Bistrifluoromethylphenyl)-2-bromo-indan-1-one:

This compound is prepared analogously to the process described in Example 1b using compound 2a; melting point: 105°C.

c) 6-(3,5-Bistrifluoromethylphenyl)-2-methyl-8,8a-dihydroindeno[1,2-d]-thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using the compound 2b; melting point: 261-264°C (dec.).

Example 3 (Compound A16):

2-Methyl-6-(3-trifluoromethoxyphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

a) 4,4,5,5-Tetramethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborolane:

2.41 g of 3-(trifluoromethoxy)brombenzene are dissolved in 25 ml of diethyl ether and added dropwise to a suspension of 0.28 g of magnesium in 25 ml of diethyl ether such that the solution remains at the boil. After addition is complete, the mixture is stirred under reflux for 2 h. The cooled solution is added dropwise to a solution of 1.16 ml of trimethyl borate in 25 ml of diethyl ether at a temperature of <-50°C and then stirred at room temperature for 2 h. 5 ml of 40% strength sulfuric acid and 1.21 g of pinacol are successively added to this solution. After 30 minutes, the solvent is removed on a Rotavapor, the residue is neutralized using saturated sodium hydrogencarbonate solution and the mixture is extracted three times with methyl tert-butyl ether. The organic phase is dried over magnesium sulfate and concentrated in vacuo. 4,4,5,5-Tetramethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]dioxaborolane is obtained, which is reacted further without further purification.

b) 5-(3-Trifluoromethoxyphenyl)indan-1-one:

This compound is prepared analogously to the process described in Example 1a using 4,4,5,5-tetramethyl-2-(3-trifluoromethoxyphenyl)-[1,3,2]-dioxaborolane; yellowish oil.

c) 2-Bromo-4-trifluoromethoxy-indan-1-one:

This compound is prepared analogously to the process described in Example 1b using the compound 3b; melting point: 64°C. 2,2-dibromo-4-trifluoromethoxyindan-1-one (yellowish oil) is isolated as a by-product.

d) 2-Methyl-6-(3-trifluoromethoxyphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using compound 3c; melting point: 210-214°C (dec.).

Example 4 (Compound A22):

2-Methyl-7-(4-trifluoromethylphenyl)-8,8a-dihydro-indeno[1,2-d]thiazol-3a-ol hydrobromide:

a) 4-(4-Trifluoromethylphenyl)indan-1-one:

This compound is prepared analogously to the process described in Example 1a using 4-bromo-indan-1-one and 4-(trifluoromethyl)phenyl-boronic acid; melting point: 75-78°C.

b) 2-Bromo-4-(4-trifluoromethylphenyl)indan-1-one:

This compound is prepared analogously to the process described in Example 1b using compound 4a; melting point: 102-105°C. A little of the corresponding dibromo compound is obtained as a by-product.

c) 2-Methyl-7-(4-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]-thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using compound 4b; melting point: 212-215°C (dec.).

Example 5 (Compound A23):

2-Methyl-5-(4-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

a) 6-(4-Trifluoromethylphenyl)indan-1-one:

This compound is prepared analogously to the procedure described in Example 1a using 6-bromoindan-1-one and 4-(trifluoromethyl)phenyl-boronic acid and reacted further without further purification.

b) 2-Bromo-6-(4-trifluoromethylphenyl)indan-1-one:

This compound is prepared analogously to the process described in Example 1b using compound 5a; melting point: 104°C. A little of the corresponding dibromo compound is obtained as a by-product (m.p.: 135°C).

c) 2-Methyl-5-(4-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using compound 5b; melting point: 220-223°C (dec.).

Example 6 (Compound A25):

6-Chloro-3a-ethoxy-2-pyridin-3-yl-8,8a-dihydro-3aH-indeno[1,2-d]thiazole:

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

This compound is prepared analogously to the process described in Example 1b using 5-chloroindan-1-one; melting point: 94-96°C. A little of the corresponding dibromo compound is obtained as a by-product.

b) 6-Chloro-3a-ethoxy-2-pyridin-3-yl-8,8a-dihydro-3aH-indeno[1,2-d]-thiazole:

1 g of 2-bromo-5-chloroindan-1-one and 622 mg of thionicotinamide are suspended in 10 ml of dry ethanol, and the mixture is stirred at room temperature for 2 h and at 70°C for 8 h. The reaction mixture is cooled, and the precipitate is filtered off with suction, washed with ethanol, stirred with a little water, again filtered off with suction and dissolved in 50 ml of ethyl acetate. This solution is rendered alkaline with triethylamine, treated with 30 ml of water and the organic phase is separated off, washed with water, dried over magnesium sulfate and concentrated in vacuo, and finally the residue is chromatographed on silica gel using ethyl acetate/n-heptane 1/1. 6-Chloro-3a-ethoxy-2-pyridin-3-yl-8,8a-dihydro-3aH-indeno[1,2-d]thiazole of melting point 89-90°C is obtained.

Example 7 (Compound A75):

6-Chloro-2-pyridin-3-yl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol of melting point 134-135°C is obtained in addition to 6-chloro-3a-ethoxy-2-pyridin-3-yl-8,8a-dihydro-3aH-indeno[1,2-d]thiazole on chromatography of Example 6b.

Example 8 (Compound A26):

6-Chloro-2-phenyl-8,8a-dihydro-indeno[1,2-d]thiazol-3a-ol:

This compound is prepared analogously to the process described in Example 6b using 2-bromo-5-chloroindan-1-one and thiobenzamide;
melting point: 155°C.

Example 9 (Compound A33): 6-Chloro-2-phenyl-8,8a-dihydroindeno[1,2-d]-thiazol-3a-ol hydrochloride:

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

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-chloroindan-1-one and thiobenzamide;
melting point: 245°C.

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

A suspension of the compound from Example 9a in ethyl acetate is treated with a saturated aqueous sodium hydrogencarbonate solution and stirred. The organic phase is separated off, washed twice with satd sodium hydrogencarbonate solution, dried over magnesium sulfate and concentrated in vacuo, and the residue is dried in high vacuum. 9b of melting point 155°C is obtained.

c) 6-Chloro-2-phenyl-8,8a-dihydro-indeno[1,2-d]thiazol-3a-ol hydrochloride:

9 g of the compound from 9b are suspended in 500 ml of ethyl acetate and treated with an excess of ethereal HCl solution in portions with stirring at ice-bath temperature. The mixture is stirred for 1 h at ice-bath temperature, and the precipitate is filtered off with suction, washed with diethyl ether and dried in high vacuum. 9c of melting point 196-199°C is obtained.

Example 10 (Compound A27):

6-Chloro-3a-methoxy-2-methyl-8,8a-dihydro-3aH-indeno[1,2-d]thiazole:

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

This compound is prepared analogously to the process described in Examples 9a-c using 2-bromo-5-chloroindan-1-one and thioacetamide; melting point: 183°C.

b) 2 g of the compound of Example 10a are introduced into 50 ml of methanol and the mixture is stirred at room temperature for 2 days. The reaction mixture is concentrated and the residue is partitioned between 200 ml of ethyl acetate and 200 ml of satd sodium hydrogencarbonate solution. The organic phase is separated off, dried over sodium sulfate and concentrated, and the residue is chromatographed on silica gel using ethyl acetate/n-heptane 1/5. 6-Chloro-3a-methoxy-2-methyl-8,8a-dihydro-3aH-indeno[1,2-d]thiazole is obtained as a waxy solid. ^{1}H NMR (d_6-dmso, 200 MHz) δ [ppm]= 7.38 (m, 3H), 4.6 (m, 1H), 3.6 (m, 1H), 3.22 (s, 3H), 3.02 (m, 1H), 2.2 (s, 3H); MS: MH^+ = 254.

Example 11 (Compound A30).

6-Chloro-2-(3-chlorophenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-chloroindan-1-one and 3-chlorothiobenzamide; melting point: 205-210°C (dec.).

Example 12 (Compound A31).

6-Chloro-2-(2,4-dichlorophenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-chloroindan-1-one and 2,4-dichlorothiobenzamide; melting point: 220-230°C (dec.).

Example 13 (Compound A37).

6-Chloro-2-ethyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-chloroindan-1-one and thiopropionamide; melting point: 230-240°C (dec.).

Example 14 (Compound A38).

6-Chloro-2-pyridin-4-yl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

0.98 g of 2-bromo-5-chloroindan-1-one and 0.55 g of thioisonicotinamide are dissolved in 40 ml of dry acetone at room temperature and treated with 0.55 ml of triethylamine. The mixture is stirred at room temperature for 2 days. The reaction mixture is concentrated, and the residue is taken up with ethyl acetate and washed twice with water and then twice with satd sodium chloride solution. The organic phase is dried over magnesium sulfate, filtered and concentrated, and the residue is chromatographed on

silica gel using ethyl acetate/n-heptane 10/1. 6-Chloro-2-pyridin-4-yl-8,8a-dihydro-indeno[1,2-d]thiazol-3a-ol of melting point 155-160°C (dec.) is obtained.

Example 15 (Compound A39):

2-Methyl-5-(4-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

A suspension of the compound from Example 5c in ethyl acetate is treated with a saturated aqueous sodium hydrogencarbonate solution and stirred. The organic phase is separated off, washed twice with satd sodium hydrogencarbonate solution, dried over magnesium sulfate and concentrated in vacuo, and the residue is dried in a high vacuum. 15 of melting point 213-217°C is obtained.

Example 16 (Compound A40):

6-Chloro-2-cyclohexyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-chloroindan-1-one and cyclohexanethiocarboxamide; melting point: 170-175°C (dec.).

Example 17 (Compound A40):

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

a) 5-Ethynylindan-1-one:

2.11 g of 5-bromoindan-1-one are suspended in 10 ml of degassed triethylamine with 67.2 mg of palladium(II) acetate and 78.6 mg of triphenylphosphine with 2.12 ml of ethynyltrimethylsilane and the mixture is stirred under reflux for 1 h. The cooled reaction mixture is concentrated, taken up with 20 ml of satd sodium hydrogencarbonate solution and 40 ml of ethyl acetate and the organic phase is washed first with water, then with satd sodium chloride solution. The organic phase is dried over magnesium sulfate, filtered and concentrated in vacuo, and the residue is

chromatographed on silica gel using n-heptane/ethyl acetate 3/1. 5-Trimethylsilanylethynylindan-1-one is obtained, which is dissolved in 25 ml of methanol and stirred at room temperature for 2 h with potassium carbonate. The reaction mixture is concentrated in vacuo; the residue is stirred with 25 ml of satd sodium hydrogencarbonate solution and 50 ml of ethyl acetate, and the organic phase is then separated off and filtered through a clarifying layer. The filtrate is dried over magnesium sulfate and concentrated in vacuo, and the residue is stirred with n-heptane. The precipitate is filtered off with suction and dried in vacuo. 5-Ethynylindan-1-one of melting point 157°C is obtained.

b) 2-Bromo-5-ethynylindan-1-one:

This compound is prepared analogously to the process described in Example 1b using compound 17a; melting point: 144°C.

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

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-ethynylindan-1-one and thiobenzamide; melting point: 133-134°C (dec.).

Example 18 (Compound A45):

6-Chloro-2-(4-chlorophenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

This compound is obtained analogously to the procedure in Example 14 using 2-bromo-5-chloroindan-1-one and 4-chlorothiobenzamide; melting point: 140-144°C.

Example 19 (Compound A48):

2-Phenyl-6-(2,2,2-trifluoroethoxy)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

a) 5-(2,2,2-Trifluoroethoxy)indan-1-one:

2.2 ml of 2,2,2-trifluoroethanol are added to a stirred mixture of 3.5 g of 5-fluoroindanone, 20 ml of anhydrous dimethylformamide and 4.1 g of anhydrous and ground potassium carbonate and the mixture is stirred at 80°C for 10 hours. The solvent is removed by distillation under reduced pressure, the residue is dissolved in ethyl acetate and the organic phase is washed a number of times with water. The indanone derivative is obtained as a brownish crystalline solid after chromatography on silica gel using a mixture of equal parts of ethyl acetate and toluene as an eluent. Melting point 93 – 97 °C.

b) 2-Bromo-5-(2,2,2-trifluoroethoxy)indan-1-one:

This compound is obtained by reaction of 0.9 g of 5-(2,2,2-trifluoroethoxy)indan-1-one with 0.2 ml of bromine in 25 ml of ethyl acetate. The compound is used further without further purification.

c) 2-Phenyl-6-(2,2,2-trifluoroethoxy)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-(2,2,2-trifluoroethoxy)indan-1-one and thiobenzamide; melting point: 240-246°C.

Example 20 (Compound A49):

6-(4-Chlorophenoxy)-2-methyl-8,8a-dihydro-indeno[1,2-d]thiazol-3a-ol hydrobromide:

a) 5-(4-Chlorophenoxy)indan-1-one:

2.82 g of 4-chlorophenol are stirred at room temperature for ½ an hour, after dissolution in 60 ml of anhydrous dimethylacetamide, with 8.2 g of anhydrous and ground potassium carbonate. After addition of 1.5 g of 5-fluoroindanone, the mixture is stirred at 120-130°C for 10 hours and, after cooling, the solvent is removed by distillation under reduced pressure. The residue is treated with water and extracted a number of times with ethyl acetate. The organic phase is washed with 2N NaOH and subsequently with water, then stirred for 15 minutes after addition of active carbon and

the solvent is removed by distillation under reduced pressure after drying over anhydrous magnesium sulfate. The partially crystalline dark residue is purified by column chromatography on silica gel using an eluent consisting of equal parts of ethyl acetate and toluene. Brown crystals, melting point 75 – 80°C.

2-Bromo-5-(4-chlorophenoxy)indan-1-one:

Approximately ½ ml of a solution of 0.25 ml of bromine in 5 ml of glacial acetic acid is added dropwise to a solution of 1.3 g of 5-(4-chlorophenoxy)indan-1-one in 30 ml of glacial acetic acid and the mixture is warmed slowly until the bromine is decolorized and until the evolution of HBr begins. It is then cooled and the remaining quantity of bromine is added dropwise at room temperature, the mixture is stirred for a further 2 hours and the solvent is removed by distillation under reduced pressure. The residual dark oil is used without further purification.

b) 6-(4-Chlorophenoxy)-2-methyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol hydrobromide:

This compound is prepared analogously to the process described in Example 1c using 2-bromo-5-(4-chlorophenoxy)indan-1-one and thioacetamide; melting point: 225-228°C.

Example 21 (Compound A62):

3a-Hydroxy-2-pyridin-4-yl-8,8a-dihydro-3aH-indeno[1,2-d]thiazole-6-carbonitrile:

a) 1-Oxoindan-5-carbonitrile:

9.5 g of 5-bromoindan-1-one and 4.93 g of CuCN are suspended in 10 ml of dimethylformamide and the mixture is refluxed for 4 hours. A solution of 18 g of iron(III) chloride in 5 ml of conc. hydrochloric acid with 30 ml of water is added dropwise with stirring to the cooled, dark-brown, viscous suspension and the mixture is then stirred at 70°C for 30 minutes. The reaction mixture is extracted three times by shaking with 50 ml of toluene, and the combined organic phases are extracted by shaking with 50 ml of

2N hydrochloric acid and 50 ml of 2N sodium hydroxide solution and then washed with water until neutral. The toluene extract is dried over magnesium sulfate and concentrated in vacuo, and the residue is recrystallized from n-heptane. 1-Oxoindan-5-carbonitrile of melting point 123 - 125°C is obtained.

b) 2-Bromo-1-oxoindan-5-carbonitrile:

The bromination of 1-oxoindan-5-carbonitrile is carried out as described in Example 1b and yields 2-bromo-1-oxoindan-5-carbonitrile of melting point 115 – 118°C.

c) 3a-Hydroxy-2-pyridin-4-yl-8,8a-dihydro-3aH-indeno[1,2-d]thiazole-6-carbonitrile:

This compound is obtained analogously to the procedure in Example 14 using 2-bromo-1-oxoindan-5-carbonitrile and thioisonicotinamide; melting point: 140°C (dec.).

Example 22 (Compound A67):

2-Ethyl-5-(4-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

355 mg (1 mmol) of the compound from Example 5b are dissolved in 5 ml of dry acetone with 2 mmol of thiopropionamide and the mixture is stirred at room temperature for 24 h. The reaction mixture is then stirred further at ice-bath temperature for 2 h, the precipitate is filtered off with suction and suspended in 20 ml of ethyl acetate, and the mixture is treated with 1.5 mmol of triethylamine and stirred at room temperature for 30 minutes. 10 ml of water are added, the mixture is stirred, and the organic phase is separated off, dried over magnesium sulfate and concentrated in vacuo. 2-Ethyl-5-(4-trifluoromethylphenyl)-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol of melting point 145°C is obtained.

Example 23 (Compound A70):

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

The compound from Example 17c is suspended in ethyl acetate, the mixture is neutralized with triethylamine, and the ethyl acetate phase is washed with water, then dried over magnesium sulfate and concentrated in vacuo. 6-Ethynyl-2-phenyl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol of melting point 118°C is obtained.

Example 24 (Compound A77):

2-(3-Chlorophenyl)-6-thiophen-2-yl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

5-thiophen-2-yl-indan-1-one:

This compound is prepared analogously to the process described in Example 1a using thiophene-2-boronic acid; melting point: 148°C.

a) 2-Bromo-5-thiophen-2-ylindan-1-one:

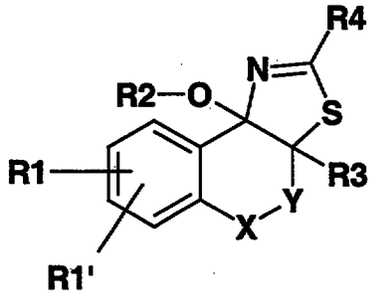
This compound is prepared analogously to the process described in Example 1b using compound 24a; melting point: 114°C.

b) 2-(3-Chlorophenyl)-6-thiophen-2-yl-8,8a-dihydroindeno[1,2-d]thiazol-3a-ol:

This compound is obtained when the compound from Example 24b is reacted with 3-chlorothiobenzamide as described in Example 22.
Melting point: 137°C.

Patent claims:

1. A compound of the formula I



I

in which

Y is a direct bond, $-CH_2-$, $-CH_2-CH_2-$;

X is CH_2, $CH(CH_3)$, $CH(C_2H_5)$, $CH(C_3H_7)$, $CH(C_6H_5)$;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine, or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H, OCH_2Ph, NH_2,NH-CO-CH_3 or $N(COOCH_2Ph)_2$;
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; NH_2, $NH-(C_1-C_6)$-alkyl, $N((C_1-C_6)-alkyl)_2$, $NH(C_1-C_7)$-acyl, phenyl, biphenyl, $O-(CH_2)_n$-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, biphenyl, naphthyl, pyridyl, furanyl or thienyl rings can each 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, $CONH_2$;

* C L M S *

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, furyl can each 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 H, (C_1-C_6)-alkyl, F, CN, N_3, O-(C_1-C_6)-alkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, where n can be 0 - 5 and in which phenyl, thienyl, pyridyl, furyl can each be substituted up to two times by Cl, F, CN, CF_3, (C_1-C_3)-alkyl, OH, O-(C_1-C_6)-alkyl; (C_2-C_6)-alkynyl, (C_2-C_6)-alkenyl, $C(O)OCH_3$, $C(O)OCH_2CH_3$, C(O)OH, $C(O)NH_2$, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $OC(O)CH_3$;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H,O-CH_2-Ph or O-(C_1-C_4)-alkyl;
$(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, CHO or CO-phenyl, or -NR6R7 is a ring such as pyrrolidine, piperidine, morpholine, piperazine, N-4-methylpiperazin-1-yl, N-4-benzylpiperazin-1-yl, phthalimidoyl;
$(CH_2)_n$-aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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

* C L M S *

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 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, 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)cyclo-alkyl, 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-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 = 0-3;

or its physiologically tolerable salts and physiologically functional derivatives.

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

Y is a direct bond;

X is CH_2;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine, or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H, O-CH_2-Ph, NH_2, NH-CO-CH_3 or N($COOCH_2Ph$)$_2$;
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; NH_2, NH-(C_1-C_6)-alkyl, N((C_1-C_6)-alkyl)$_2$, NH(C_1-C_7)-acyl, phenyl, biphenyl, O-$(CH_2)_n$-phenyl, where n can be 0-6; 1- or 2-naphthyl, 2-, 3-

* C L M S *

or 4-pyridyl, 2- or 3-furanyl or 2- or 3-thienyl, where the phenyl, biphenyl, naphthyl, pyridyl, furanyl or thienyl rings can each 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, furyl can each 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 H, (C_1-C_6)-alkyl, F, CN, N_3, O-(C_1-C_6)-alkyl, $(CH_2)_n$-phenyl, $(CH_2)_n$-thienyl, $(CH_2)_n$-pyridyl, $(CH_2)_n$-furyl, where n can be 0-5 and in which phenyl, thienyl, pyridyl, furyl can each be substituted up to two times by Cl, F, CN, CF_3, (C_1-C_3)-alkyl, OH, O-(C_1-C_6)-alkyl; (C_2-C_6)-alkynyl, (C_2-C_6)-alkenyl, $C(O)OCH_3$, $C(O)OCH_2CH_3$, C(O)OH, $C(O)NH_2$, $C(O)NHCH_3$, $C(O)N(CH_3)_2$, $OC(O)CH_3$;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H,O-CH_2-Ph or O-(C_1-C_4)-alkyl;
$(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, CO-(C_1-C_6)-alkyl, CHO or CO-phenyl or -NR6R7 is a ring such as pyrrolidine, piperidine, morpholine,

piperazine, N-4-methylpiperazin-1-yl, N-4-benzylpiperazin-1-yl, phthalimidoyl;
$(CH_2)_n$-aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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-methyl-imidazol-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, 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-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 = 0-3;

or its physiologically tolerable salts and physiologically functional derivatives.

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

Y is a direct bond;

X is CH_2;

R1, R1' independently of one another are H, F, Cl, Br, I, CF3, NO_2, CN, COOH, COO(IC$_1$-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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine, or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H, O-CH_2-Ph, NH_2, NH-CO-CH_3 or N$(COOCH_2Ph)_2$;

* C L M S *

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;

NH_2, NH-$(C_1$-$C_6)$-alkyl, $N((C_1$-$C_6)$-alkyl$)_2$, $NH(C_1$-$C_7)$-acyl, phenyl, biphenyl, 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, biphenyl, naphthyl, pyridyl, furanyl or thienyl rings can each 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, furyl can each 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 H, F;

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, it being possible in the alkyl radicals for one or more, or all hydrogens to be replaced by fluorine or a hydrogen to be replaced by OH, $OC(O)CH_3$, OC(O)H,O-CH_2-Ph or O-$(C_1$-$C_4)$-alkyl;
$(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, $(C_1$-$C_6)$-alkyl,

* C L M S *

$(C_3$-$C_6)$-cycloalkyl, CO-$(C_1$-$C_6)$-alkyl, CHO or CO-phenyl, or -NR6R7 is a ring such as pyrrolidine, piperidine, morpholine, piperazine, N4-methylpiperazin-1-yl, N4-benzylpiperazin-1-yl, phthalimidoyl;

$(CH_2)_n$-aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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-methyl-imidazol-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, 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-methylpiperazin-1-yl, $(CH2)_n$-phenyl, O-$(CH_2)_n$ -phenyl, S-$(CH_2)_n$ -phenyl, SO_2-$(CH_2)_n$-phenyl, where n = 0-3;

or its physiologically tolerable salts.

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

Y is a direct bond;

X is CH_2;

R1, R1' independently of one another are H, F, Cl, Br, NO_2, CN, COOH, $(C_1$-$C_6)$-alkyl, $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, O-$(C_1$-$C_6)$-alkyl, OCF_3, OCH_2CF_3, phenyl, O-$(CH_2)_n$-phenyl, where n can be 0-6, 1- or 2-naphthyl, 2- or 3-thienyl, where the phenyl, naphthyl or thienyl rings can each 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;

* C L M S *

R2 is H, $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, $(CH_2)_n$-phenyl, where n can be 0-5;

R3 is H, F;

R4 is $(C_1\text{-}C_8)$-alkyl, $(C_3\text{-}C_7)$-cycloalkyl, $(CH_2)_n$-NR6R7, where n can be 1-6 and R6 and R7 independently of one another can be H, $(C_1\text{-}C_6)$-alkyl, or –NR6R7 is a ring such as pyrrolidine, piperidine, morpholine, piperazine, N4-methylpiperazin-1-yl, N4-benzylpiperazin-1-yl, phthalimidoyl;
$(CH_2)_n$-aryl, where n can be 0-6 and aryl can be phenyl, biphenyl, 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-methyl-imidazol-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-$(C_1\text{-}C_6)$-alkyl, pyrrolidin-1-yl, morpholin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-methylpiperazin-1-yl;
or its physiologically tolerable salts.

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

Y is a direct bond;
X is CH_2,
R1 is Cl;
R1' is H;
R2 is H;
R3 is H;
R4 is phenyl;
or its physiologically tolerable salts.

* C L M S *

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

7. A pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 5 and one or more slimming preparations.

8. A compound as claimed in one or more of claims 1 to 5 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 5 for use as a medicament for the prophylaxis or treatment of type II diabetes.

10. A compound as claimed in one or more of claims 1 to 5 in combination with at least one further anorectic active compound for use as a medicament for the prophylaxis or treatment of obesity.

11. A compound as claimed in one or more of claims 1 to 5 in combination with at least one further anorectic active compound for use as a medicament for the prophylaxis or treatment of type II diabetes.

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

13. The use of the compounds as claimed in one or more of claims 1 to 5 for the production of a medicament or the prophylaxis or treatment of obesity.

14. The use of the compounds as claimed in one or more of claims 1 to 5 for the production of a medicament or the prophylaxis or treatment of type II diabetes.

* C L M S *