NOVEL CARBOXYLIC ACID DERIVATIVES, THEIR PREPARATION AND USE IN TREATING CANCER

BACKGROUND

Cancer is a disease for which many potentially effective treatments are available. However, due to the prevalence of cancers of various types and the serious effects cancer can have, more effective treatments, especially those with fewer adverse side effects than currently available forms of treatment, are needed.

SUMMARY OF THE INVENTION

This invention relates to novel carboxylic acid derivatives, their preparation and use in treating cancer in which endothelin is upregulated, in a mammal, for example, a human.

Endothelin is a peptide which is composed of 21 amino acids and is synthesized and released by the vascular endothelium. Endothelin exists in three isoforms, ET-1, ET-2 and ET-3. As used herein the term "endothelin" or "ET" refers to one or all isoforms of endothelin. Endothelin is a potent vasoconstrictor and has a potent effect on vessel tone. It is known that this vasoconstriction is caused by binding of endothelin to its receptor (*Nature, 332,* (1988) 411-415; *FEBS Letters, 231,* (1988) 440-444 and *Biochem. Biophys. Res. Commun., 154,* (1988) 868-875).

Increased or abnormal release of endothelin causes persistent vasoconstriction in the peripheral, renal and cerebral blood vessels, which may lead to illnesses. It has been reported in the literature that elevated levels of

endothelin were found in the plasma of patients with hypertension, acute myocardial infarct, pulmonary hypertension, Raynaud's syndrome, atherosclerosis and in the airways of asthmatics (*Japan J. Hypertension, 12,* (1989) 79, *J. Vascular Med. Biology 2,* (1990) 207, *J. Am. Med. Association 264,* (1990) 2868).

Accordingly, substances which specifically inhibit the binding of endothelin to the receptor should also antagonize the various above-mentioned physiological effects of endothelin and therefore be valuable drugs. For example, the compounds of the present invention can be used for the treatment of hypertensions, pulmonary hypertension, myocardial infarct, angina pectoris, acute kidney failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty, benign prostate hyperplasia, or hypertension or kidney failure caused by ischemia or intoxication as described in WO96/11914 and WO95/26716, the teaching of both of which are incorporated herein by reference in their entirety.

We have found that certain carboxylic acid derivatives of Formula I or Ia which are inhibitors of endothelin receptors are also useful in treating cancer, such as prostate cancer. These carboxylic acid derivatives are described herein and also in WO96/11914 and WO95/26716, the teachings of both of which are incorporated herein by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a method for treating cancer in an individual, for example, a human, wherein the cancer is a tumor in which endothelin is upregulated (e.g. tumors of the prostate, lung, liver, breast, brain, stomach, colon,

endometrium, testicle, thyroid, pituitary, bladder, kidney, pancreas and meninges). By treating is meant inhibiting (partially or totally) formation of a solid tumor in which endothelin is upregulated, reversing development of a solid tumor in which endothelin is upregulated or reducing its further progression, by administering to the individual an effective amount of one or more compound(s) of Formula I and/or Formula Ia as described below. As used herein the term an effective amount is a quantity sufficient to inhibit (partially or totally) growth of a solid tumor in which endothelin is upregulated, reverse development of a solid tumor in which endothelin is unregulated or reduce its further progression. In the present invention, Formula Ia is a subgroup of the Formula I.

One or more compounds of Formula I and Ia may be administered alone or with pharmaceutically accepted carrier or diluent appropriate for the desired route of administration. Administration can be by any of the means which are conventional for pharmaceutical, preferably oncological, agents, including oral and parenteral means such as subcutaneously, intravenously, intramuscularly, intraperitoneally, nasally or rectally.

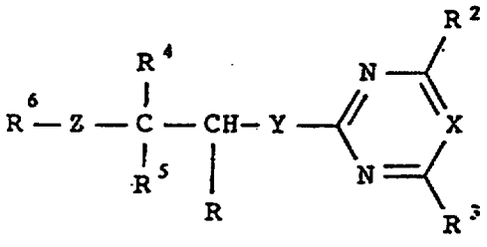
The dosage administered to the mammal, such as a human, includes an effective amount of a compound of Formula I or Formula Ia. For a particular condition or method of treatment, the dosage can be determined empirically, using known methods, and will depend upon factors such as the biological activity; toxicity profile; the means of administration; the age, sex, health and body weight of the recipient; the nature and extent of the symptoms; the frequency of treatment; the administration of other therapies; and the effect desired.

A typical daily dose of the compound of Formula I or Ia will be from about 0.5 to about 5000 milligram per kilogram of body weight by oral administration and from

about 0.1 to about 1000 milligrams per kilogram of body weight by parenteral administration. In one embodiment, wherein administration is parenteral, a daily dose will be from about 50 to about 500 milligrams per kilogram of body weight. In a particular embodiment, wherein the administration is parenterally, a daily dose will be from about 100 to about 300 milligrams per kilogram of body weight (e.g. 100, 150 or 220 milligrams per kilogram of body weight).

The novel compounds can be used in conventional solid or liquid pharmaceutical forms, e.g., as uncoated or (film) coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellent gases (cf. H. Sucker *et al.*: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1991). The administration forms obtained in this way normally contain from 0.1 to 90% by weight of the active substance.

The carboxylic acid derivatives useful in the method of the invention are compounds of Formula I:



I

where R is formyl, tetrazolyl, cyano, a COOH group or a radical which can be hydrolyzed to COOH, and the other substituents have the following meanings:

R^2 hydrogen, hydroxyl, NH_2, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

X nitrogen or CR^{14} where R^{14} is hydrogen or C_{1-5}-alkyl, or CR^{14} forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C_{1-4}-alkyl groups and in which in each case a methylene group can be replaced by oxygen, sulfur, -NH or $-NC_{1-4}$-alkyl;

R^3 hydrogen, hydroxyl, NH_2, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, $-NH-O-C_{1-4}$-alkyl, C_1-C_4-alkylthio or CR^3 is linked to CR^{14} as indicated above to give a 5- or 6-membered ring;

R^4 and R^5 (which can be identical or different):

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, amino, C_1-C_4-alkylamino or C_1-C_4-dialkylamino; or

phenyl or naphthyl, which are connected together in the ortho positions via a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2-, NH- or N-alkyl group, or C_3-C_7-cycloalkyl; or

R^4 is C_1-C_{10}-alkyl which can carry from one to five halogen atoms and/or one of the following radicals: C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, C_1-

C_8-alkylcarbonyl, C_1-C_8-alkoxy-carbonyl, phenyl, phenoxy or phenylcarbonyl, where the phenyl radicals in turn can carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

C_1-C_{10}-aklyl which can carry from one to five halogen atoms and carries one of the following radicals: a five-membered heteroaromatic ring which contains from one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry from one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio and/or phenyl;

C_3-C_{12}-cycloalkyl or C_3-C_{12}-cycloalkenyl, each of which can contain one oxygen or sulfur atom and can carry from one to five halogen atoms and/or one of the following radicals: C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, C_1-C_8-alkyl-carbonyl, C_1-C_8-alkoxycarbonyl, phenyl, phenoxy or phenyl-carbonyl, where the phenyl radicals in turn can carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

C_3-C_6-alkenyl or C_3-C_6-alkynyl, each of which can carry from one to five halogen atoms and/or one of the following radicals: C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, phenyl,

phenoxy or phenylcarbonyl, where the phenyl radicals in turn can carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

a five- or six-membered heteroaromatic ring which contains from one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry from one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, where the phenyl radicals in turn can carry from one to five halogen atoms and/or from one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

R^4 and R^5 form, together with the adjacent carbon atom, a 3- to 8-membered ring which can contain one oxygen or sulfur atom and can carry from one to three of the following radicals: C_1-C_4-alkyl, halogen, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-akylthio [sic];

R^5 is hydrogen, C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxyalkyl, C_1-C_4-alkylthioalkyl, phenyl or R^5 is linked to R^4 as indicated above to form a 3- to 8-membered ring;

R^6 hydrogen, C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, where each of these radicals

can be substituted one or more times by: halogen, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxy-carbonyl, C_{3-8}-alkylcarbonylalkyl, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, phenyl or phenyl or phenoxy which is substituted one or more times, for example one to three times, by halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, methylenedioxy or ethylenedioxy;

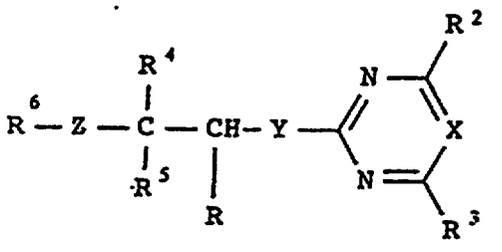
a five- or six-membered heteroaromatic moiety containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

with the proviso that R^6 can be hydrogen only when Z is not a single bond;

Y sulfur or oxygen or a single bond;

Z sulfur or oxygen or a single bond.

In particular embodiments, carboxylic acid derivatives useful in the method of the invention are compounds of Formula Ia which are a subgroup of Formula I:



Ia

where R is formyl, tetrazolyl, cyano, a COOH group or a radical which can be hydrolyzed to COOH, and the other substituents have the following meanings:

R^2 hydrogen, hydroxyl, NH_2, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

X nitrogen or CR^{14} where R^{14} is hydrogen or C_{1-5}-alkyl, or CR^{14} forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C_{1-4}-alkyl groups and in which in each case a methylene group can be replaced by oxygen, sulfur, -NH or $-NC_{1-4}$-alkyl;

R^3 hydrogen, hydroxyl, NH_2, $NH(C_1-C_4\text{-Alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, -NH-O-C_{1-4}-alkyl, C_1-C_4-alkylthio or CR^3 is

linked to CR^{14} as indicated above to give a 5- or 6-membered ring;

R^4 and R^5 (which can be identical or different):

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, amino, C_1-C_4-alkylamino or C_1-C_4-dialkylamino; or

phenyl or naphthyl, which are connected together in the ortho positions via a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO2, NH or N-alkyl group or C_3-C_7-cycloalkyl;

R^6 hydrogen, C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, where each of these radicals can be substituted one or more times by: halogen, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkyl- thio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxy-carbonyl, C_{3-8}-alkylcarbonylalkyl, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, phenyl or phenyl or phenoxy which is substituted one or more times, eg. one to three times, by halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloakoxy or C_1-C_4-alkylthio;

phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl,

amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, methylenedioxy or ethylenedioxy;

a five- or six-membered heteroaromatic moiety containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

with the proviso that R6 can be hydrogen only when Z is not a single bond;

Y sulfur or oxygen or a single bond;

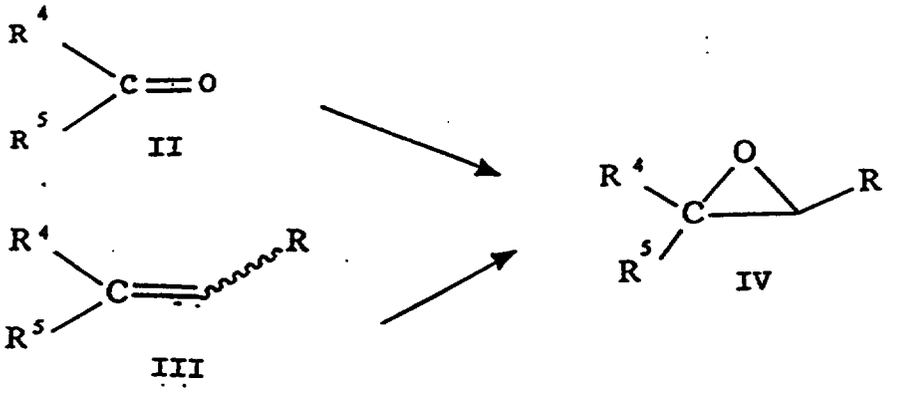
Z sulfur, oxygen, -SO-, $-SO_2-$ or a single bond.

The compounds, and the intermediates for preparing the compounds of Formula I and Ia, such as IV and VI, may have one or more asymmetrically substituted carbon atoms. Such compounds may be in the form of the pure enantiomers or pure diastereomers or a mixture thereof. The use of an enantiomerically pure compound as active substance is preferred.

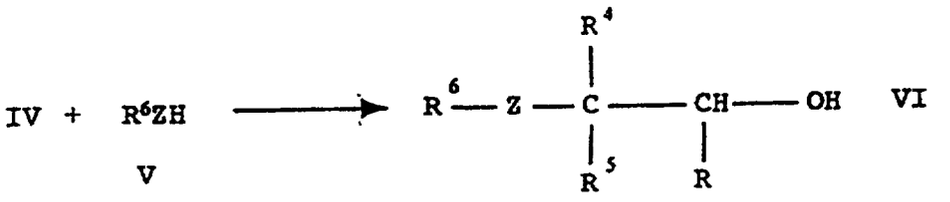
The invention furthermore relates to the use of the above-mentioned carboxylic acid derivatives for producing drugs, in particular for producing endothelin receptor inhibitors.

The invention furthermore relates to the preparation of the compounds of the Formula IV in enantiomerically pure form. Enantioselective epoxidation of an olefin with two phenyl substituents is known (*J. Org. Chem. 59*, 1994, 4378-4380).

The preparation of the compounds according to the invention where Z is sulfur or oxygen starts from the epoxides IV, which are obtained in a conventional manner, for example as described in J. March, *Advanced Organic Chemistry*, 2nd ed., 1983, page 862 and page 750, from the ketones II or the olefins III:



Carboxylic acid derivatives of the general Formula VI can be prepared by reacting the epoxides of the general Formula IV (eg. with R = $COOR^{10}$) with alcohols or thiols of the general formula V where R^6 and Z have the meanings stated above.



To do this, compounds of the general formula IV are heated with compounds of the formula V, in the molar ratio of about 1:1 to 1:7, preferably 1 to 3 mole equivalents, to 50-200°C, preferably 80-150°C.

The reaction can also take place in the presence of a diluent. All solvents which are inert toward the reagents used can be used for this purpose.

Examples of such solvents or diluents are water, aliphatic, alicyclic and aromatic hydrocarbons, which may in each case be chlorinated, such as hexane, cyclohexane, petroleum ether, naphtha, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers such as diisopropyl ether, dibutyl ether, methyl tert-butyl ether, propylene oxide, dioxane and tetrahydrofuran, ketones such as acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, nitriles such as acetonitrile and propionitrile, alcohols, such as methanol, ethanol, isopropanol, butanol and ethylene glycol, esters such as ethyl acetate and amyl acetate, amides such as dimethylformamide, dimethylacetamide and N-methyl-pyrrolidone, sulfoxides and sulfones, such as dimethyl sulfoxide and sulfolane, bases such as pyridine, cyclic ureas such as 1,3-dimethylimidazolidin-2-one and 1,3-dimethyl-3,4,5,6-tetra-hydro-2(1H)-pyrimidinone.

The reaction is preferably carried out at a temperature in the range from 0°C to the boiling point of the solvent or mixture of solvents.

The presence of a catalyst may be advantages. Suitable catalysts are strong organic and inorganic acids, and Lewis acids. Examples thereof are, *inter alia*, sulfuric acid, hydrochloric acid trifluoroacetic acid, p-toluenesulfonic acid, boron trifluoride etherate and titanium(IV) alcoholates.

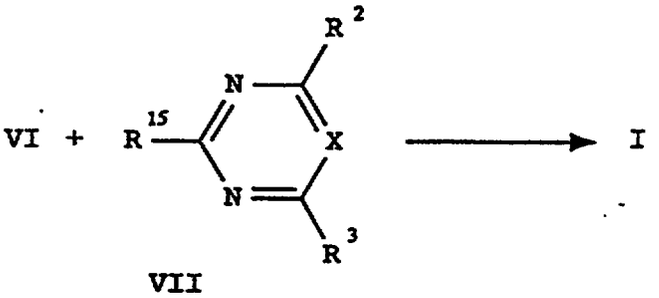
Compounds of the Formula VI where R^4 and R^5 are cycloalkyl can also be prepared by subjecting compounds of the Formula VI where R^4 and R^5 are phenyl, naphthyl, or phenyl or naphthyl substituted as described above, to a nuclear hydrogenation.

Compounds of the Formula VI can be obtained in enantiomerically pure form by starting from enantiomerically pure compounds of the Formula IV and reacting them in the manner described with compounds of the Formula V.

It is furthermore possible to obtain enantiomerically pure compounds of the Formula VI by carrying out a classical racemate resolution on racemic or diastereomeric compounds of the Formula VI using suitable enantiomerically pure bases such as brucine, strychnine, quinine, quinidine, cinchonidine, cinchonine, yohimbine, morphine, dehydroabietylamine, ephedrine (-), (+), deoxyephedrine (+), (-), threo-2-amino-1-(p-nitrophenyl)-1,3-propanediol (+), (-), threo-2-(N,N-dimethylamino)-1-(p-nitrophenyl)-1,3-propanediol (+), (-), α-(2-naphthyl)ethylamine (+), (-), aminomethylpinane, N,N-dimethyl-1-phenylethylamine, N-methyl-1-phenylethylamine, 4-nitrophenylethylamine, pseudoephedrine, norephedrine, norpseudoephedrine, amino acid derivatives, peptide derivatives.

The compounds according to the invention where Y is oxygen, and the remaining substituents have the meanings

stated under the general Formulas I and Ia, can be prepared, for example, by reacting the carboxylic acid derivatives of the general formula VI where the substituents have the stated meanings with compounds of the general Formula VII



VII

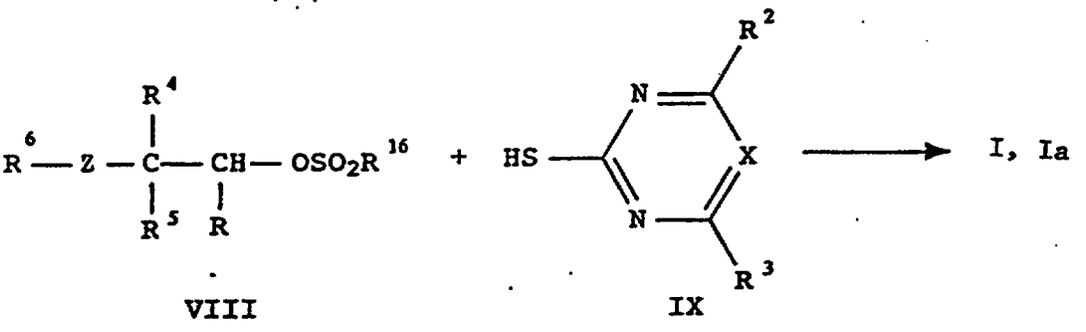
where R^{15} is a halogen or R^{16}-SO_2-, where R^{16} can be C_1-C_4-alkyl, C_1-C_4-haloalkyl or phenyl. The reaction preferably takes place in one of the above-mentioned inert diluents with the addition of a suitable base, that is of a base which deprotonates the intermediate VI, in a temperature range from room temperature to the boiling point of the solvent.

Compounds of the Formula VII are known, some of them can be bought, or they can be prepared in a generally known manner.

It is possible to use as base an alkali metal or alkaline earth metal hydride such as sodium hydride, potassium hydride, or calcium hydride, a carbonate such as an alkali metal carbonate, for example, sodium or potassium carbonate, an alkali metal or alkaline earth metal hydroxide such as sodium or potassium hydroxide, an organometallic compound such as butyllithium, or an alkali metal amide such as lithium diisopropylamide.

The compounds according to the invention where Y is sulfur, and the remaining substituents have the meanings

stated under the general Formulas I and Ia, can be prepared, for example, by reacting carboxylic acid derivatives of the general Formula VIII, which can be obtained in a known manner from compounds of the general formula VI and in which the substituents have the above-mentioned meanings, with compounds of the general formula IX, where R^2, and R^3 and X have the meanings stated under general Formulas I and Ia.

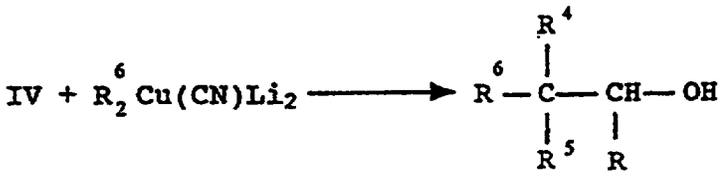


VIII IX

The reaction preferably takes place in one of the above-mentioned inert diluents with the addition of a suitable base, that is a base which deprotonates the intermediate IX, in a temperature range from room temperature to the boiling point of the solvent.

It is possible to use as base, besides those mentioned above, organic bases such as triethylamine, pyridine, imidazole or diazabicycloundecene.

Carboxylic acid derivatives of the Formula VIa (Z in formula VI = direct linkage) can be prepared by reacting epoxides of the Formula IV with cuprates of the Formula XI:



XI VIa

The cuprates can be prepared as described in *Tetrahedron Letters 23*, (1982) 3755.

Compounds of the Formulas I and Ia can also be prepared by starting from the corresponding carboxylic acid, that is compounds of the Formulas I and Ia where R is COOH, and initially converting these in a conventional manner into an activated form, such as a halide, an anhydride or imidazolide, and then reacting the latter with an appropriate hydroxy compound HOR^{10}. This reaction can be carried out in the usual solvents and often requires addition of a base, in which case those mentioned above are suitable. These two steps can also be simplified, for example, by allowing the carboxylic acid to act on the hydroxy compound in the presence of a dehydrating agent such as a carbodiimide.

In addition, it is also possible for compounds of the Formula I to be prepared by starting from the salts of the corresponding carboxylic acids, that is from compounds of the Formulas I and Ia where R is COR^1 and R^1 is OM, where M can be an alkali metal cation or the equivalent of an alkaline earth metal cation. These salts can be reacted with many compounds of the Formula R^1-A where A is a conventional nucleofugic leaving group, for example halogen such as chlorine, bromine, iodine, or aryl- or alkylsulfonyl which is unsubstituted or substituted by halogen, alkyl or haloalkyl, such as toluenesulfonyl and methylsulfonyl, or another equivalent leaving group. Compounds of the formula R^1-A with a reactive substituent A are known or can be easily obtained with general expert knowledge. This reaction can be carried out in conventional solvents and advantageously takes place with the addition of a base, in which case those mentioned above are suitable.

The radical R in Formula I and Ia may vary widely. For example, R is a group



where R^1 has the following meanings:

a) hydrogen;

b) succinimidyloxy;

c) a five-membered heteroaromatic moiety linked by a nitrogen atom, such as pyrrolyl, pyrazolyl, imidazolyl and triazolyl, which may carry one or two halogen atoms, in particular fluorine and chlorine and/or one or two of the following radicals:

C_1-C_4-alkyl such as methyl, ethyl, 1-propyl, 2-propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 2-butyl;

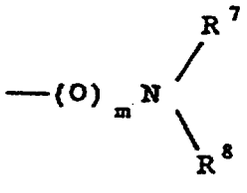
C_1-C_4-haloalkyl, in particular C_1-C_2-haloalkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, dichlorofluoromethyl, trichloromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro 2-fluoroethyl, 2,2,2-trichloroethyl and pentafluoroethyl;

C_1-C_4-haloalkoxy, in particular C_1-C_2-haloalkoxy such as difluoromethoxy, trifluoromethoxy, chlorodifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-1,1,2-trifluoroethoxy and pentafluoroethoxy, in particular trifluoromethoxy;

C_1-C_4-alkoxy such as methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy, 1-methylpropoxy, 2-methylpropoxy, 1,1-dimethylethoxy, in particular methoxy, ethoxy, 1-methylethoxy;

C_1-C_4-alkylthio such as methylthio, ethylthio, propylthio, 1-methylethylthio, butylthio, 1-methylpropylthio, 2-methylpropylthio, 1,1-dimethylethylthio, in particular methylthio and ethylthio;

d) R^1 furthermore is a radical



where m is 0 or 1 and R^7 and R^8, which can be identical or different, have the following meanings: hydrogen, C_1-C_8-alkyl, in particular C_1-C_4-alkyl as mentioned above; C_3-C_6-alkenyl such as 2-propenyl, 2-butenyl, 3-butenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-

pentenyl, 4-pentenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 3-methyl-3-butenyl, 1,1-dimethyl-2-propenyl, 1,2-dimethyl-2-propenyl, 1-ethyl-2-propenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-methyl-2-pentenyl, 4-methyl-2-pentenyl, 3-methyl-3-pentenyl, 4-methyl-3-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 3-methyl-4-pentenyl, 4-methyl-4-pentenyl, 1,1-dimethyl-2-butenyl, 1,1-dimethyl-3-butenyl, 1,2-dimethyl-2-butenyl, 1,2-dimethyl-3-butenyl, 1,3-dimethyl-2-butenyl, 1,3-dimethyl-3-butenyl, 2,2-dimethyl-3-butenyl, 2,3-dimethyl-2-butenyl, 2,3-dimethyl-3-butenyl, 1-ethyl-2-butenyl, 1-ethyl-3-butenyl, 2-ethyl-2-butenyl, 2-ethyl-3-butenyl, 1,1,2-trimethyl-2-propenyl, 1-ethyl-1-methyl-2-propenyl and 1-ethyl-2-methyl-2-propenyl, in particular 2-propenyl, 2-butenyl, 3-methyl-2-butenyl and 3-methyl-2-pentenyl;

C_3-C_6-alkynyl such as 2-propynyl, 2-butynyl, 3-butynyl, 1-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-methyl-3-butynyl, 2-methyl-3-butynyl, 1-methyl-2-butynyl, 1,1-dimethyl-2-propynyl, 1-ethyl-2-propynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-methyl-2-pentynyl, 1-methyl-2-pentynyl, 1-methyl-3-pentynyl, 1-methyl-4-pentynyl, 2-methyl-3-pentynyl, 2-methyl-4-pentynyl, 3-methyl-4-pentynyl, 4-methyl-2-pentynyl, 1,1-dimethyl-2-butynyl, 1,1-dimethyl-3-butynyl, 1,2-dimethyl-3-butynyl, 2,2-dimethyl-3-butynyl, 1-ethyl-2-butynyl, 1-ethyl-3-butynyl, 2-ethyl-3-butynyl and 1-ethyl-1-methyl-2-propynyl, preferably 2-

propynyl, 2-butynyl, 1-methyl-2-propynyl and 1-methyl-2-butynyl, in particular 2-propynyl

C_3-C_8-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, cyclooctyl, where these alkyl, cycloalkyl, alkenyl and alkynyl groups can each carry one to five halogen atoms, in particular fluorine or chlorine and/or one or two of the following groups:

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-haloalkoxy as mentioned above, C_3-C_6-alkenyloxy, C_3-C_6-alkenylthio, C_3-C_6-alkynyloxy, C_3-C_6-alkynylthio, where the alkenyl and alkynyl constituents present in these radicals preferably have the above-mentioned meanings;

C_1-C_4-alkylcarbonyl such as, in particular, methylcarbonyl, ethylcarbonyl, propylcarbonyl, 1-methylethylcarbonyl, butylcarbonyl, 1-methylpropylcarbonyl, 2-methylpropylcarbonyl, 1,1-dimenthylethylcarbonyl;

C_1-C_4-alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, 1-methylethoxycarbonyl, butyloxycarbonyl, 1-methylpropyloxycarbonyl, 2-methylpropyloxycarbonyl, 1,1-dimethylethoxycarbonyl;

C_3-C_6-alkenylcarbonyl, C_3-C_6-alkynylcarbonyl, C_3-C_6-alkenyloxycarbonyl and C_3-C_6-alkynyloxycarbonyl, where the alkenyl and alkynyl

radicals are preferably defined as detailed above;

phenyl, unsubstituted or substituted one or more times, for example, one to three times, by halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio, such as 2-fluorophenyl, 3-chlorophenyl, 4-bromophenyl, 2-methylphenyl, 3-nitrophenyl, 4-cyanophenyl, 2-trifluoromethylphenyl, 3-methoxyphenyl, 4-trifluoroethoxyphenyl, 2-methylthiophenyl, 2,4-dichlorophenyl, 2-methoxy-3-methyl-phenyl, 2,4-dimethoxyphenyl, 2-nitro-5-cyanophenyl, 2,6-difluorophenyl;

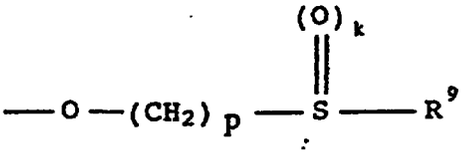
di-C_1-C_4-alkylamino such as, in particular, dimethylamino, dipropylamino, N-propyl-N-methylamino, N-propyl-N-ethylamino, diisopropylamino, N-isopropyl-N-methylamino, N-isopropyl-N-ethylamino, N-isopropyl-N-propylamino;

R^7 and R^8 furthermore phenyl which can be substituted by one or more, for example, one to three, of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio, as mentioned above in particular;

or R^7 and R^8 together form a C_4-C_7-alkylene chain which is closed to form a ring, is unsubstituted or substituted, for example, substituted by C_1-C_4-alkyl, and may contain a heteroatom selected from the group consisting of oxygen, sulfur, or

nitrogen, such as $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-(CH_2)_7-$, $-(CH_2)_2-O-(CH_2)_2-$, $-CH_2-S-(CH_2)_3-$, $-(CH_2)_2-O-(CH_2)_3-$, $-NH-(CH_2)_3-$, $-CH_2-NH-(CH_2)_2-$, $-CH_2-CH=CH-CH_2-$, $-CH=CH-(CH_2)_3-$;

e) R^1 furthermore is a group



where k is 0, 1 and 2, p is 1, 2, 3 and 4 and R^9 is C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or unsubstituted or substituted phenyl, as mentioned above in particular.

f) R^1 furthermore a radical OR^{10}, where R^{10} is:

hydrogen, the cation of an alkali metal such as lithium, sodium, potassium or the cation of an alkaline earth metal such as calcium, magnesium, and barium or an environmentally compatible organic ammonium ion such as tertiary C_1-C_4-alkyl-ammonium or the ammonium ion;

C_3-C_8-cycloalkyl as mentioned above, which may carry one to three C_1-C_4-alkyl groups;

C_1-C_8-alkyl such as, in particular, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1-

dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethylbutyl, 2-ethylbutyl, 1-ethyl-2-methylpropyl, which can carry one to five halogen atoms, in particular fluorine and chlorine and/or one of the following radicals:

C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, C_1-C_4-alkylcarbonyl, C_3-C_8-cycloalkyl, C_1-C_4-alkoxycarbonyl, phenyl, phenoxy or phenylcarbonyl, where the aromatic radicals in turn can carry in each case one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio, as mentioned above in particular;

a C_1-C_8-alkyl as mentioned above, which can carry one to five halogen atoms, in particular fluorine and/or chlorine, and carries one of the following radicals: a 5-membered heteroaromatic moiety containing one to three nitrogen atoms, or a 5-membered heteroaromatic moiety containing a nitrogen atom and an oxygen or sulfur atom, which can carry one to four halogen atoms and/or one or two of the following radicals:

nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, phenyl, C_1-C_4-haloalkoxy and/or C_1-C_4-

alkylthio. Particular mention may be made of: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-triazol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3-isopropyl-5-isoxazolyl, 3-methyl-5-isoxazolyl, 2-oxazolyl, 2-thiazolyl, 2-imidazolyl, 3-ethyl-5-isoxazolyl, 3-phenyl-5-isoxazolyl, 3-tert-butyl-5-isoxazolyl;

a C_2-C_6-alkyl group which carries one of the following radicals in position 2: C_1-C_4-alkoxyimino, C_3-C_6-alkynyloxyimino, C_3-C_6-haloalkenyloxyimino or benzyloxyimino;

a C_3-C_6-alkenyl or C_3-C_6-alkynyl group, it being possible for these groups in turn to carry one to five halogen atoms;

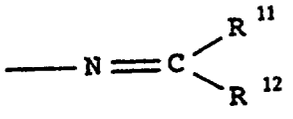
R^{10} furthermore a phenyl radical which can carry one to five halogen atoms and/or one to three of the following radicals: nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy,

C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio, as mentioned above in particular;

a 5-membered heteroaromatic moiety which is linked via a nitrogen atom, contains one to three nitrogen atoms and can carry one or two halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, phenyl, C_1-C_4-haloalkoxy and/or C_1-C_4-

alkylthio. Particular mention may be made of: 1-pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, 3,5-dimethyl-1-pyrazolyl, 3-phenyl-1-pyrazolyl, 4-phenyl-1-pyrazolyl, 4-chloro-1-pyrazolyl, 4-bromo-1-pyrazolyl, 1-imidazolyl, 1-benzimidazolyl, 1,2,4-triazol-1-yl, 3-methyl-1,2,4-tri-azol-1-yl, 5-methyl-1,2,4-triazol-1-yl, 1-benzotriazolyl, 3,4-dichloro-1-imidazolyl;

R^{10} furthermore is a group



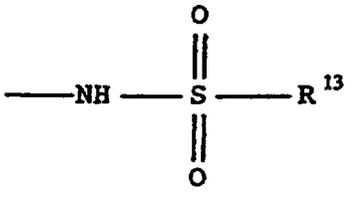
where R^{11} and R^{12}, which can be identical or different, are:

C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl, it being possible for these radicals to carry a C_1-C_4-alkoxy, C_1-C_4-alkylthio and/or an unsubstituted or substituted phenyl radical, as mentioned above in particular;

phenyl which can be substituted by one or more, for example one to three, of the following radicals: halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio, where these radicals are, in particular, those mentioned above;

or R^{11} and R^{12} together form a C_3-C_{12}-alkylene chain which can carry one to three C_1-C_4-alkyl groups and contain a heteroatom from the group consisting of oxygen, sulfur and nitrogen, as mentioned in particular for R^7 and R^8.

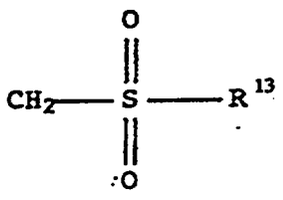
g) R^1 furthermore is a radical



where R^{13} is:
C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl as mentioned above in particular, it being possible for these radicals to carry a C_1-C_4-alkoxy, C_1-C_4-alkylthio and/or a phenyl radical as mentioned above;

phenyl, unsubstituted or substituted, in particular as mentioned above.

h) R^1 is a radical



where R^{13} has the above-mentioned meaning.

R can furthermore be:
tetrazolyl or cyano.

In a specific embodiment the carboxylic acid derivatives of the general Formula I, both as pure enantiomers and pure diastereomers or as mixture thereof, are those where the substituents have the following meanings:

R^2 hydrogen, hydroxyl, $N(C_1-C_4\text{-alkyl})_2$, the C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio groups and halogen atoms mentioned in detail for R^1, especially chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy;

X nitrogen or CR^{14} where

R^{14} is hydrogen or alkyl, or CR^{14} forms together with CR^3 a 4- to 5-membered alkylene or alkenylene ring in which, in each case, a methylene group can be replaced by oxygen or sulfur, such as $-CH_2-CH_2-O-$, $-CH=CH-O-$, $-CH_2-CH_2-CH_2-O-$, $-CH=CH-CH_2O$, in particular hydrogen, $-CH_2-CH_2-O-$, $-CH(CH_3)-CH(CH_3)-O-$, $-C(CH_3)=C(CH_3)-O-$, $-CH=C(CH_3)-O-$ or $-C(CH_3)=C(CH_3)-S$;

R^3 is hydrogen, hydroxyl, $N(C_1-C_4\text{-alkyl})_2$, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio groups and halogen atoms mentioned for R^1, especially chlorine, methyl, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy or is linked to R^{14} as mentioned above to give a 5- or 6-membered ring;

R^4 and R^5 phenyl or naphthyl, which can be substituted by one or more, for example, one to three, of the following radicals: halogen, nitro, cyano, hydroxyl, mercapto, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxycarbonyl; in particular as mentioned for R^7 and R^8, and, or example, 3-hydroxyphenyl, 4-dimethylamino-phenyl, 2-mercaptophenyl, 3-methoxycarbonylphenyl, 4-acetyl-phenyl, 1-naphthyl, 2-naphthyl, 3-bromo-2-naphthyl, 4-methyl-1-naphthyl, 5-methoxy-1-naphthyl, 6-trifluoromethyl-1-naphthyl, 7-chlor-1-naphthyl, 8-hydroxy-1-naphthyl; or R^4 and R^5 form together with the adjacent carbon atom a 3- to 6-membered ring which can contain an oxygen or sulfur atom and is unsubstituted or carries from one to three, depending on the ring size, of the following radicals:
C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio as mentioned above in general and in particular; and

phenyl or naphthyl, which are connected together in the ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group, or C_3-C_7-cycloalkyl;

R^4 C_1-C_{10}-alkyl as specifically mentioned for R^1, which can carry from one to five halogen atoms such as fluorine, chlorine, bromine, iodine, in particular fluorine and chlorine, and/or one of the following radicals: alkoxy, alkylthio, cyano, alkylcarbonyl, alkoxycarbonyl, phenyl, phenoxy,

phenyl-carbonyl as mentioned in general and in particular for R^1;

C_1-C_{10}-alkyl as mentioned above, which can carry from one to five halogen atoms as mentioned above, in particular fluorine and chlorine, and carries a 5-membered heteroaromatic ring which is unsubstituted or substituted, as mentioned above for R^1;

C_3-C_{12}-cycloalkyl, in particular C_3-C_7-cycloalkyl, or C_3-C_{12}-cycloalkenyl, in particular C_4-C_7-cycloalkenyl, it being possible for one methylene group in the saturated or unsaturated ring to be replaced by an oxygen or sulfur atom, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, cyclopropenyl, dihydrofuranyl, dihydrothienyl, dihydropyranyl, dihydrothiopyranyl, where the cycloalkyl and cycloalkenyl radicals can be substituted by from one to five halogen atoms as mentioned above, especially fluorine or chlorine, and/or one of the following radicals: C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, phenyl, phenoxy, phenylcarbonyl as mentioned above in general and in particular;

C_3-C_6-alkenyl or C_3-C_6-alkynyl as mentioned for R^1, which can carry from one to five halogen atoms as mentioned above, in particular fluorine and chlorine, and/or one of the following radicals:

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, phenyl, phenoxy, phenylcarbonyl as mentioned above in general and in particular;

5- or 6-membered hetaryl such as furyl, thienyl, pyrryl, pyrazolyl, imidazolyl, triazolyl, isoxazolyl, oxazolyl, isothiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, for example 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothizolyl, 4-isothiazolyl, 5-isothiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, oxa-2,4-diazolyl, oxa-3,4-diazolyl, thia-2,4-diazolyl, thia-3,4-diazolyl [sic] and triazolyl, where the heteroaromatic rings can carry from one to five halogen atoms as mentioned above, in particular fluorine and chlorine, and/or from one to three of the following radicals:

C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano, nitro, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, phenyl, phenoxy, phenylcarbonyl as mentioned above in general and in particular;

R^5 hydrogen, C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_8-cycloalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxyalkyl, C_1-C_4-alkylthioalkyl or phenyl as mentioned above for R^4 in particular;

R^6 is C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl as mentioned above in particular, it being possible for these radicals in each case to be substituted one or more times by: halogen, hydroxyl, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkylthio, C_1-C_6-haloalkoxy, C_1-C_4-alkylcarbonyl, hydroxycarbonyl, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, hydroxycarbonyl, C_1-C_4-alkoxycarbonyl, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino or unsubstituted or substituted phenyl or phenoxy, as mentioned above in particular;

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino or C-C_4-dialkylamino, as mentioned in particular for R^7 and R^4;

a five- or six-membered heteraromatic moiety which contains one to three nitrogen atoms and/or one sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio, as mentioned for R^4 in particular;

Y sulfur, oxygen or a single bond;

Z sulfur, oxygen -SO-, $-SO_2-$ or a single bond.

In a further embodiment, compounds of the Formula I and Ia, both as pure enantiomers and pure diastereomers or as mixture thereof, are those in which the substituents have the following meanings:

R^2 C_1-C_4-alkyl, C_1-C_4-alkoxy

X nitrogen or CR^{14}, where

R^{14} is hydrogen or alkyl, or CR^{14} forms together with CR^3 a 4- or 5-membered alkylene or alkenylene ring such as $-CH_2-CH_2-O-$, -CH=CH-O-, $-CH_2-CH_2-CH_2-O-$, $-CH=CH-CH_2O-$, in particular hydrogen, $-CH_2-CH_2-O-$, $-CH(CH_3)-CH(CH_3)-O-$, $-C(CH_3)=C(CH_3)-O-$, $-CH=C(CH_3)-O-$ or $-C(CH_3)=C(CH_3)-S$;

R^3 the C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio groups mentioned for R^1, or is linked to R^{14} as mentioned above to give a 5- or 6-membered ring;

R^4 and R^5 phenyl (identical or different) which can be substituted by one or more, for example, one to three, of the following radicals: halogen, nitro, hydroxyl, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio or

R^4 and R^5 are phenyl groups which are connected together in the ortho positions by a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO_2, NH or N-alkyl group; or

R^4 and R^5 are C_3-C_7-cycloalkyl;

R^6 C_1-C_8-alkyl, C_3-C_6-alkenyl or C_3-C_8-cycloalkyl, it being possible for these radicals in each case to be substituted one or more times by: halogen, hydroxyl, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_1-C_4-alkylthio;

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino or C_1-C_4-dialkylamino;

a five- or six-membered heteroaromatic moiety which contains a nitrogen atom and/or a sulfur or oxygen atom and which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and/or C_1-C_4-alkylthio;

Y sulfur, oxygen or a single bond;

Z sulfur, oxygen, -SO-, -SO_2- or a single bond.

The beneficial effect of the compounds can be shown in the following tests:

EVALUATION OF BIOLOGICAL ACTIVITY *IN VIVO*

Compounds of the invention may be further tested in any of the various preclinical assays for *in vivo* anticancer activity.

For example, human tumors which have been grown in nude mice can be transplanted into new recipient mice using tumor fragments which are about 50 mg in size. The day of transplantation is designated as day 0. Five to fifteen days later, the mice are treated with the test compounds given as an intravenous or intraperitoneal injection, in groups of five to ten mice at each dose. Compounds are given daily for either 5, 10 or 15 days, at dosed from 0.1 - 1000 mg/kg of body weight.

Tumor diameters and body weights are measured periodically. Tumor mass is calculated using the diameters measured with Vernier calipers, and the formula:

$$(\text{length} \times \text{width}_2)/2 = \text{mg of tumor weight}$$

Mean tumor weights are calculated for each treatment group relative tot he untreated control tumors. The DU-145 Model is a specific example of this type of assay and is described below.

DU-145 MODEL

Human tumor fragments from prostate (HTB 81), which had been grown in nude mice were implanted subcutaneously via trochar, in the dorsal side of new recipient nude mice, as is well known in the art. The day of implantation is designated as day 0.

Treatment was commenced on day 11 post implantation using Compound I-1 of Table I. There were 6 mice in each treatment group with the mode of administration and amounts administered (mg/kg of body weight) described in Table XI. Compound I-1 was administered once a day for 10 days

commencing, as earlier stated, at day 11 post implantation (Q1D x 10:11).

Table IX shows that all treatment groups responded to administration of Compound I-1, as evidenced by a reduction in the %T/C Mean Tumor Weight (MTW) value.

TABLE IX
USE OF COMPOUND I-1 IN THE DU-145 PROSTATE TUMOR MODEL

Dose	Days for Tumor Weight = 1000mg	Mean Tumor Weight (MTW) on Day 33 (mg)	MTW % T/C
Control	32.6	1232	100.00
100 mg/kg IV,Q1Dx10:11	39.3	561	45.54
150mg/kg IV,Q1DX10:11	37.4	793	64.37
150mg/kg IP,Q1DX10:11	59.3	407	33.04
220mg/kg IP,Q1DX10:11	50.9	470	38.15

RECEPTOR BINDING STUDIES

Cloned human ET_A receptor-expressing CHO cells and guinea pig cerebellar membranes with > 60 % ET_B compared with ET_A receptors were used for binding studies.

The ET_A receptor-expressing CHO cells were grown in F_{12} medium containing 10% fetal calf serum, 1% glutamine, 100 U/ml penicillin and 0.2% streptomycin (Gibco BRL, Gaithersburg, MD, USA). After 48 h, the cells were washed with PBS and incubated with 0.05% trypsin-containing PBS for 5 min. Neutralization was then carried out with F_{12} medium, and the cells were collected by centrifugation at 300 x g. To lyze the cells, the pellet was briefly washed with lysis buffer (5 mM Tris-HCl, pH 7.4 with 10% glycerol)

and then incubated at a concentration of 10^7 cells/ml of lysis buffer at 4°C for 30 min. The membranes were centrifuged at 20,000 x g for 10 min., and the pellet was stored in liquid nitrogen.

Guinea pig cerebella were homogenized in a Potter-Elvejhem homogenizer and membranes were obtained by differential centrifugation at 1000 x g for 10 min. and repeated centrifugation of the supernatant at 20,000 x g for 10 min.

BINDING ASSAYS

For the ET_A and ET_B receptor binding assay, the membranes were suspended in incubation buffer (50 mM Tris-HCl, pH 7.4 with 5 mM $MnCl_2$, 40 µg/ml; bacitracin and 0.2% BSA) at a concentration of 50 µg of protein per assay mixture and incubated with 25 pM [^{125}I]-ET_1 (ET_A receptor assay) or 25 pM [^{125}I]-RZ_3 (ET_B receptor assay) in the presence and absence of test substance at 25°C. The nonspecific binding was determined using 10^{-7} M ET_1. After 30 min., the free and bound radioligand were separated by filtration through GF/B glass fiber filters (Whatman, England) on a Skatron cell collector (Skatron, Lier, Norway) and the filters were washed with ice-cold Tris-HCl buffer, pH 7.4 with 0.2% BSA. The radioactivity collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

The K_i values shown in Table A were determined by non-linear regression analysis using the LIGAND program.

Table A shows the effect of compounds of the Formula I as the K_i [mol/l] determined in the experiments.

Table A K_i [mol/l]

Compound	ET-A	ET-B
4.42	2.5×10^{-7}	3.0×10^{-6}
4.58	1.6×10^{-7}	4.7×10^{-6}

FUNCTIONAL *in vitro* ASSAY SYSTEM TO LOOK FOR ENDOTHELIN RECEPTOR (SUBTYPE A) ANTAGONISTS

This assay system is a functional, cell-based assay for endothelin receptors. When certain cells are stimulated with endothelin 1 (ET1) they show an increase in the intracellular calcium concentration. This increase can be measured in intact cells loaded with calcium-sensitive dyes.

1-Fibroblasts which had been isolated from rats and in which an endogenous endothelin receptor of the A subtype had been detected were loaded with the fluorescent dye Fura 2-an as follows: after trypsinization, the cells were resuspended in buffer A (120 mM NaCl, 5 mM KCl, 1.5 mM $MgCl_2$, 1 mM $CaCl_2$, 25 mM HEPES, 10 mM glucose, pH 7.4) to a density of 2×10^6/ml and incubated with Fura 2-am (2 μM), Pluronics F-127 (0.04%) and DMSO (0.2%) at 37°C in the dark for 30 min. The cells were then washed twice with buffer A and resuspended at 2×10^6/ml.

The fluorescence signal from 2×10^5 cells per ml with Ex/Em 380/510 was recorded continuously at 30°C. The test substances and, after an incubation time of 3 min., ET1 were added to the cells, and the maximum change in the fluorescence was determined. The response of the cells to ET1 without previous addition of a test substance was used as control and was set equal to 100%.

Table B indicates the effect of some compounds of the Formula I as the IC_{50} [mol/l] determined in the experiments.

Table B

Compound	IC_{50} [mol/l]
4.42	7.4×10^{-7}
4.58	1.0×10^{-6}

TESTING OF ET ANTAGONISTS *in vivo*

Male SD rats weighing 250-300 g were anesthetized with amobarbital, artificially ventilated, vagotomized and pithed. The carotid artery and jugular vein were catheterized.

In control animals, intravenous administration of 1 µg/kg ET1 led to a distinct rise in blood pressure which persisted for a lengthy period.

The test animals received an i.v. injection of the test compounds (1 ml/kg) 5 min. before the administration of ET1. To determine the ET-antagonistic properties, the rise in blood pressure in the test animals was compared with that in the control animals.

ENDOTHELIN-1-INDUCED SUDDEN DEATH IN MICE

The principle of the test is the inhibition of the sudden heart death caused in mice by endothelin, which is probably induced by constriction of the coronary vessels, by pretreatment with endothelin receptor antagonists. Intravenous injection of 10 nmol/kg endothelin in a volume of 5 ml/kg of body weight results in death of the animals within a few minutes.

The lethal endothelin-1 dose is checked in each case on a small group of animals. If the test substance is administrated intravenously, the endothelin-1 injection

which was lethal in the reference group usually takes place 5 min. thereafter. With other modes of administration, the times before administration are extended, where appropriate up to several hours.

The survival rate is recorded, and effective doses which protect 50% of the animals (ED 50) from endothelin-induced heart death for 24 h. or longer are determined.

FUNCTIONAL TEST ON VESSELS FOR ENDOTHELIN RECEPTOR ANTAGONISTS

Segments of rabbit aorta are, after an initial tension of 2 g and a relaxation time of 1 h. in Krebs-Henseleit solution at 37°C and pH 7.3-7.4, first induced to contract with K^+. After washing out, an endothelin dose-effect plot up to the maximum is constructed.

Potential endothelin antagonists are administered to other preparations of the same vessel 15 min. before starting the endothelin dose-effect plot. The effects of the endothelin are calibrated as a % of the K^+-induced contraction. Effective endothelin antagonists result in a shift to the right in the endothelin dose-effect plot.

Synthesis examples of Compound of Formula Ia

Example 1

Methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate

5g (19.6 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate were dissolved in 50 ml of absolute methanol and, at 0°C, 0.1 ml of boron trifluoride etherate was added. The mixture was stirred at 0°C for 2 h. and at room temperature for a further 12 h. The solution vent was distilled out, the residue was taken up in ethyl acetate, washed with

sodium bicarbonate solution and water and dried over magnesium sulfate. After removal of the solvent by distillation there remained 5.5g (88%) of a pale yellow oil.

Example 2
Methyl 2-hydroxy-3-phenoxy-3,3-diphenylpropionate

5g (19.6 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate and 5.6g (60 mmol) of phenol were heated together at 100°C for 6 h. Removal of the excess phenol by distillation under high vacuum and purification of the residue by chromatography on silica gel with hexane/ethyl acetate mixtures resulted in 4.9g (77%) of a pale yellow oil.

Example 3
Methyl 2-(4,6-dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate

2.86g (10 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenyl-propionate were dissolved in 40 ml of dimethylformamide, and 0.3g (12 mmol) of sodium hydride was added. The mixture was stirred for 1 h. and then 2.2g (10 mmol) of 4,6-dimethoxy-2-methylsulfonylpyrimidine were added. After stirring at room temperature for 24 h., cautious hydrolysis was carried out with 10 ml of water, the pH was adjusted to 5 with acetic acid, and the solvent was removed by distillation under high vacuum. The residue was taken up in 100 ml of ethyl acetate, washed with water and dried over magnesium sulfate, and the solvent was distilled out. The residue was mixed with 10 ml of ether, and the resulting precipitate was filtered off with suction. After drying, 3.48g (82%) of a white powder remained.

Example 4
2-(4,6-Dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid

2.12g (5 mmol) of methyl 2-(4,6-dimethoxy-pyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml of dioxane, 10 ml of 1 N KOH solution were added, and the mixture was stirred at 100°C for 3 h. The solution was diluted with 300 ml of water and extracted with ethyl acetate to remove unreacted ester. The aqueous phase was then adjusted to pH 1-2 with dilute hydrochloric acid and extracted with ethyl acetate. After drying over magnesium sulfate and removal of the solvent by distillation, the residue was mixed with an ester/hexane mixture, and the precipitate which formed was filtered off with suction. After drying, 1.85g (90%) of a white powder remained.

Melting point 167°C

Example 5
Sodium 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenyl-propionate

1.68g (4 mmol) or 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionic acid are dissolved in 4 ml of 1N NaOH + 100 ml of water. The solution is freeze-dried, and the sodium salt of the carboxylic acid used is obtained quantitatively.

10g (34.9 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml each of methanol and glacial acetic acid, 1 ml of $RuO(OH)_2$ in dioxane was added, and hydrogenation was carried out with H_2 in an autoclave at 100°C under 100 bar for 30 h. The catalyst was filtered off, the mixture was concentrated, mixed with

ether and washed with NaCl solution, and the organic phase was dried and concentrated. 10,1g of methyl 3,3-dicyclohexyl-2-hydroxy-3-methoxypropionate were obtained was an oil.

Example 7
Methyl 2-(4,6-dimethoxy-pyrimidin-2-ylthio)-3-methoxy-3,3-diphenylpropionate

7.16g (25 mmol) of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropionate were dissolved in 50 ml of dichloromethane, 3g (30 mmol) of triethylamine were added, and 3.2g (28 mmol) of methane-sulfonyl chloride were added dropwise while stirring. The mixture was stirred at room temperature for 2 h., washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken up in DMF and added dropwise at 0°C to a suspension of 12.9g (75 mmol) of 4,6-dimethoxypyrimidine-2-thiol and 8.4g (100 mmol) of sodium bicarbonate in 100 ml of DMF. After stirring at room temperature for 2 h. and at 60°C for a further 2 h., the mixture was poured into 1 liter of ice-water, and the resulting precipitate was filtered off with suction. After drying, 3.19g (29%) of a white powder remained.

Example 8
Methyl 2-hydroxy-3,3-diphenylbutyrate

1.5g (5.9 mmol) of methyl 3,3-diphenyl-2,3-epoxypropionate dissolved in 10 ml of absolute ether were added dropwise to a cuprate solution which had been prepared from 635 mg (7 mmol) of copper(I) cyanide dissolved in 10 ml of absolute ether and 8.14 ml (13 mmol) of a 1.6 normal methyllithium solution and had been cooled to -78°C. The solution was stirred at -78°C for 1 h. and then allowed to warm to room

temperature. It was subsequently diluted with 100 ml of ether and 100 ml of water, and the ether phase was washed with dilute citric acid and with sodium bicarbonate solution and dried over magnesium sulfate. The crude product was purified by chromatography on silica gel with cyclohexane/ethyl acetate mixtures to result in 250 mg (16%) of a pale yellow oil.

Example 9
2-Hydroxy-3-methoxy-3,3-diphenylpropionic acid

91.11g (0.5 mol) of benzophenone and 45.92g (0.85 mol) of sodium methoxide were suspended in 150 ml of methyl tert-butyl ether (MTB) at room temperature. After cooling to -10°C, 92.24g (0.85 mol) of methyl chloroacetate were added in such a way that the internal temperature rose to 40°C while continuing to cool in a bath at -10°C. The mixture was then stirred without cooling at the autogenous temperature for one hour. After addition of 250 ml of water and brief stirring, the aqueous phase was separated off. The MTB phase was washed with 250 ml of dilute sodium chloride solution. After the solvent had been changed to methanol (250 ml), a solution of 1g of p-toluenesulfonic acid in 10 ml of methanol was added at room temperature. The mixture was stirred at autogenous temperature for one hour and then heated to reflux. While distilling out the methanol, 400g of a 10% strength sodium hydroxide solution was added dropwise, and finally 60 ml of water were added. The methanol was distilled out until the bottom temperature reached 97°C. After cooling to 55°C, 190 ml of MTB were added and the mixture was acidified to pH 2 with about 77 ml of concentrated HCl. After cooling to room temperature, the aqueous phase was separated off and the organic phase was concentrated by distilling out 60 ml of MTB. The product was crystallized by adding 500 ml of heptane and

slowly cooling to room temperature. The coarsely crystalline solid was filtered off with suction, washed with heptane and dried to constant weight in a vacuum oven at 40°C.

Yield: 108.9g (80%), HPLC >99.5% area.

Example 10

S-2-Hydroxy-3-methoxy-3,3-diphenylpropionic acid (racemate resolution with L-proline methyl ester)

148.8g of a 30% strength methanolic sodium methanolate solution (0.826 mol) were added dropwise to 240g of a 57% strength methanolic L-proline methyl ester hydrochloride solution (0.826 mol) at room temperature, and 2.4 l of MTB and 225g (0.826 mol) of 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid were added. After 2680 mol of MTB/methanol mixture had been distilled out with simultaneous dropwise addition of 2.4 l of MTB, the mixture was slowly cooled to room temperature, the crystals (R-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid x L-proline methyl ester) were filtered off with suction, and the solid was washed with 150 ml of MTB. The filtrate was concentrated by distilling out 1.5 l of MTB, and 1.0 l of water was added. The pH was adjusted to 1.2 with concentrated hydrochloric acid at room temperature and, after stirring and phase separation, the aqueous phase was separated off and extracted with 0.4 l of MTB. The combined organic phases were extracted with 0.4 l of water. The residue after the MTB had been stripped off was dissolved in 650 ml of toluene under reflux, and the product was crystallized by seeding and slow cooling. Filtration with suction, washing with toluene and drying in a vacuum oven resulted in 78.7g of S-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (yield 35% based on the racemate).

Chiral HPLC: 100% pure
HPLC: 99.8%

Example 11
S-2-Hydroxy-3-methoxy-3,3-diphenylpropionic acid (racemate resolution with (S)-1-(4-nitrophenyl)ethylamine)

30.5g (0.184 mol) of (S)-1-(4-nitrophenyl)ethylamine were added to 100g (0.368 mol) of 2-hydroxy-3-methoxy-3,3-diphenylpropionic acid in 750 ml of acetone and 750 ml of MTB under reflux, the mixture was seeded, boiled under reflux for one hour and slowly cooled to room temperature for crystallization. The crystals (S-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid x (S)-1-(4-nitrophenyl)ethylamine) were filtered off with suction and washed with MTB. The residue was suspended in 500 ml of water and 350 ml of MTB and then the pH was adjusted to 1.2 with concentrated hydrochloric acid at room temperature, and, after stirring and phase separation, the aqueous phase was separated off and extracted with 150 ml of MTB. The combined organic phases were extracted with 100 ml of water. 370 ml of MTB were distilled out and then 390 ml of n-heptane were added under reflux, and the mixture was slowly cooled to room temperature while the product crystallized. Filtration with suction, washing with n-heptane and drying in a vacuum oven resulted in 35.0g of S-2-hydroxy-3-methoxy-3,3-diphenylpropionic acid (yield 35% based on the racemate).
Chiral HPLC: 100% pure
HPLC: 99.8%

Example 12
Benzyl 3-methoxy-2-(4-methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-yloxy)-3,3-diphenylpropionate

24.48g (90 mmol) of 3-methoxy-3,3-diphenyl-2-hydroxypropionic acid were dissolved in 150 ml of DMF, and 13.7g (99 mmol) of potassium carbonate were added. The suspension was stirred at room temperature for 30 min. Then 10.7 ml (90 mmol) of benzyl bromide were added dropwise over the course of 5 min., and the mixture was stirred for 1 h., during which the temperature rose to 32°C.

To this mixture were successively added 24.84g (180 mmol) of K_2CO_3 and 20.52g (90 mmol) of 2-methanesulfonyl-4-methoxy-6,7-dihydro-5H-0cyclopentapyrimidine, and the mixture was stirred at 80°C for 3 h.

For workup, the contents of the flask were diluted with about 600 ml of H_20 and cautiously acidified with concentrated HCl, and 250 ml of ethyl acetate were added. 31.4g of pure product precipitated and were filtered off.

The ethyl acetate phase was separated from the mother liquor, the aqueous phase was extracted again with ethyl acetate, and the combined organic phases were concentrated. The oily residue (19g) was purified by chromatography (cyclohexane/ethyl acetate = 9/1) to result in a further 10.5g of pure product.

Total yield: 41.9g (82.2 mmol) = 91%
Melting point 143-147°C
MS: MH+ = 511

Example 13
3-Methoxy-2-(4-methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-yl-oxy)-3,3-diphenylpropionic acid

40g (78.4 mmol) of benzyl 3-methoxy-2-(4-methoxy-6,7-dihydro-5H-cyclopentapyrimidin-2-yloxy)-3,3-diphenylpropionate were dissolved in 400 ml of ethyl acetate/methanol (4:1), about 500 mg of palladium on active carbon (10%) were added, and the mixture was exposed to a hydrogen atmosphere until no further gas was taken up. The catalyst was filtered off, the solution was evaporated, and the residue was crystallized from ether.

Example 14

Ethyl 2S-3,3-diphenyloxirane-2-carboxylate

2.57g (10.2 mmol) of ethyl 3,3-diphenylacrylate and 464 mg of 4-phenylpyridine N-oxide were dissolved in 24 ml of methylene chloride, and 432 mg (6.5 mol%) of (S,S)-(+)-N,N'-bis(3,5-ditert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride were added. While cooling in ice, 6.4 ml of a 12% strength sodium hypochlorite solution were added, and the mixture was stirred while cooling in ice for 30 min. and at room temperature overnight. The solution was diluted to 200 ml with water, extracted with ether, dried and evaporated. 2.85g of a colorless oil were obtained. Purification by MPLC (cyclohexane:ethyl acetate = 9:1) resulted in 1.12g of oil with an enantiomer ratio of about 8:1 in favor of the S configuration.

^{1}H-=NMR [$CDCl_3$],
δ = 1.0 (t, 3H); 3.9 (m, 3H); 7.3 (m, 10H)

Example 15

2-Methylthio-6,7-dihydro-5H-cyclopentapyrimidin-4-ol

46.9g (330 mmol) of methyl cyclopentanone-2-carboxylate and 53.5g (192 mmol) of S-methylisothiourea sulfate were

successively added to 29.6g (528 mmol) of KOH in 396 ml of methanol, and the mixture was stirred at room temperature overnight, acidified with 1N hydrochloric acid and diluted with water. The crystals which separated out were filtered off with suction and dried. 20g of crystals were obtained.

Example 16
4-Chloro-2-methylthio-6,7-dihydro-5H-cyclopentapyrimidine

255 ml of phosphorus oxychloride were added to 20g (110 mmol) of Example 15, and the mixture was stirred at 80°C for 3 hours. Phosphorus oxychloride was evaporated off, ice was added to the residue, and the crystals which separated out were filtered off with suction. 18.5g of a brownish solid were obtained.

Example 17
4-Methoxy-2-methylthio-6,7-dihydro-5H-cyclopentapyrimidine

18.05g (90 mmol) of 4-chloro-2-methylthio-6,7-dihydro-5H-cyclopentapyrimidine were dissolved in 200 ml of methanol. At 45°C, 16.7g of sodium methoxide (as 30% strength solution in methanol) were added dropwise, and the mixture was stirred for 2 hours. The solution was evaporated, taken up in ethyl acetate and acidified with dilute hydrochloric acid, and the ethyl acetate extract was evaporated. 15.5g of an oil remained.

^{1}H-NMR [DMSO],
δ = 2.1 (quintet, 2H); 2.5 (s, 3H);
2.8 (dt, 4H); 3.9 (s, 3H) ppm

Example 18
2-Methylthio-4-methoxy-6,7-dihydro-5H-cyclopentapyrimidine

15g (76.2 mmol) of 4-methoxy-2-methylthio-6,7-dihydro-5H-cyclo-pentapyrimidine were dissolved in 160 ml of glacial acetic acid/methylene chloride (1:1), and 1.3g of sodium tungstate were added. At 35°C, 17.5 ml (170 mmol) of a 30% strength H_2O_2 solution were added dropwise. The mixture was then diluted with 500 ml of water and 100 ml of methylene chloride, and the organic phase was separated off, dried and evaporated. 14g of oil remained and were crystallized from ether.

^{1}H=NMR [$CDCl_3$],
δ = 2.2 (quintet, 2H); 3.0 (dt., 4H);
3.3 (s, 3H); 4.1 (s, 3H) ppm

Example 19
1-Benzenesulfonyl-3-(4,6-dimethoxy-2-pyrimidinyloxy)-4-methoxy-4,4-diphenyl-2-butanone

0.37g (2.4 mmol) of phenyl methyl sulfone were dissolved in 10 ml of dry THF and then, at -70°C, 2 eq. of butyllithium (2.94 ml; 1.6 molar solution in hexane) were added dropwise. After 1 h. at -70°C, 1g (2.4 mmol) of methyl 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionate dissolved in 5ml of THF was added dropwise. The reaction mixture was then stirred at -70°C for 1 h. and at -10°C for 1 h. and then warmed to room temperature.

For workup, about 10 ml of saturated NH_4Cl solution were added dropwise, thorough extraction with ethyl acetate was carried out, and the combined organic phases were washed with saturated NaCl solution and dried over NA_2SO_4. The

residue obtained after drying and concentration was purified by chromatography on silica gel (n-heptane/ethyl acetate 15% → 30%) and subsequently MPLC on RP silica gel (acetonitrile/H_2O + TFA); 0.3g of a white amorphous powder was obtained as product.

Example 20
3,3-Diphenyloxirane-2-carbonitrile

3.1g (54.9 mmol) of sodium methoxide were suspended in 20 ml of dry THF and then, at -10°C, a mixture of 5g (27.4 mmol) of benzophenone and 4.2g (54.9 mmol) of chloroacetonitrile was added dropwise.

The reaction mixture was stirred at -10°C for about 2 h., then poured into water and extracted several times with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated, and the residue was purified by chromatography on silica gel (n-heptane/ethyl acetate). Yield: 1.2g (20%)

^{1}H-NMR [$CDCl_3$],
δ = 3.9 (s, 1H); 7.4-7.5 (m, 10 H) ppm

Example 21
2-Hydroxy-3-methoxy-3,3-diphenylpropionitrile

6.5g (29.4 mmol) of 3,3-diphenyloxirane-2-carbonitrile were dissolved in 60 ml of methanol and, at 0°C, about 2ml of boron trifluoride etherate solution were added. The mixture was stirred further at 0°C for 1 h. and then at room temperature overnight. For workup it was diluted with diethyl ether and washed with saturated NaCl solution, and the organic phase was dried over Na_2SO_4 and concentrated.

The residue comprised 7.3g of a white amorphous powder which was used directly in the subsequent reactions.

^{1}H-NMR [$CDCl_3$],
δ = 2.95 (broad s, OH), 3.15 (s, 3H),
5.3 (s, 1H), 7.3-7.5 (m, 10) ppm

Example 22
2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methoxy-3,3-diphenylpropionitrile

7.3g (28.8 mmol) of 2-hydroxy-3-methoxy-3,3-diphenylpropionitrile were dissolved in 90 ml of DMF, and 4g (28.8 mmol) of K_2CO_3 and 6.3g (28 mmol) of 2-methanesulfonyl-4,6-dimethoxypyrimidine were added. The mixture was stirred at room temperature for about 12 h., then poured into water and extracted with ethyl acetate. The combined organic phases were washed again with H_2O, dried and concentrated. The residue obtained in this way was then purified by chromatography on silica gel (n-heptane/ethyl acetate).
Yield: 6.9g of white amorphous powder

FAB-MS: 392 ($M+H^+$)
^{1}ZHZ-NMR [$CDCl_3$],
δ = 3.3 (s, 3H); 4.95 (s, 6H), 5.85 (s, 1H);
6.3(s, 1H); 7.3-7.5 (m, 10H) ppm

Example 23
5-[1-(4,6-Dimethoxy-2-pyrimidinyloxy)-2-methoxy-2,2-diphenyl-ethyl]-1H-tetrazole

0.5g (1.3 mmol) of nitrile was dissolved in 10 ml of toluene, and 85mg (1.3 mmol) of NaN_3 and 460 mg (1.4 mmol) of Bu_3SnCl were successively added, and then the mixture

was refluxed for about 40 h. Cooling was followed by dilution with ethyl acetate and washing with 10% aqueous KF solution and with NaCl solution. After drying over $MgSO_4$ and concentration there remained 1.0g of a yellow oil, which was purified by chromatography on silica gel (n-heptane/ethyl acetate).

Concentration of the fractions resulted in 60 mg of the 1H-tetrazole and 110 mg of the 1-methyltetrazole, each as amorphous white solids.

5-[1-(4,6-Dimethoxy-2-pyrmidinyloxy)-2-methoxy-2,2-diphenylethyl]-1H-tetrazole

Electrospray-MS: 435 ($M+H^+$)
^1H-NMR ($CDCl_3$):
δ (ppm) 3.28 (s, 3H), 3.85 (s, 6H), 5.75 (s, 1H), 7.25-7.40 (m, 10H), 7.50 (s, 1H).

5-[1-(4,6-Dimethoxy-2-pyrimidinyloxy)-2-methoxy-2,2-diphenylethyl]-1-methyltetrazole

Electrospray-MS; 471 ($M+H^+$)
^1H-NMR ($CDCl_3$):
δ (ppm) 3.0 (s, 3H), 3.35 (s, 3H), 3.80 (s, 6H), 5.75 (s, 1H)
7.30-7.40 (m, 11H).

Example 24

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methylsulfinyl-3,3-diphenylpropionic acid

1.2g (2.9 mmol) of 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methylthio-3,3-diphenylpropionic acid were introduced into

15 ml of glacial acetic acid at 0°C and 294 µl of 30% strength H_2O_2 were added dropwise. The mixture was stirred at room temperature overnight, poured into water, extracted with CH_2Cl_2 and washed with sodium thiosulfate solution and brine. After drying, 1g of substance was isolated as a white foam.

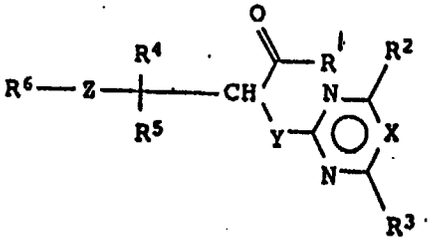
Example 25

2-(4,6-Dimethoxy-2-pyrimidinyloxy)-3-methylsulfonyl-3,3-diphenylpropionic acid

0.6g (1.45 mmol) of 2-(4,6-dimethoxy-2-pyrimidinyloxy)-3-methyl-sulfinyl-3,3-diphenylpropionic acid was introduced into 15 ml of glacial acetic acid at room temperature, and 294 µl of 30% strength H_2O_2 were added dropwise. The mixture was stirred at room temperature overnight, heated at 50°C for a further 3 h., poured into water and washed with sodium thiosulfate solution and brine. After drying, 400 mg were isolated as a white solid.

The compounds listed in Table I can be prepared in a similar way.

Table I



No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-1	OMe	Phenyl	Methyl	OMe	OMe	CH	O	O	81
I-2	OH	Phenyl	Methyl	OMe	OMe	CH	O	O	167
I-3	OH	Phenyl	CH_2-CH_2-S-CH_3	OMe	OMe	CH	O	O	
I-4	OH	Phenyl	Ethyl	OMe	OMe	CH	O	O	81 (decomp.)
I-5	OH	Phenyl	iso-Propyl	OMe	OMe	CH	O	O	182
I-6	OH	Phenyl	Methyl	OMe	OMe	CH	O	S	168
I-7	OH	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	CH	O	O	
I-8	OH	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	CH	S	O	
I-9	OH	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	C-$CH(CH_3)_2$	O	O	
I-10	OH	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	OMe	C-$CH(CH_3)_3$	O	O	
I-11	OH	Phenyl	CH_2-CH_2-SO_2-$CH(CH_3)_2$	OMe	NH-OCH_3	CH	O	O	
I-12	OH	Phenyl	n-Propyl	OMe	OMe	CH	O	O	174
I-13	OMe	Phenyl	n-Propyl	OMe	OMe	CH	O	O	
I-14	OH	Phenyl	n-Propyl	OEt	OEt	CH	O	O	

Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-15	OH	Phenyl	n-Butyl	OMe	OMe	CH	O	O	
I-16	OH	Phenyl	iso-Butyl	OMe	OMe	CH	O	O	
I-17	OH	Phenyl	iso-Butyl	OMe	O-CH_2-CH_2-C		O	O	
I-18	OH	Phenyl	tert.-Butyl	OMe	OMe	CH	O	O	
I-19	OH	Phenyl	Cyclopropyl	OMe	OMe	CH	O	O	
I-20	OH	Phenyl	Cyclopentyl	OMe	OMe	CH	O	O	
I-21	OH	Phenyl	Cyclohexyl	OMe	OMe	CH	O	O	
I-22	OH	Phenyl	$(CH_3)_3C$-CH_2-CH_2	OEt	OEt	CH	O	O	
I-23	OH	Phenyl	$(CH_3)_2CH$-CH_2-CH_2-CH_2	OMe	OMe	CH	O	O	173
I-24	OH	Phenyl	HO-CH_2-CH_2	OMe	OMe	CH	O	O	
I-25	OH	Phenyl	HO_2C-$(CH_2)_2$-	OMe	OMe	CH	O	O	
I-26	OH	Phenyl	Cyclopropylmethyl	OMe	OMe	CH	O	O	115
I-27	OH	Phenyl	H	OMe	OMe	CH	O	O	
I-28	OH	Phenyl	Methyl	OMe	OMe	CH	O	-	
I-29	OH	Phenyl	Phenyl	OMe	OMe	CH	O	O	136
I-30	OH	Phenyl	Phenyl	OMe	O-$CH(CH_3)$-CH_2-C		O	O	
I-31	OMe	Phenyl	Phenyl	OMe	OMe	CH	O	O	
I-32	OH	Phenyl	4-Isopropyl-Phenyl	OMe	OMe	CH	O	O	
I-33	OH	Phenyl	4-Me-S-Phenyl	OMe	OMe	CH	O	O	
I-34	OH	Phenyl	4-Me-O-Phenyl	OMe	OMe	CH	O	O	
I-35	OH	Phenyl	3-Et-Phenyl	OMe	OMe	CH	O	O	
I-36	OH	Phenyl	2-Me-Phenyl	OMe	OMe	CH	O	O	

Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-37	OH	Phenyl	2-Cl-Phenyl	OMe	OMe	CH	O	O	
I-38	OH	Phenyl	3-Br-Phenyl	OMe	OMe	CH	O	O	
I-39	OH	Phenyl	4-F-Phenyl	OMe	OMe	CH	O	O	
I-40	OH	Phenyl	4-F-Phenyl	OMe	OMe	CH	S	O	
I-41	OH	Phenyl	4-CH_3-Phenyl	OMe	OMe	CH	O	O	
I-42	OH	Phenyl	3-NO_2-Phenyl	OMe	OMe	CH	O	O	
I-43	OH	Phenyl	2-HO-Phenyl	OMe	OMe	CH	O	O	
I-44	OH	Phenyl	3,4-Dimethoxyphenyl	OMe	OMe	CH	O	O	
I-45	OH	Phenyl	3,4-Methylenedioxyphenyl	OMe	OMe	CH	O	O	
I-46	OH	Phenyl	3,4,5-Trimethoxyphenyl	OMe	OMe	CH	O	O	
I-47	OH	Phenyl	Benzyl	OMe	OMe	CH	O	O	
I-48	OH	Phenyl	2-Cl-Benzyl	OMe	OMe	CH	O	O	
I-49	OH	Phenyl	3-Br-Benzyl	OMe	OMe	CH	O	O	
I-50	OH	Phenyl	4-F-Benzyl	OMe	OMe	CH	O	O	
I-51	OH	Phenyl	2-Me-Benzyl	OMe	OMe	CH	O	O	
I-52	OH	Phenyl	2-Me-Benzyl	OMe	O-CH=CH-C		O	O	
I-53	OH	Phenyl	3-Et-Benzyl	OMe	OMe	CH	O	O	
I-54	OH	Phenyl	4-Iso-Propyl-Benzyl	OMe	OMe	CH	O	O	
I-55	OH	Phenyl	4-NO_2-Propyl-Benzyl	OMe	OMe	CH	O	O	
I-56	OH	Phenyl	2-Me-5-Propyl-Benzyl	OMe	OMe	CH	O	O	
I-57	OH	Phenyl	2-Me-5-Propyl-Benzyl	OEt	OEt	CH	O	O	
I-58	OH	Phenyl	4-Me-2-Propyl-Benzyl	OMe	OMe	CH	O	O	

Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-59	OH	Phenyl	3,4-Methylenedioxybenzyl	OMe	OMe	CH	O	O	
I-60	OH	4-F-Phenyl	Methyl	OMe	OMe	CH	O	O	163-165 (decomp.)
I-61	OMe	4-F-Phenyl	Methyl	OEt	OEt	CH	O	O	
I-62	OH	4-Cl-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-63	OH	4-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-64	OH	4-Me-O-Phenyl	Ethyl	OMe	OMe	CH	O	O	
I-65	OH	4-Me-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-66	OH	4-Me-Phenyl	Methyl	OMe	$O-CH_2-CH_2-C$		O	O	
I-67	OH	3-CF_3-Phenyl	n-Propyl	OMe	OMe	CH	O	O	
I-68	OH	3-CF_3-Phenyl	n-Propyl	OMe	$O-CH(CH_3)-CH_2-C$		O	O	
I-69	OH	4-NO_2-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-70	OH	4-NO_2-Phenyl	Methyl	OMe	O-CH=CH-C		O	O	
I-71	OH	3-Cl-Phenyl	Ethyl	OMe	OMe	CH	O	O	
I-72	OH	2-F-Phenyl	Methyl	OMe	OMe	CH	O	O	193-194 (decomp.)
I-73	OH	2-F-Phenyl	Methyl	OMe	OMe	CH	S	O	
I-74	OH	2-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-75	OH	2-Me-O-Phenyl	Methyl	OMe	OMe	CH	O	S	
I-76	OH	3,4-Dimethoxyphenyl	Methyl	OMe	OMe	CH	O	O	
I-77	OH	3,4-Methylenedioxyphenyl	Methyl	OMe	OMe	CH	O	O	
I-78	OH	p-CF_3-Phenyl	Methyl	OMe	OMe	CH	O	O	
I-79	OH	Phenyl	Methyl	OMe	OEt	CH	O	O	

Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-80	OMe	Phenyl	Methyl	OMe	OEt	CH	S	O	
I-81	OH	Phenyl	Ethyl	OMe	NH-OMe	CH	O	O	
I-82	OH	p-Me-O-Phenyl	n-Propyl	OMe	OCF_3	CH	O	O	
I-83	OH	Phenyl	Methyl	OMe	CF_3	CH	O	O	
I-84	OH	Phenyl	Methyl	OMe	CF_3	N	O	O	
I-85	OH	3,4-Dimethoxyphenyl	Benzyl	Me	Me		O	O	
I-86	OH	3,4-Dimethoxyphenyl	Methyl	OMe	$O\text{-}CH_2\text{-}CH_2\text{-}C$		O	O	
I-87	OH	Phenyl	Methyl	OMe	$O\text{-}CH_2\text{-}CH_2\text{-}C$		O	O	126 (decomp.)
I-88	OH	Phenyl	Methyl	OMe	$O\text{-}CH(CH_3)\text{-}CH_2\text{-}C$		O	O	
I-89	OH	Phenyl	Methyl	OMe	$N(CH_3)\text{-}CH{=}CH\text{-}C$		O	O	118
I-90	OH	Phenyl	Methyl	OMe	$S\text{-}C(CH_3){=}C(CH_3)\text{-}C$		O	O	
I-91	OH	Phenyl	Methyl	OMe	$O\text{-}C(CH_3){=}CH\text{-}C$		O	O	
I-92	OH	Phenyl	Methyl	Me	$O\text{-}C(CH_3){=}CH\text{-}C$		O	O	
I-93	OH	Phenyl	Methyl	Me	$O\text{-}CH{=}CH\text{-}C$		O	O	
I-94	OH	4-F-phenyl	Methyl	Me	$S\text{-}CH{=}CH\text{-}C$		O	O	
I-95	OH	4-F-phenyl	H	OMe	OMe	CH	O	O	
I-96	OH	Phenyl	Methyl	OMe	$CH_2\text{-}CH_2\text{-}CH_2\text{-}C$		O	O	149-151 (decomp.)
I-97	OH	Phenyl	Methyl	Methyl	$CH_2\text{-}CH_2\text{-}CH_2\text{-}C$		O	O	157 (decomp.)
I-98	OH	Phenyl	Methyl	Ethyl	$CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}C$		O	O	
I-99	OH	Phenyl	Methyl	OMe	$CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}C$		O	O	
I-100	OH	Phenyl	Methyl	Me	Me	CH	O	O	
I-101	OH	Phenyl	Methyl	Et	Et	CH	O	O	

Table I (continued)

No.	R'	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-102	OH	Phenyl	Methyl	Me	Me	C-CH_3	O	O	
I-103	OH	Phenyl	Methyl	OMe	Me	CH	O	O	
I-104	OH	Cyclohexyl	Methyl	OMe	OMe	CH	O	O	
I-105	OH	Cyclohexyl	Methyl	OMe	CH_2-CH_2-CH_2-C		O	O	
I-106	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	S	S	
I-107	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	S	134
I-108	OCH_3	Phenyl	Methyl	OCH_3	OCH_3	CH	S	S	
I-109	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-110	OCH_3	2-Fluorophenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-111	OC_2H_5	3-Chlorophenyl	Methyl	OCH_3	OCH_3	N	O	O	
I-112	$ON(CH_3)_2$	4-Bromophenyl	Methyl	CF_3	CF_3	CH	S	O	
I-113	O-CH_2-C=CH	Phenyl	Ethyl	OCH_3	CF_3	CH	O	O	
I-114	OH	Phenyl	Propyl	OCH_3	OCF_3	CH	O	S	
I-115	OCH_3	Phenyl	i-Propyl	OCH_3	CH_3	CH	O	O	
I-116	OC_2H_5	Phenyl	s-Butyl	OCH_3	Cl	CH	S	O	
I-117	$ON(CH_3)_2$	2-Methylphenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-118	$ON(CH_3)_2$	3-Methoxyphenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-119	$ON=C(CH_3)_2$	4-Nitrophenyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-120	$ON(CH_3)_2$	Phenyl	1-Phenylpropyn-3-yl	OCH_3	OCF_3	N	O	S	
I-121	$ON=C(CH_3)_2$	2-Hydroxyphenyl	Methyl	OCH_3	CH_3	N	O	O	
I-122	$ONSO_2C_6H_5$	3-Trifluoromethylphenyl	Methyl	OCH_3	Cl	N	O	O	
I-123	NHPhenyl	4-Dimethylaminophenyl	Methyl	OCH_3	OCH_3	CH	S	O	

Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-124	OC_2H_5	Phenyl	Trifluoroethyl	CH_3	CH_3	CH	O	O	
I-125	$ON(CH_3)_2$	Phenyl	Benzyl	Cl	Cl	CH	O	O	
I-126	$ON(CH_3)_2$	Phenyl	2-Methoxyethyl	OCH_3	-O-CH_2-CH_2-		S	O	
I-127	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-128	OH	Phenyl	Phenyl	OCH_3	-O-CH_2-CH_2-		O	O	
I-129	OH	Phenyl	Phenyl	OCH_3	OCH_3	N	O	O	
I-130	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	O	
I-131	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	S	
I-132	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	S	
I-133	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-134	OH	Phenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-135	OH	-$(CH_2)_5$-	Phenyl	Phenyl	OCH_3	CH	O	O	
I-136	OH	Phenyl	2-Thiazolyl	OCH_3	OCH_3	CH	O	O	
I-137	OCH_3	2-Fluorophenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-138	OC_2H_5	3-Chlorophenyl	Phenyl	OCH_3	OCH_3	N	O	O	
I-139	$ON(CH_3)_2$	4-Bromophenyl	Phenyl	CF_3	CF_3	CH	O	O	
I-140	O-CH_2=CH	Phenyl	2-Fluorophenyl	OCH_3	CF_3	CH	O	O	
I-141	OH	Phenyl	3-Chlorophenyl	OCH_3	OCF_3	CH	O	S	
I-142	OCH_3	Phenyl	4-Bromophenyl	OCH_3	CH_3	CH	O	O	
I-143	OC_2H_5	Phenyl	4-Thiazolyl	OCH_3	Cl	CH	S	O	
I-144	$ON(CH_3)_2$	2-Methylphenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-145	$ON=C(CH_3)_2$	3-Methoxyphenyl	Phenyl	OCH_3	OCH_3	CH	O	O	

Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-146	OH	Phenyl	Methyl	OCH_3	-CH_2-CH_2-CH_2-C		O	O	
I-147	OH	4-Fluorophenyl	Methyl	OCH_3	OCH_3	CH	O	O	168 (decomp.)
I-148	OH	4-Fluorophenyl	Methyl	OCH_3	-CH_2-CH_2-CH_2-C		O	O	
I-149	NH-SO-C_6H_5	4-Nitrophenyl	Phenyl	OCH_3	OCH_3	CH	O	O	
I-150	OCH_3	Phenyl	3-Imidazolyl	OCH_3	-O-CH_2-CH_2		O	O	
I-151	OC_2H_5	Phenyl	4-Imidazolyl	OCH_3	CF_3	N	S	O	
I-152	$ON(CH_3)_2$	Phenyl	2-Pyrazolyl	OCH_3	OCF_3	N	O	S	
I-153	$ON=C(CH_3)_2$	2-Hydroxyphenyl	Phenyl	OCH_3	CH_3	N	O	O	
I-154	NH-SO_2-C_6H_5	3-Trifluoromethylphenyl	Phenyl	OCH_3	Cl	N	O	O	
I-155	NHPhenyl	4-Dimethylaminophenyl	Phenyl	OCH_3	OCH_3	CH	S	O	
I-156	ONa	Phenyl	Phenyl	OCH_3	OCH_3	CH	S	S	
I-157	O-CH_2-C≡C	Phenyl	Phenyl	OCH_3	OCH_3	N	S	S	
I-158	OH	Phenyl	Phenyl	CF_3	CF_3	CH	O	S	
I-159	OCH_3	Phenyl	Phenyl	OCF_3	OCF_3	CH	O	O	
I-160	OC_2H_5	Phenyl	2-Dimethylaminophenyl	CH_3	CH_3	CH	O	O	
I-161	$ON(CH_3)_2$	Phenyl	3-Hydroxyphenyl	Cl	Cl	CH	O	O	
I-162	$ON=C(CH_3)_2$	Phenyl	4-Trifluoromethylphenyl	OCH_3	-O-CH_2-CH_2-		S	O	
I-163	NH-SO_2-C_6H_5	Phenyl	2-Oxazolyl	OCH_3	CF_3	N	S	S	
I-164	OH	Phenyl	Methyl	CH_3	CH_3	CH	O	O	
I-165	OH	Cyclohexyl	Methyl	OCH_3	OCH_3	CH	O	O	
I-166	OH	Cyclohexyl	Methyl	OCH_3	CH_2-CH_2-CH-C		O	O	
I-167	OH	Phenyl	Methyl	$N(CH_3)_2$	$N(CH_3)_2$	CH	O	O	

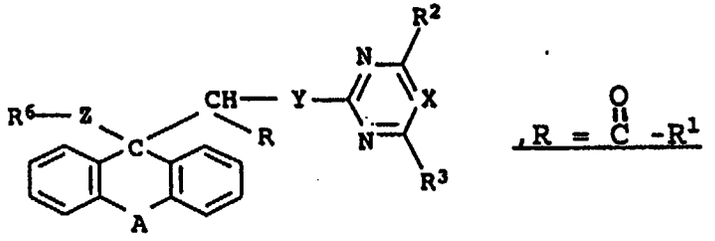
Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-168	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	SO_2	
I-169	OH	Phenyl	Methyl	OCH_3	OCH_3	CH	O	SO_2	
I-170	OH	3-F-Phenyl	Me	OMe	OMe	CH	O	O	
I-171	OH	3-F-Phenyl	Me	OMe	CH_2-CH_2-CH_2-C		O	O	
I-172	OH	4-F-Phenyl	Me	OMe	CH_2-CH_2-CH_2-C		O	O	142-143 191°C
I-173	OH	3-MeO-Phenyl	Me	OMe	CH_2-CH_2-CH_2-C		O	O	158-161 (decomp.)
I-174	OH	3-MeO-Phenyl	Me	OMe	OMe	CH	O	O	
I-175	OH	3-MeO-Phenyl	Et	OMe	CH_2-CH_2-CH_2-C		O	O	
I-176	OH	Phenyl	HO-CH_2-CH_2	OMe	CH_2-CH_2-CH_2-C		O	O	
I-177	OH	Phenyl	Me	NMe_2	NMe_2	N	O	O	181
I-178	OH	Phenyl	Me	OMe	OMe	N	O	O	
I-179	OH								
I-180	NH-SO_2-Phenyl	Phenyl	Me	OMe	OMe	CH	O	O	
I-181	NH-SO_2-Me	Phenyl	Me	OMe	OMe	CH	O	O	
I-182	CH_2-SO_2-Phenyl	Phenyl	Me	OMe	OMe	CH	O	O	
I-183	CH_2-SO_2-Me	Phenyl	Me	OMe	OMe	CH	O	O	
I-184	-CN	Phenyl	Me	OMe	OMe	CH	O	O	
I-185	Tetrazolyl	Phenyl	Me	OMe	OMe	CH	O	O	
I-186	NH-SO_2-Phenyl	Phenyl	Me	OMe	OMe	CH	O	O	
I-187	N-Methyltetrazolyl	Phenyl	Me	OMe	OMe	CH	O	O	167
I-188	ONa	Phenyl	Me	OMe	-O-CH_2-CH_2-C-		O	O	122-139 (zers.)

Table I (continued)

No.	R^1	R^4, R^5	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
I-189	OH	o-F-Phenyl	Me	OMe	-O-CH_2-CH_2-C-		O	O	140-144 (decomp.)
I-190	OH	m-Me-Phenyl	Me	OMe	OMe	CH	O	O	169-177
I-191	OH	m-Me-Phenyl	Me	OMe	-O-CH_2-CH_2-C-		O	O	119-135 (decomp.)
I-192	OH	p-F-Phenyl	Me	OMe	Me	CH	O	O	137-140 (decomp.)
I-193	OH	m-F-Phenyl	Me	Me	-O-CH_2-CH_2-C-		O	O	150-152
I-194	OH	p-F-Phenyl	Me	Me	-O-CH_2-CH_2-C-		O	O	169-170

Table II



No.	R^1	A	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
II-1	OH	Bond	Methyl	OMe	OMe	CH	O	O	96-98
II-2	OH	CH_2	Methyl	OMe	OMe	CH	O	O	
II-3	OH	CH_2-CH_2	Methyl	OMe	OMe	CH	O	O	
II-4	OH	CH=CH	Methyl	OMe	OMe	CH	O	O	

Table II (continued)

No.	R^1	A	R^6	R^2	R^3	X	Y	Z	m.p.[°C]
II-5	OH	O	Methyl	OMe	OMe	CH	O	O	
II-6	OH	S	Methyl	OMe	OMe	CH	O	O	
II-7	OH	$NH(CH_3)$	Methyl	OMe	OMe	CH	O	O	
II-8	OH	Bond	Isopropyl	OMe	OMe	CH	O	O	137-139
II-9	OH	Bond	p-Isopropylphenyl	OMe	OMe	CH	O	O	
II-10	OH	Bond	Benzyl	OMe	OMe	CH	O	O	
II-11	OH	CH=CH	Ethyl	OMe	OMe	CH	O	O	
II-12	OH	CH=CH	$(CH_3)_2$-CH_2-CH_2	OMe	OMe	CH	O	O	
II-13	OH	CH=CH	Cyclopropylmethyl	OMe	OMe	CH	O	O	
II-14	OH	CH=CH	Methyl	OMe	O-CH_2-CH_2-C		O	O	
II-15	OH	CH_2-CH_2	Ethyl	OMe	O-CH=CH-C		O	O	
II-16	OH	CH_2=CH_2	Methyl	OMe	CH_2-CH_2-CH_2-C		O	O	
II-17	OH	Bond	Methyl	OMe	CH_2-CH_2-CH_2-C		O	O	147

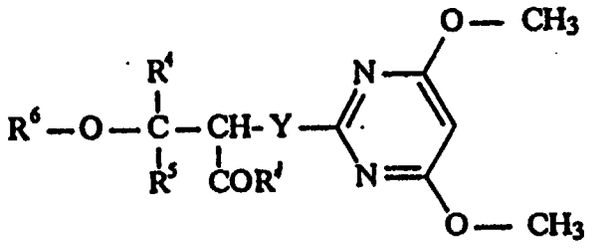


Table IV

R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z
OH	Phenyl	Methyl	Methyl	OCH_3	OCH_3	CH	S	S
OH	Phenyl	Methyl	Methyl	OCH_3	OCH_3	CH	O	S
OCH_3	Phenyl	Methyl	Methyl	OCH_3	OCH_3	CH	S	S
OH	Phenyl	i-Propyl	Methyl	OCH_3	OCH_3	CH	O	O
OCH_3	2-Fluorophenyl	Ethyl	Methyl	OCH_3	OCH_3	CH	O	O
OC_2H_5	3-Chlorophenyl	Propyl	Methyl	OCH_3	OCH_3	N	O	O
$ON(CH_3)_2$	4-Bromophenyl	i-Propyl	Methyl	CF_3	CF_3	CH	S	O
$ON{=}C(CH_3)_2$	2-Thienyl	Methyl	Methyl	OCF_3	OCF_3	CH	O	S
$HNSO_2C_6H_5$	3-Thienyl	Methyl	Methyl	CH_3	CH_3	CH	O	O
NHPhenyl	2-Furyl	Methyl	Methyl	Cl	Cl	CH	O	O
ONa	3-Furyl	Methyl	Methyl	OCH_3	$-OCH_2-CH_2-$		S	O
$O-CH_2-C{\equiv}CH$	Phenyl	Ethyl	Ethyl	OCH_3	CF_3	CH	O	O
OH	Phenyl	Propyl	Propyl	OCH_3	OCF_3	CH	O	S
OCH_3	Phenyl	i-Propyl	i-Propyl	OCH_3	CH_3	CH	O	O
OC_2H_5	Phenyl	Methyl	s-Butyl	OCH_3	Cl	CH	S	O
$ON(CH_3)_2$	2-Methylphenyl	Methyl	Methyl	OCH_3	OCH_3	CH	O	O
$ON(CH_3)_2$	3-Methoxyphenyl	Methyl	Methyl	OCH_3	OCH_3	CH	O	O
$ON{=}C(CH_3)_2$	4-Nitrophenyl	Methyl	Methyl	OCH_3	OCH_3	CH	O	O
NHPhenyl	2-Oxazolyl	Methyl	Methyl	CF_3	CF_3	N	S	O

Table IV (continued)

R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z
ONa	4-Oxazolyl	Methyl	3-Propenyl [sic]	OCF_3	OCF_3	N	O	S
$O-CH_2-C\equiv CH$	5-Oxazolyl	Methyl	3-Propynyl [sic]	CH_3	CH_3	N	O	O
OH	3-Isoxazolyl	Methyl	Cyclopentyl	Cl	Cl	N	O	O
OCH_3	4-Isoxazolyl	Methyl	Cyclohexyl	OCH_3	$-O-CH_2-CH_2-$		O	O
OC_2H_5	5-Isoxazolyl	Methyl	Cyclopropylmethyl	OCH_3	CF_3	N	S	O
$ON(CH_3)_2$	Phenyl	Methyl	1-Phenyl-3-propynyl [sic]	OCH_3	OCF_3	N	O	S
$ON=C(CH_3)_2$	2-Hydroxyphenyl	Methyl	Methyl	OCH_3	CH_3	N	O	O
$ONSO_2C_6H_5$	3-Trifluoromethylphenyl	Methyl	Methyl	OCH_3	Cl	N	O	O
NHPhenyl	4-Dimethylaminophenyl	Methyl	Methyl	OCH_3	OCH_3	CH	S	O
ONa	2-Imidazolyl	Ethyl	Methyl	OCH_3	OCH_3	CH	S	S
$O-CH_2-C\equiv CH$	4-Imidazolyl	Propyl	Methyl	OCH_3	OCH_3	N	S	S
OH	3-Pyrazolyl	i-Propyl	Methyl	CF_3	CF_3	CH	O	S
OCH_3	4-Pyrazolyl	Methyl	Methyl	OCF_3	OCF_3	CH	O	O
OC_2H_5	Phenyl	Methyl	Trifluoroethyl	CH_3	CH_3	CH	O	O
$ON(CH_3)_2$	Phenyl	Methyl	Benzyl	Cl	Cl	CH	O	O
$ON(CH_3)_2$	Phenyl	Methyl	2-Methoxyethyl	OCH_3	$-O-CH_2-CH_2-$		S	O
$ON=C(CH_3)_2$	Phenylpropyl	Methyl	3-Methoxycarbonyl- [sic]	OCH_3	CF_3	N	S	S
NH-Phenyl	2-Pyridyl	Methyl	2-Chloroethyl	OCH_3	OCF_3	N	S	S
ONa	3-Pyridyl	Methyl	Methyl	OCH_3	CH_3	N	O	O
$O-CH_2-C\equiv CH$	4-Pyridyl	Methyl	Methyl	OCH_3	Cl	N	O	O

Table IV (continued)

R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z
OCH_3	Phenyl	CH_3	Phenyl	OCH_3	OCH_3	CH	O	O
OH	Phenyl	CH_3	Phenyl	OCH_3	OCH_3	CH	O	O
OH	Phenyl	CH_3	Phenyl	OCH_3	$-O-CH_2-CH_2-$		O	O
OH	Phenyl	CH_3	Phenyl	OCH_3	OCH_3	N	O	O
OH	Phenyl	CH_3	Phenyl	OCH_3	OCH_3	CH	S	O
OH	Phenyl	CH_3	Phenyl	OCH_3	OCH_3	CH	S	S
OH	Phenyl	CH_3	Phenyl	OCH_3	OCH_3	CH	O	S
OH	Phenyl	H	Phenyl	OCH_3	OCH_3	CH	O	O
OH	Phenyl	i-Propyl	Phenyl	OCH_3	OCH_3	CH	O	O
OH	CH_3	CH_3	Phenyl	OCH_3	OCH_3	CH	O	O
OH	$-(CH_2)_5-$		Phenyl	Phenyl	OCH_3	CH	O	O
OH	Phenyl	CH_3	2-Thiazolyl	OCH_3	OCH_3	CH	O	O
OH	2-Thienyl	CH_3	Phenyl	OCH_3	OCH_3	CH	O	O
OCH_3	2-Fluorophenyl	Ethyl	Phenyl	OCH_3	OCH_3	CH	O	O
OC_2H_5	3-Chlorophenyl	Propyl	Phenyl	OCH_3	OCH_3	N	O	O
$ON(CH_3)_2$	4-Bromophenyl	i-Propyl	Phenyl	CF_3	CF_3	CH	S	O
$ON=C(CH_3)_2$	2-Thienyl	Methyl	Phenyl	OCF_3	OCF_3	CH	O	S
$NH-SO_2-C_6H_5$	3-Thienyl	Methyl	Phenyl	CH_3	CH_3	CH	O	O
NHPhenyl	2-Furyl	Methyl	Phenyl	Cl	Cl	CH	O	O
ONa	3-Furyl	Methyl	Phenyl	OCH_3	$-O-CH_2-CH_2-$		S	O
$O-CH_2\equiv CH$	Phenyl	Ethyl	2-Fluorophenyl	OCH_3	CF_3	CH	O	O

Table IV (continued)

R	R^4	R^5	R^6	R^2	R^3	X	Y	Z
OH	Phenyl	Propyl	3-Chlorophenyl	OCH_3	OCF_3	CH	O	S
OCH_3	Phenyl	i-Propyl	4-Bromophenyl	OCH_3	CH_3	CH	O	O
OC_2H_5	Phenyl	Methyl	4-Thiazolyl	OCH_3	Cl	CH	S	O
$ON(CH_3)_2$	2-Methylphenyl	Methyl	Phenyl	OCH_3	OCH_3	CH	O	O
$ON=C(CH_3)_2$	3-Methoxyphenyl	Methyl	Phenyl	OCH_3	OCH_3	CH	O	O
$NH-SO-C_6H_5$	4-Nitrophenyl	Methyl	Phenyl	OCH_3	OCH_3	CH	O	O
NHPhenyl	Methyl	Methyl	Phenyl	CF_3	CF_3	N	S	O
ONa	Methyl	Methyl	2-Methylphenyl	OCF_3	OCF_3	N	O	S
$O-CH_2-C\equiv CH$	Methyl	Methyl	3-Methoxyphenyl	CH_3	CH_3	N	O	O
OH	Methyl	Methyl	4-Nitrophenyl	Cl	Cl	N	O	O
OCH_3	Phenyl	Methyl	3-Imidazolyl	OCH_3	$-O-CH_2-CH_2-$		O	O
OC_2H_5	Phenyl	Methyl	4-Imidazolyl	OCH_3	CF_3	N	S	O
$ON(CH_3)_2$	Phenyl	Methyl	2-Pyrazolyl	OCH_3	OCF_3	N	O	S
$ON=C(CH_3)_2$	2-Hydroxyphenyl	Methyl	Phenyl	OCH_3	CH_3	N	O	O
$NH-SO_2-C_6H_5$	3-Trifluoromethylphenyl	Methyl	Phenyl	OCH_3	Cl	N	O	O
NHPhenyl	4-Dimethylaminophenyl	Methyl	Phenyl	OCH_3	OCH_3	CH	S	O
ONa	3-Imidazolyl	Ethyl	Phenyl	OCH_3	OCH_3	CH	S	S
$O-CH_2-C\equiv CH$	4-Imidazolyl	Propyl	Phenyl	OCH_3	OCH_3	N	S	S
OH	3-Pyrazolyl	i-Propyl	Phenyl	CF_3	CF_3	CH	O	S
OCH_3	4-Pyrazolyl	Methyl	Phenyl	OCF_3	OCF_3	CH	O	O
OC_2H_5	Phenyl	Methyl	2-Dimethylaminophenyl	CH_3	CH_3	CH	O	O

Table IV (continued)

R^1	R^4	R^5	R^6	R^2	R^3	X	Y	Z
$ON(CH_3)_2$	Phenyl	Methyl	3-Hydroxyphenyl	Cl	Cl	CH	O	O
$ON=C(CH_3)_2$	Phenyl	Methyl	4-Trifluoromethyl-phenyl	OCH_3	$-O-CH_2-CH_2-$		S	O
$NH-SO_2-C_6H_5$	Phenyl	Methyl	2-Oxazolyl	OCH_3	CF_3	N	S	S
NH-Phenyl	2-Pyridyl	Methyl	4-Isoxazolyl	OCH_3	OCF_3	N	S	S
ONa	3-Pyridyl	Methyl	Phenyl	OCH_3	CH_3	N	O	O
$O-CH_2-C\equiv CH$	4-Pyridyl	Methyl	Phenyl	OCH_3	Cl	N	O	O

Synthesis of compounds of the Formula VI

Example 26

Methyl 3-methoxy-3-(3-methoxyphenyl-2-hydroxybutyrate

19.5 g (88 mmol) of methyl 3-(3-methoxyphenyl)-2,3-epoxybutyrate are dissolved in 200 ml of absolute methanol, and 0.1 ml of boron trifluoride etherate is added. The mixture is stirred at room temperature for 12 hours and the solvent is removed by distillation. The residue is taken up in ethyl acetate, washed with sodium bicarbonate solution and water and dried over sodium sulfate. After removal of the solvent by distillation, 21.1 g of a pale yellow remain.

Yield: 94% (1:1 mixture of diastereomers)

Example 27

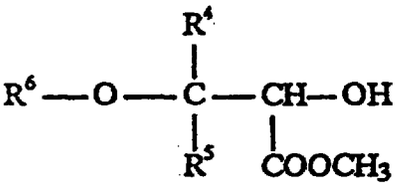
Methyl 3-benzyloxy-3-phenyl-2-hydroxybutyrate

9.6 g (50 mmol) of methyl 3-phenyl-2,3-epoxybutyrate are dissolved in 150 ml of benzyl alcohol, and 0.5 ml of concentrated sulfuric acid is added. The mixture is stirred at 50°C for 6 hours and allowed to cool to room temperature. After neutralization with sodium bicarbonate solution, the excess benzyl alcohol is removed by distillation under high vacuum, and the residue is purified by flash chromatography on silica gel with 9:1 n-hexane/ethyl acetate. After removal of the solvent by distillation, 6.5 g of a colorless oil remain.

Yield: 43% (3:2 mixture of diastereomers)

All the compounds mentioned in Table V were prepared in a similar way.

Table V: Intermediates of the Formula VI with $R^1 = OCH_3$



No.	R^6	R^4	R^5	DR*	M.p.[°C]
1.1	Methyl	3-Methoxyphenyl	Methyl	1:1	Oil
1.2	Benzyl	Phenyl	Methyl	3:2	Oil
1.3	Methyl	2-Fluorophenyl	Methyl	1:1	Oil
1.4	Methyl	4-i-Propylphenyl	Methyl		
1.5	Methyl	2-Methylphenyl	Methyl	2:1	Oil
1.6	Methyl	3-Methylphenyl	Methyl		
1.7	Methyl	4-Methylphenyl	Methyl	3:2	Oil
1.8	Methyl	3-Nitrophenyl	Methyl		
1.9	Methyl	4-Bromophenyl	Methyl	3:1	Oil
1.10	Methyl	2-Furyl	Methyl		
1.11	Methyl	3-Furyl	Methyl		
1.12	Methyl	2-Thienyl	Methyl		
1.13	Methyl	3-Thienyl	Methyl		
1.14	Methyl	2-Pyridyl	Methyl		
1.15	Methyl	3-Pyridyl	Methyl		
1.16	Methyl	4-Pyridyl	Methyl		
1.17	Methyl	2-Thiazolyl	Methyl		
1.18	Methyl	3-Isoxazolyl	Methyl		
1.19	Methyl	4-Imidazolyl	Methyl		
1.20	Methyl	2-Pyrazolyl	Methyl		
1.21	Methyl	4-Chlorophenyl	Methyl	2:1	Oil
1.22	Benzyl	3-Methylphenyl	Methyl	1:1	Oil
1.23	Methyl	4-Fluorophenyl	Methyl	1:1	Oil
1.24	Benzyl	4-Bromophenyl	Methyl	1:1	Oil
1.25	Benzyl	4-Chlorophenyl	Methyl	3:2	Oil
1.26	Benzyl	4-Fluorophenyl	Methyl	1:1	Oil
1.27	Methyl	Phenyl	Ethyl	1:1	Oil
1.28	Methyl	3-Nitrophenyl	Methyl	2:1	Oil
1.29	Ethyl	4-Methylphenyl	Methyl	1:1	Oil
1.30	Benzyl	4-Methylphenyl	Methyl	1:1	Oil
1.31	Benzyl	Phenyl	Ethyl	1:0	Oil
1.32	4-Fluorobenzyl	Phenyl	Methyl	1:1	Oil

* Diastereomer ratio

Synthesis of compounds of the general Formula I:

Example 28

Methyl 3-benzyloxy-3-phenyl-2-(4,6-dimethoxy-2-pyrimidinyl)oxybutyrate

3 g (10 mmol) of methyl 3-benxyloxy-3-phenyl-2-hydroxybutyrate (Compound 1.1) are dissolved in 40 me of dimethylformamide, and 0.3 g (12 mmol) of sodium hydride is added. The mixture is stirred for 1 hour and then 2.2 g (10 mmol) of 4,6-dimethoxy-2-methylsulfonylpyrimidine are added. The mixture is stirred at room temperature for 24 hours and then cautiously hydrolyzed with 10 ml of water, the pH is adjusted to 5 with acetic acid, and the solvent is removed by distillation under high vacuum. The residue is taken up in 100 ml of ethyl acetate, washed with water, dried over sodium sulfate and distilled to remove solvents. 10 mol of methyl t-butyl either are added to the residue, and the precipitate is filtered off with suction. Drying results in 2.4 g of a white powder.

Yield: 55% (1:1 mixture of diastereomers)

M.P.: 115-117°C

Example 29

3-Benxyloxy-3-phenyl-2-(4,6-dimethoxy-2-pyrimidinyl)-oxybutyric acid

1.4 g (3 mmol) of methyl 3-benxyloxy-3-phenyl-2-(4,6-dimethoxy-2-pyrimidinyl)oxybutyrate Example 3 (now 37) are dissolved in 20 ml of methanol and 20 ml of tetrahydrofuran, and 3.7 g of 10% NaOH solution are added. The mixture is stirred at 60°C for 6 hours and at room temperature for 12 hours, the solvent is removed by distillation under reduced pressure, and the residue is taken up in 100 ml of water. The mixture is extracted with ethyl acetate to remove unreacted ester. The aqueous phase is then adjusted to pH 1-2 with dilute hydrochloric acid and extracted with ethyl acetate. After drying over

magnesium sulfate and removal of the solvent by distillation, a small amount of acetone is added to the residue, and the precipitate is filtered off with suction. Drying results in 1.2 g of a white powder.

Yield: 88% (3:2 mixture of diastereomers)

M.P.: 165°C (decomposition)

Example 30

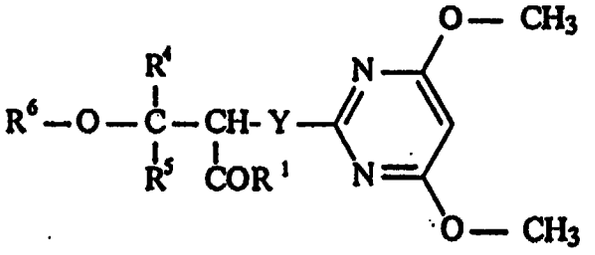
Methyl 3-benxyloxy-3-phenyl-2-[(4,6-dimethoxy-2-pyrimidinyl)thio]butyrate

11 g (25 mmol) of methyl 3-benzyloxy-3-phenyl-2-hydroxybutyrate (Compound 1.1) are dissolved in 50 ml of dichloromethane, 3 g (30 mmol) of triethylamine are added and, while stirring, 3.2 g (28 mmol) of methanesulfonyl chloride are added dropwise. The mixture is stirred at room temperature for 2 hours, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is taken up in DMF and added dropwise to a suspension of 12.9 g (75 mmol) of 4,6-dimethoxypyrimidine-2-thiol and 8.4 g (100 mmol) of sodium bicarbonate in 100 mo of DMF at 0°C. After stirring at room temperature for 2 hours and at 60°C for a further 2 hours, the mixture is poured into 1 liter of ice water and the precipitate is filtered off with suction. Drying results in 3.2 g of a white powder.

Yield: 29% (1:1 mixture of diastereomers)

The compounds specified in Table VI were prepared in a similar manner to the above examples.

Table VI



No.	R^6	R^4	R^5	Y	R^1	Diastereomers	M.p. (°C)
2.1	Benzyl	Phenyl	Methyl	O	OCH_3	1:1	115-117
2.2	Benzyl	Phenyl	Methyl	O	OH	3:2	165 (decomp.)
2.3	Benyzl	Phenyl	Methyl	S	OCH_3	1:1	
2.4	Benyzl	Phenyl	Methyl	S	OH		
2.5	Methyl	2-Fluorophenyl	Methyl	O	OCH_3	1:1	126-128
2.6	Methyl	2-Fluorophenyl	Methyl	O	OH	2:1	185-186
2.7	Methyl	3-Methoxyphenyl	Methyl	O	OCH_3	1:0 (5:1)	131-132 (93-95)
2.8	Methyl	3-Methoxyphenyl	Methyl	O	OH	1:0	187-189
2.9	Methyl	4-i-Propylphenyl	Methyl	O	OCH_3		
2.10	Methyl	4-i-Propylphenyl	Methyl	O	OH		
2.11	Methyl	2-Methylphenyl	Methyl	O	OCH_3	3:1	122-124
2.12	Methyl	2-Methylphenyl	Methyl	O	OH	1:1	135-137

Table VI (continued)

No.	R^6	R^4	R^5	Y	R^1	Diastereomers	M.p. (°C)
2.13	Methyl	3-Methylphenyl	Methyl	O	OCH_3	1:1	105-110
2.14	Methyl	3-Methylphenyl	Methyl	O	OH	1:1	130-132
2.15	Methyl	4-Methylphenyl	Methyl	O	OCH_3	1:1	99-102
2.16	Methyl	4-Methylphenyl	Methyl	O	OH	1:1	145-147
2.17	Methyl	4-Bromophenyl	Methyl	O	OCH_3	1:0	148-150
2.18	Methyl	4-Bromophenyl	Methyl	O	OH	1:0	189-190
2.19	Methyl	2-Furyl	Methyl	O	OCH_3		
2.20	Methyl	2-Furyl	Methyl	O	OH		
2.21	Methyl	3-Furyl	Methyl	O	OCH_3		
2.22	Methyl	3-Furyl	Methyl	O	OH		
2.23	Methyl	2-Thienyl	Methyl	O	OCH_3		
2.24	Methyl	2-Thienyl	Methyl	O	OH		
2.25	Methyl	2-Pyridyl	Methyl	O	OCH_3	2:1	Oil
2.26	Methyl	2-Pyridyl	Methyl	O	ONa		175-176
2.27	Methyl	3-Pyridyl	Methyl	O	OCH_3		
2.28	Methyl	3-Pyridyl	Methyl	O	OH		
2.29	Methyl	4-Pyridyl	Methyl	O	OCH_3		
2.30	Methyl	4-Pyridyl	Methyl	O	OH		
2.31	Methyl	3-Chlorophenyl	Methyl	O	OCH_3		
2.32	Methyl	3-Chlorophenyl	Methyl	O	OH		
2.33	Methyl	2-Thiazolyl	Methyl	O	OCH_3		

Table VI (continued)

No.	R^6	R^4	R^5	Y	R^1	Diastereomers	M.p. (°C)
2.34	Methyl	2-Thiazolyl	Methyl	O	OH		
2.35	Methyl	3-Isoxazolyl	Methyl	O	OCH_3		
2.36	Methyl	3-Isoxazolyl	Methyl	O	OH		
2.37	Methyl	4-Imidazolyl	Methyl	O	OCH_3		
2.38	Methyl	4-Imidazolyl	Methyl	O	OH		
2.39	Methyl	2-Pyrazolyl	Methyl	O	OCH_3		
2.40	Methyl	2-Pyrazolyl	Methyl	O	OH		
2.41	Benzyl	4-Chlorophenyl	Methyl	O	OCH_3	1:1	112-114
2.42	Benzyl	4-Chlorophenyl	Methyl	O	OH		
2.43	i-Propyl	2-Fluorophenyl	Methyl	O	OCH_3	4:1	115-120
2.44	i-Propyl	2-Fluorophenyl	Methyl	O	OH	2:1	143-145
2.45	Methyl	4-Fluorophenyl	Methyl	O	OCH_3	1:1	122-125
2.46	Methyl	4-Fluorophenyl	Methyl	O	OH	3:1	170-172
2.47	Benzyl	3-Methylphenyl	Methyl	O	OCH_3	1:1	94- 95
2.48	Benzyl	3-Methylphenyl	Methyl	O	OH	1:1	154-156
2.49	Methyl	4-Chlorophenyl	Methyl	O	OCH_3	1:1	125-127
2.50	Methyl	4-Chlorophenyl	Methyl	O	OH	5:1	206-207
2.51	Methyl	Phenyl	Ethyl	O	OCH_3	1:0	95-100
2.52	Methyl	Phenyl	Ethyl	O	OH	1:0	140-142
2.53	Benzyl	4-Fluorophenyl	Methyl	O	OCH_3	1:1	95- 98
2.54	Benzyl	4-Fluorophenyl	Methyl	O	OH	4:1	153-154

Table VI (continued)

No.	R^6	R^4	R^5	Y	R^1	Diastereomers	M.p. (°C)
2.55	4-Fluoro-benzyl	Phenyl	Methyl	O	OCH_3	1:0	152-153
2.56	4-Fluoro-benzyl	Phenyl	Methyl	O	OH	7:3	160-162
2.57	4-Bromobenzyl	Phenyl	Methyl	O	OCH_3	9:1	158-160
2.58	4-Bromobenzyl	Phenyl	Methyl	O	OH	1:0	203-204
2.59	Benzyl	2-Fluorophenyl	Methyl	O	OCH_3	1:0	129-130
2.60	Benzyl	2-Fluorophenyl	Methyl	O	OH	1:0	200-201
2.61	Benzyl	4-Bromophenyl	Methyl	O	OCH_3	1:1	78- 79
2.62	Benzyl	4-Bromophenyl	Methyl	O	OH	1:1	156-158
2.63	Benzyl	4-Methylphenyl	Methyl	O	OCH_3	1:1	Oil
2.64	Benzyl	4-Methylphenyl	Methyl	O	OH	4:1	158-159
2.65	Benzyl	Phenyl	Ethyl	O	OCH_3	1:0	110-112
2.66	Benzyl	Phenyl	Ethyl	O	OH	1:0	92- 93
2.67	Ethyl	4-Methylphenyl	Methyl	O	OCH_3	1:0	117-119
2.68	Ethyl	4-Methylphenyl	Methyl	O	OH	1:1	Oil
2.69	Methyl	2-Furyl	H	O	OCH_3	1:1	Oil
2.70	Methyl	2-Furyl	H	O	OH	1:1	Oil
2.71	4-Chloro-benzyl	Phenyl	Methyl	O	OCH_3	1:0	172-174
2.72	4-Chloro-benzyl	Phenyl	Methyl	O	OH	1:0	60- 61

Table VI (continued)

No.	R^6	R^4	R^5	Y	R^1	Diastereomers	M.p. (°C)
2.73	2-Butyl	4-Bromophenyl	Methyl	O	OCH_3	-	104-106
2.74	2-Butyl	4-Bromophenyl	Methyl	O	OH	1:0	153-154
2.75	n-Propyl	4-Fluorophenyl	Methyl	O	OCH_3	9:1	119-120
2.76	n-Propyl	4-Fluorophenyl	Methyl	O	OH	9:1	104-105
2.77	Methyl	3-Nitrophenyl	Methyl	O	OCH_3	1:1	101-102
2.78	Methyl	3-Nitrophenyl	Methyl	O	OH	1:1	165-172
2.79	Methyl	4-Trifluorophenyl	Methyl	O	OCH_3	1:0	112-113
2.80	Methyl	4-Trifluorophenyl	Methyl	O	OH	4:1	68- 70
2.81	Methyl	3-Thienyl	H	O	OCH_3	1:1	80- 82
2.82	Methyl	3-Thienyl	H	O	OH	1:1	Oil
2.83	4-Chloro-benzyl	Phenyl	Methyl	O	OCH_3	0:1	112-113
2.84	4-Chloro-benzyl	Phenyl	Methyl	O	OCH_3	0:1	60- 61
2.85	Methyl	Phenyl	Ethyl	O	OCH_3	1:3	125-130
2.86	Methyl	Phenyl	Ethyl	O	OH	0:1	133-135
2.87	Benzyl	3-Methoxyphenyl	Methyl	O	OCH_3	3:1	86- 87
2.88	Benzyl	3-Methoxyphenyl	Methyl	O	OH	1:0	155
2.89	Benzyl	3-Methoxyphenyl	Methyl	O	OH	0:1	138-140
2.90	2-Phenylethyl	Phenyl	Methyl	O	OH	1:0	147-149
2.91	Methyl	3-Furyl	H	O	OCH_3	1:1	Oil
2.92	Methyl	3-Furyl	H	O	OH	1:1	131-135

Table VI (continued)

No.	R^6	R^4	R^5	Y	R^1	Diastereomers	M.p. (°C)
2.93	3-CF_3-benzyl	Phenyl	Methyl	O	OCH_3	2:1	151-152
2.94	3-CF_3-benzyl	Phenyl	Methyl	O	OH	1:1	Oil
2.95	2-Fluoro-benzene [sic]	Phenyl	Methyl	O	OCH_3	2:1	170-173
2.96	2-Fluoro-benzene [sic]	Phenyl	Methyl	O	OH	1:0	160-162
2.97	2-Fluoro-benzyl	Phenyl	Methyl	O	OH	1:3	138-141
2.98	3-Fluoro-benzyl	Phenyl	Methyl	O	OCH_3	1:1	81- 86
2.99	3-Fluoro-benzyl	Phenyl	Methyl	O	OH	4:1	195-197
2.100	3-Fluoro-benzyl	Phenyl	Methyl	O	ONa	3:1	250-260
2.101	4-Fluoro-benzyl	Phenyl	Methyl	O	OCH_3	1:1	112-115
2.102	4-Fluoro-benzyl	Phenyl	Methyl	O	OH		

Synthesis of compounds of the general Formula VI

Example 31

28.2 g (0.3 mol) of phenol and 19.2 g (0.1 mol) of methyl 3-phenyl-2,3-epoxybutyrate are heated together at 1-- °C for 6 hours. Removal of the excess phenol by distillation under high vacuum and purification of the residue by chromatography on silica gel with hexane/ethyl acetate mixtures result in 17.9 g of a pale yellow oil.

Yield: 62.5%

Example 32

Methyl 3-(4-bromophenyl)oxy-3-phenyl-2-hydroxybutyrate

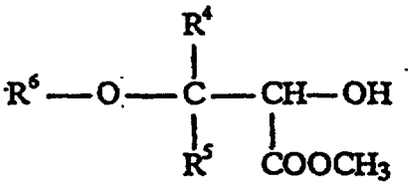
51.9 g (0.3 mol) of 4-bromophenol and 19.2 g (0.1 mol) of methyl 3-phenyl-2,3-epoxybutyrate are stirred at 100 °C for 8 hours and at room temperature for 12 hour. After removal of the excess phenol by distillation, the residue is purified by flash chromatography (silica gel, n-hexane/ethyl acetate 9:1) to result in 7.2 g of a white solid.

Yield: 20%

M.P.: 133 - 135 °C

The compounds specified in Table VII were prepared in a similar way:

Table VII: Intermediates of the Formula VI with $R^1 = OCH_3$



	R^6	R^4	R^5	M.p. [°C]
3.1	Phenyl	Phenyl	Methyl	Oil
3.2	4-Bromophenyl	Phenyl	Methyl	130-133
3.3	Phenyl	Methyl	Methyl	
3.4	Phenyl	Phenyl	i-Propyl	
3.5	2-Fluorophenyl	Phenyl	Methyl	
3.6	3-Fluorophenyl	Phenyl	Methyl	Oil
3.7	4-Fluorophenyl	Phenyl	Methyl	Oil
3.8	4-Chlorophenyl	Phenyl	Methyl	
3.9	4-Nitrophenyl	Phenyl	Methyl	
3.10	4-Methylphenyl	Phenyl	Methyl	Oil
3.11	Phenyl	2-Fluorophenyl	Methyl	
3.12	Phenyl	3-Methoxyphenyl	Methyl	
3.13	Phenyl	4-i-Propylphenyl	Methyl	
3.14	Phenyl	2-Methylphenyl	Methyl	
3.15	Phenyl	3-Nitrophenyl	Methyl	
3.16	Phenyl	4-Bromophenyl	Methyl	
3.17	Phenyl	2-Furyl	Methyl	
3.18	Phenyl	2-Thienyl	Methyl	Oil
3.19	Phenyl	3-Furyl	Methyl	
3.20	Phenyl	3-Thienyl	Methyl	
3.21	3-Methylphenyl	Phenyl	Methyl	Oil
3.22	2-Methylphenyl	Phenyl	Methyl	Oil
3.23	4-i-Propylphenyl	Phenyl	Methyl	Oil
3.24	Phenyl	4-Chlorophenyl	Methyl	Oil

Synthesis of compounds of the general Formula I:

Example 33

Methyl 3-phenoxy-3-phenyl-2-(4,6-dimethoxy-2-pyrimidinyl)-oxybutyrate

4.4 g (15.4 mmol) of methyl 3-phenoxy-3-phenyl-2-hydroxybutyrate (Compound 1.1) are dissolved in 40 mol of DMF, and 0.46 g (18.4 mmol) of sodium hydride is added. The mixture is stirred for 1 hour and then 3.4 g (15.4 mmol) of 4,6-dimethoxy-2-methylsulfonylpyrimidine are added. The mixture is stirred at room temperature for 24 hours and then cautiously hydrolyzed with 10 mo of water, the pH is adjusted to 5 with acetic acid, and the solvent is removed by distillation under high vacuum. The residue is taken up in 100 mo of ethyl acetate, washed with water, dried over sodium sulfate and distilled to remove solvents. 10 ml of methyl t-butyl ether are added to the residue, and the precipitate is filtered off with suction. Drying results in 1.6 g of a white powder.

Yield: 24.5 %

M.P.: 143 - 145°C

Example 34

3-Phenoxy-3-phenyl-2-(4,6-dimethoxy-2-pyrimidinyl)-oxybutyric acid

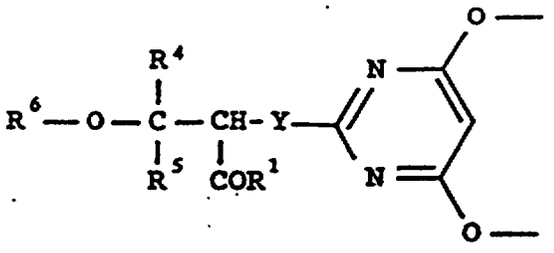
1.3 g of methyl 3-phenoxy-3-phenyl-2-(4,6-dimethoxy-2-pyrimidinyl)oxybutyrate (Example 6 change to 42) are dissolved in 20 ml of MeOH and 40 ml of THF, and 3.7 g of 10% NaOH solution are added. The mixture is stirred at 60°C for 6 hours and at room temperature for 12 hours, the solvent is removed by distillation under reduced pressure, and the residue is taken up in 100 ml of water. Unreacted ester is extracted with ethyl acetate. The aqueous phase is then adjusted to pH 1-2 with dilute hydrochloric acid and extracted with ethyl acetate. Drying over magnesium

sulfate and removal of the solvent by distillation result in 1.0 g of a white powder.
Yield: 79.7%
M.P.: 50-55°C

Example 35
Methyl 3-phenoxy-3-phenyl-2-[(4,6-dimethoxy-2-pyrimidinyl)thio]butyrate
7.2 g (25 mmol) of methyl 3-phenoxy-3-phenyl-2-hydroxybutyrate (Compound 1.1) are dissolved in 50 ml of dichloromethane, 3 g (30 mmol) of triethylamine are added and, while stirring, 3.2 g (28 mmol) of methanesulfonyl chloride are added dropwise. The mixture is stirred at room temperature for 2 hours, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is taken up in 100 mo of DMF and added dropwise to a suspension 12.9 g (75 mmol) of 4,6-dimethoxypyrimidine-2-thiol and 8.4 g (100 mmol) sodium bicarbonate in 100 ml of DMF at 0° C. After stirring at room temperature for 2 hours and at 60°C for further 2 hours, the mixture is poured into 1 liter of ice-water, and the precipitate is filtered off with suction. Drying results in 4.2 g of a white powder.
Yield: 38%

The compounds specified in Table VIII were prepared in a similar way to the above examples.

Table VIII



Ex. No.	R^6	R^4	R^5	R^1	Y	M.p. [°C]
4.1	Phenyl	Phenyl	Methyl	OCH_3	O	100–103
4.2	Phenyl	Phenyl	Methyl	OH	O	50–55
4.3	Phenyl	Phenyl	Methyl	OCH_3	S	
4.4	Phenyl	Phenyl	Methyl	OH	S	
4.5	Phenyl	Phenyl	i-Propyl	OCH_3	O	
4.6	Phenyl	Phenyl	i-Propyl	OH	O	
4.7	Phenyl	Methyl	Methyl	OCH_3	O	
4.8	Phenyl	Methyl	Methyl	OH	O	
4.9	4-Bromophenyl	Phenyl	Methyl	OCH_3	O	130–135
4.10	4-Bromophenyl	Phenyl	Methyl	OH	O	155–160
4.11	2-Fluorophenyl	Phenyl	Methyl	OCH_3	O	128–134
4.12	2-Fluorophenyl	Phenyl	Methyl	OH	O	170–171
4.13	3-Fluorophenyl	Phenyl	Methyl	OCH_3	O	85– 90
4.14	3-Fluorophenyl	Phenyl	Methyl	OH	O	167–169
4.15	4-Fluorophenyl	Phenyl	Methyl	OCH_3	O	115–116
4.16	4-Fluorophenyl	Phenyl	Methyl	OH	O	122–125
4.17	4-Chlorophenyl	Phenyl	Methyl	OCH_3	O	Oil
4.18	4-Chlorophenyl	Phenyl	Methyl	OH	O	94– 98
4.19	4-Methylphenyl	Phenyl	Methyl	OCH_3	O	100–114
4.20	4-Methylphenyl	Phenyl	Methyl	OH	O	Oil
4.21	4-Nitrophenyl	Phenyl	Methyl	OCH_3	O	
4.22	4-Nitrophenyl	Phenyl	Methyl	OH	O	
4.23	Phenyl	2-Fluorophenyl	Methyl	OCH_3	O	130–132
4.24	Phenyl	2-Fluorophenyl	Methyl	OH	O	194–195
4.25	Phenyl	3-Methoxyphenyl	Methyl	OCH_3	O	Oil
4.26	Phenyl	3-Methoxyphenyl	Methyl	OH	O	Oil
4.27	Phenyl	4-i-Propylphenyl	Methyl	OCH_3	O	
4.28	Phenyl	4-i-Propylphenyl	Methyl	OH	O	
4.29	Phenyl	4-Bromophenyl	Methyl	OCH_3	O	129–131
4.30	Phenyl	4-Bromophenyl	Methyl	OH	O	Oil

Table VIII (continued)

Ex. No.	R^6	R^4	R^5	R^1	Y	M.p. [°C]
4.31	Phenyl	2-Furyl	Methyl	OCH_3	O	
4.32	Phenyl	2-Furyl	Methyl	OH	O	
4.33	Phenyl	3-Furyl	Methyl	OCH_3	O	
4.34	Phenyl	3-Furyl	Methyl	OH	O	
4.35	Phenyl	2-Thienyl	Methyl	OCH_3	O	
4.36	Phenyl	2-Thienyl	Methyl	OH	O	
4.37	Phenyl	3-Thienyl	Methyl	OCH_3	O	
4.38	Phenyl	3-Thienyl	Methyl	OH	O	
4.39	3-Methylphenyl	Phenyl	Methyl	OCH_3	O	155
4.40	3-Methylphenyl	Phenyl	Methyl	OH	O	100-101
4.41	4-i-Propyl-phenyl	Phenyl	Methyl	OCH_3	O	130-131
4.42	4-i-Propyl-phenyl	Phenyl	Methyl	OH	O	230
4.43	Phenyl	4-Chlorophenyl	Methyl	OCH_3	O	143-144
4.44	Phenyl	4-Chlorophenyl	Methyl	OH	O	90- 92
4.45	Phenyl	2-Methylphenyl	Methyl	OCH_3	O	179-180
4.46	Phenyl	2-Methylphenyl	Methyl	OH	O	
4.47	2-Methylphenyl	Phenyl	Methyl	OCH_3	O	95-114
4.48	2-Methylphenyl	Phenyl	Methyl	OH	O	80- 85
4.49	Phenyl	4-Methylphenyl	Methyl	OCH_3	O	110-112
4.50	Phenyl	4-Methylphenyl	Methyl	OH	O	156-157
4.51	Phenyl	3-Methylphenyl	Methyl	OCH_3	O	Oil
4.52	Phenyl	3-Methylphenyl	Methyl	OH	O	158-160
4.53	4-Methoxy-phenyl	Phenyl	Methyl	OCH_3	O	157-158
4.54	4-Methoxy-phenyl	Phenyl	Methyl	OH	O	106-107
4.55	Phenyl	4-Fluorophenyl	Methyl	OCH_3	O	160-165
4.56	Phenyl	4-Fluorophenyl	Methyl	OH	O	99-100

Table VIII (continued)

Ex. No.	R^6	R^4	R^5	R^1	Y	M.p. [°C]
4.57	4-Methylthio-phenyl	Phenyl	Methyl	OCH_3	O	160-163
4.58	4-Methylthio-phenyl	Phenyl	Methyl	OH	O	248-250
4.59	4-t-Butyl-phenyl	Phenyl	Methyl	OCH_3	O	106-110
4.60	4-t-Butyl-phenyl	Phenyl	Methyl	OH	O	250
4.61	Phenyl	Phenyl	Ethyl	OCH_3	O	115-117
4.62	Phenyl	Phenyl	Ethyl	OH	O	84- 85
4.63	4-Acetoxy-phenyl	Phenyl	Methyl	OCH_3	O	157-159
4.64	4-Hydroxy-phenyl	Phenyl	Methyl	OH	O	80- 90

Example 36

Receptor binding data were measured by the binding assay described above for the compounds listed below. The results are shown in Table III.

Table III

Receptor binding data (K_i values)

Compound	ET_A [nM]	ET_B [nM]
I-2	6	34
I-29	86	180
I-5	12	160
I-4	7	2500
I-87	1	57
I-89	86	9300
I-103	0.4	29
I-107	3	485
I-12	19	1700
I-26	23	2000
I-23	209	1100
I-47	150	1500
I-60	33	970
I-96	0.6	56
II-3	107	7300
II-1	28	2300

Equivalents

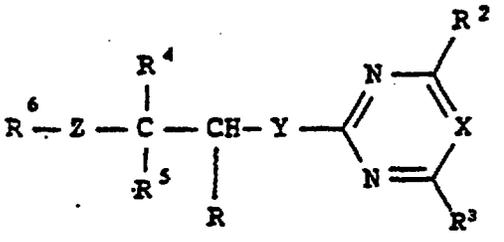
Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention

described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A method of treating cancer in a human in need of treatment, comprising administering to the human a compound of Formula Ia in sufficient quantity to inhibit growth of a solid tumor in which endothelin is upregulated, wherein Formula Ia is:



Ia

where R is formyl, tetrazolyl, cyano, a COOH group or a radical which can be hydrolyzed to COOH, and the other substituents have the following meanings:

R^2 hydrogen, hydroxyl, NH_2, $NH(C_1-C_4\text{-alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy or C_1-C_4-alkylthio;

X nitrogen or CR^{14} where R^{14} is hydrogen or C_{1-5}-alkyl, or CR^{14} forms together with CR^3 a 5- or 6-membered alkylene or alkenylene ring which can be substituted by one or two C_{1-4}-alkyl groups and in which in each case a methylene group can be replaced by oxygen, sulfur, -NH or $-NC_{1-4}$-alkyl;

R^3 hydrogen, hydroxyl, NH_2, $NH(C_1-C_4\text{-Alkyl})$, $N(C_1-C_4\text{-alkyl})_2$, halogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, $-NH-O-C_{1-4}$-alkyl, C_1-C_4-alkylthio or CR^3 is

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linked to CR^{14} as indicated above to give a 5- or 6-membered ring;

R^4 and R^5 (which can be identical or different):

phenyl or naphthyl, which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, amino, C_1-C_4-alkylamino or C_1-C_4-dialkylamino; or

phenyl or naphthyl, which are connected together in the ortho positions via a direct linkage, a methylene, ethylene or ethenylene group, an oxygen or sulfur atom or an SO2, NH or N-alkyl group or C_3-C_7-cycloalkyl;

R^6 hydrogen, C_1-C_8-alkyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl or C_3-C_8-cycloalkyl, where each of these radicals can be substituted one or more times by: halogen, nitro, cyano, C_1-C_4-alkoxy, C_3-C_6-alkenyloxy, C_3-C_6-alkynyloxy, C_1-C_4-alkyl- thio, C_1-C_4-haloalkoxy, C_1-C_4-alkylcarbonyl, C_1-C_4-alkoxy-carbonyl, C_{3-8}-alkylcarbonylalkyl, C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, phenyl or phenyl or phenoxy which is substituted one or more times, eg, one to three times, by halogen, nitro, cyano, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloakoxy or C_1-C_4-alkylthio; phenyl or naphthyl, each of which can be substituted by one or more of the following radicals: halogen, nitro, cyano, hydroxyl, amino, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-

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alkoxy, C_1-C_4-haloalkoxy, phenoxy, C_1-C_4-alkylthio, C_1-C_4-alkylamino, C_1-C_4-dialkylamino, methylenedioxy or ethylenedioxy;

a five- or six-membered heteroaromatic moiety containing one to three nitrogen atoms and/or one sulfur or oxygen atom, which can carry one to four halogen atoms and/or one or two of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_1-C_4-alkylthio, phenyl, phenoxy or phenylcarbonyl, it being possible for the phenyl radicals in turn to carry one to five halogen atoms and/or one to three of the following radicals: C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy and/or C_1-C_4-alkylthio;

with the proviso that R6 can be hydrogen only when Z is not a single bond;

Y sulfur or oxygen or a single bond;

Z sulfur, oxygen, -SO-, -SO_2- or a single bond.

2. The method of Claim 1 wherein for the compound of Formula Ia R is a COOH group, R^2 is -OMe, R^3 is -OMe, R^4 is phenyl, R^5 is phenyl, R^6 is methyl, X is CR^{14}, R^{14} is H, Y is oxygen, and Z is oxygen.

3. The method of Claim 1 wherein for the compound of Formula Ia R is a COOH group, R^2 is methyl, R^3 is methyl, R^4 is phenyl, R^5 is phenyl, R^6 is methyl, X is CR^{14}, R^{14} is H, Y is oxygen, and Z is oxygen.

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4. The method of Claim 1 wherein for the compound of Formula Ia R is a COOH group, R^2 is methyl, R^3 is methyl, R^4 is phenyl, R^5 is phenyl, R^6 is methyl, X is CR^{14}, R^{14} is H, Y is oxygen, and Z is a single bond.

5. The method of Claim 1 wherein the cancer is prostate cancer.

6. The method of Claim 2 wherein the cancer is prostate cancer.

7. The method of Claim 3 wherein the cancer is prostate cancer.

8. The method of Claim 4 wherein the cancer is prostate cancer.

9. The use of a compound of the formula Ia as defined in any one of claims 1 to 4 for administration to a human to inhibit growth of a solid tumor in which endothelin is upregulated.

10. A process for the manufacture of a medicament for inhibiting growth in a human of a solid tumor in which endothelin is upregulated, the process being characterized in the use, as an essential constituent of said medicament, of a compound of the formula Ia as defined in any one of Claims 1 to 4.

11. The use according to Claim 9, or a process according to Claim 10, wherein the solid tumor is selected from tumors of the prostate, lung, liver, breast, brain, stomach, colon, endometrium, testicle, thyroid, pituitary, bladder, kidney, pancreas and meninges.

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12. The use or process according to Claim 11 wherein the solid tumor is prostate cancer.

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