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[54] **ACYL COMPOUNDS**

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[21] Appl. No.: **998,755**

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Related U.S. Application Data

[63] Continuation of Ser. No. 654,479, Feb. 13, 1991, abandoned.

[30] **Foreign Application Priority Data**

Feb. 19, 1990 [CH] Switzerland 518/90
Jul. 5, 1990 [CH] Switzerland 2234/90

[51] **Int. Cl.**[6] **C07D 257/04**; A61K 31/41
[52] **U.S. Cl.** **514/381**; 548/253
[58] **Field of Search** 514/381; 548/253

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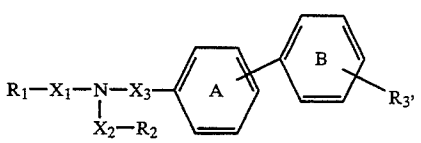
[57] **ABSTRACT**

Compounds of the formula



(I)

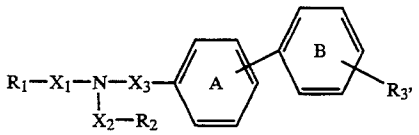
in which R_1 is an aliphatic hydrocarbon radical which is unsubstituted or substituted by halogen or hydroxyl, or a cycloaliphatic or araliphatic hydrocarbon radical; X_1 is CO, SO_2, or —O—C(=O)— with the carbon atom of the carbonyl group being attached to the nitrogen atom shown in formula I; X_2 is a divalent aliphatic hydrocarbon radical which is unsubstituted or substituted by hydroxyl, carboxyl, amino, guanidino or a cycloaliphatic or aromatic radical, or is a divalent cycloaliphatic hydrocarbon radical, it being possible for a carbon atom of the aliphatic hydrocarbon radical to be additionally bridged by a divalent aliphatic hydrocarbon radical; R_2 is carboxyl which, if desired, is esterified or amidated, substituted or unsubstituted amino, formyl which, if desired, is acetalized, 1H-tetrazol-5-yl, pyridyl, hydroxyl which, if desired, is etherified, $S(O)_m$—R where m is 0, 1 or 2 and R is hydrogen or an aliphatic hydrocarbon radical, alkanoyl, unsubstituted or N-substituted sulfamoyl or PO_nH_2 where n is 2 or 3; X_3 is a divalent aliphatic hydrocarbon; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or haloalkylsulfamoyl; and the rings A and B independently of one another are substituted or unsubstituted; in free form or in salt form, can be prepared in a manner known per se and can be used, for example, as medicament active ingredients.

7 Claims, No Drawings

ACYL COMPOUNDS

This application is a continuation of application Ser. No. 654,479, filed Feb. 13, 1991, now abandoned.

The invention relates to compounds of the formula



(I)

in which R_1 is an aliphatic hydrocarbon radical which is unsubstituted or substituted by halogen or hydroxyl, or a cycloaliphatic or araliphatic hydrocarbon radical; X_1 is CO, SO_2, or —O—C(=O)— with the carbon atom of the carbonyl group being attached to the nitrogen atom shown in formula I; X_2 is a divalent aliphatic hydrocarbon radical which is unsubstituted or substituted by hydroxyl, carboxyl, amino, guanidino or a cycloaliphatic or aromatic radical, or is a divalent cycloaliphatic hydrocarbon radical, it being possible for a carbon atom of the aliphatic hydrocarbon radical to be additionally bridged by a divalent aliphatic hydrocarbon radical; R_2 is carboxyl which, if desired, is esterified or amidated, substituted or unsubstituted amino, formyl which, if desired, is acetalised, 1H-tetrazol-5-yl, pyridyl, hydroxyl which, if desired, is etherified, $S(O)_m$—R where m is 0, 1 or 2 and R is hydrogen or an aliphatic hydrocarbon radical, alkanoyl, unsubstituted or N-substituted sulfamoyl or PO_nH_2 where n is 2 or 3; X_3 is a divalent aliphatic hydrocarbon; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or haloalkylsulfamoyl; and the rings A and B independently of one another are substituted or unsubstituted; in free form or in salt form, to a process for the preparation of these compounds, to the use of these compounds and to pharmaceutical preparations containing such a compound I in free form or in the form of a pharmaceutically acceptable salt.

The compounds I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds I have, for example, at least one basic centre, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as C_1–C_4 alkanecarboxylic acids which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as C_1–C_4alkane- or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic centre. The compounds I having at least one acid group (for example COOH or 5-tetrazolyl) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

An aliphatic hydrocarbon radical is, for example, lower alkyl, lower alkenyl or secondarily lower alkynyl.

An aliphatic radical substituted by halogen or hydroxyl is, for example, halo-lower alkyl, -lower alkenyl or -lower alkynyl, or hydroxy-lower alkyl, -lower alkenyl or -lower alkynyl.

A cycloaliphatic hydrocarbon radical is in particular cycloalkyl and secondarily cycloalkenyl.

A suitable araliphatic radical is in particular phenyl-lower alkyl, also phenyl-lower alkenyl or -lower alkynyl.

A divalent hydrocarbon radical which bridges a C atom of an aliphatic radical X_2 is, for example, C_2–C_6alkylene, in particular C_4–C_5alkylene.

A cycloaliphatic radical is, for example, a cycloalkyl or, secondarily, cycloalkenyl which is unsubstituted, monosubstituted or, furthermore, polysubstituted, for example disubstituted, for example by carboxyl which, if desired, is esterified or amidated or formyl which, if desired, is acetalised.

An aromatic radical is, for example, a carbocyclic or heterocyclic aromatic radical, in particular phenyl or in particular an appropriate 5- or 6-membered and monocyclic radical which has up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl. Appropriate aromatic radicals are radicals which may be monosubstituted or polysubstituted, for example di- or trisubstituted, for example by identical or different radicals, for example selected from the group comprising: halogen, hydroxyl which, if desired, is etherified, $S(O)_m$—R and an aliphatic hydrocarbon radical which may be interrupted by —O— and which is unsubstituted or substituted by halogen or hydroxyl and which may be additionally substituted, for example by carboxyl which, if desired, is esterified or amidated or formyl which, if desired, is acetalised.

A divalent aliphatic hydrocarbon radical (X_2) is, for example, alkylene or alkylidene.

A divalent cycloaliphatic hydrocarbon radical is, for example, cycloalkylene.

Esterified carboxyl is, for example, carboxyl which is esterified by an alcohol which is derived from an aliphatic or araliphatic hydrocarbon radical, such as lower alkyl, phenyl-lower alkyl, lower alkenyl and secondarily lower alkynyl, and which may be interrupted by —O—, such as lower alkoxy-lower alkyl, -lower alkenyl and -lower alkynyl. Examples which may be mentioned are lower alkoxy-, phenyl-lower alkoxy-, lower

Amidated carboxyl is, for example, carbamoyl in which the amino group is unsubstituted or monosubstituted or, independently of one another, disubstituted by an aliphatic or araliphatic hydrocarbon radical or disubstituted by a divalent aliphatic hydrocarbon radical which may be interrupted by O or may be condensed at two adjacent carbon atoms with a benzene ring, in particular lower alkylene or lower alkyleneoxy-lower alkylene. Examples of appropriately substituted amino groups which may be mentioned are lower alkyl-, lower alkenyl-, lower alkynyl-, phenyl-lower alkyl-, phenyl-lower alkenyl-, phenyl-lower alkynyl-, di-lower alkyl-, N-lower alkyl-N-phenyl-lower alkyl- and diphenyl-lower alkylamino and also quinol-1-yl, isoquinol-2-yl, lower alkylene- and lower alkyleneoxy-lower alkyleneamino.

Substituted amino has the meanings indicated in connection with substituted carbamoyl and is furthermore acylamino, such as lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonylamino.

Acetalised formyl is, for example, di-lower alkoxymethyl or oxy-lower alkyleneoxymethylene.

Etherified hydroxyl is, for example, hydroxyl etherified by an alipahtic alcohol, in particular lower alkoxy or lower alkenyloxy, and is also a phenyl-lower alkoxy or phenoxy radical.

In N-substituted sulfamoyl, the substituted amino group has the meanings indicated in connection with substituted carbamoyl.

An aliphatic hydrocarbon radical which is interrupted by —O— is in particular lower alkoxy-lower alkyl, -lower alkenyl or-lower alkynyl, or lower alkenyloxy-lower alkyl, -lower alkenyl or -lower alkynyl.

Above and below, Unsaturated aliphatic, cycloaliphatic and araliphatic substituents are primarily not linked to an aromatic radical via the C atom from which a multiple bond extends.

(Hetero)aromatic radicals, if not defined differently, are in particular in each case unsubstituted or mono- or polysubstituted, for example disubstituted or trisubstituted, in particular, for example, by a substitutent selected from the group comprising halogen, hydroxyl which, if desired, is etherified, $S(O)_m$—R and a hydrocarbon radical which is unsubstituted or substituted, for example by halogen or hydroxyl, and which may be interrupted by —O—.

The rings A and B are primarily a 4-biphenylyl, also a 2- or 3-biphenylyl ring system, where the radical R_3 is preferably located in the ortho-position of ring B. Correspondingly, the rings A and B are unsubstituted or monosubstituted or polysubstituted, for example disubstituted or trisubstituted, for example by identical or different radicals, for example selected from the group comprising: halogen, hydroxyl which, if desired, is etherified, $S(O)_m$—R and a hydrocarbon radical which is unsubstituted or substituted by halogen or hydroxyl and which may be interrupted by —O—.

The general definitions used above and below, unless defined differently, have the following meanings:

The expression "lower" means that corresponding groups and compounds in each case in particular comprise not more than 7, preferably not more than 4, carbon atoms.

Halogen is in particular halogen of atomic number not more than 35, such as fluorine, chlorine or bromine, and also includes iodine.

Alkanoyl is, for example, lower alkanoyl and is in particular C_2–C_7 alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C_2–C_5alkanoyl is preferred.

Haloalkylsulfamoyl is in particular halo-C_1–C_7alkanesulfamoyl and is, for example, trifluoromethane-, difluoromethane-, 1,1,2-trifluoromethane- or heptafluoropropanesulfamoyl. Halo-C_1–C_4alkanesulfamoyl is preferred.

Lower alkyl is in particular C_3–C_7alkyl, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and also includes corresponding pentyl, hexyl and heptyl radicals. C_1–C_4alkyl is preferred.

Lower alkenyl is in particular C_3–C_7alkenyl and is, for example, 2-propenyl or 1-, 2- or 3-butenyl. C_3–C_5alkenyl is preferred.

Lower alkynyl is in particular C_3–C_7alkynyl and is preferably propargyl.

Halo-lower alkyl is in particular halo-C_1–C_4alkyl, such as trifluoromethyl, 1,1,2-trifluoro-2-chloroethyl or chloromethyl.

Halo-lower alkenyl is in particular halo-C_3–C_5alkenyl, such as 3-chloroallyl.

Halo-lower alkynyl is in particular halo-C_3–C_5alkynyl, such as 3-chloropropargyl.

Hydroxy-lower alkyl is in particular hydroxy-C_1–C_4alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Hydroxy-lower alkenyl is in particular hydroxy-C_3–C_5alkenyl, such as 3-hydroxyallyl.

Hydroxy-lower alkynyl is in particular hydroxy-C_3–C_5alkynyl, such as 3-hydroxypropargyl.

Cycloalkyl is in particular C_3–C_7cycloalkyl and is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

Cycloalkenyl is in particular C_3–C_7cycloalkenyl and is preferably cyclopent-2- and -3-enyl, or cyclohex-2- and -3-en-yl.

Phenyl-lower alkyl is in particular phenyl-C_1–C_4alkyl and is preferably benzyl, 1- and 2-phenethyl, while phenyl-lower alkenyl and phenyl-lower alkynyl are in particular phenyl-C_3-C_5alkenyl and-alkynyl, in particular 3-phenylallyl and 3-phenylpropargyl.

Pyrrolyl is, for example, 2- or 3-pyrrolyl. Pyrazolyl is 3- or 4-pyrazolyl. Imidazolyl is 2- or 4-imidazolyl. Triazolyl is, for example, 1,3,5-1H-triazol-2-yl or 1,3,4-triazol-2-yl. Tetrazolyl is, for example, 1,2,3,4-tetrazol-5-yl, furyl is 2- or 3-furyl and thienyl is 2- or 3-thienyl, while suitable pyridyl is 2-, 3- or 4-pyridyl.

Alkylene is in particular C_1–C_{10}alkylene or lower alkylene, such as C_1–C_7alkylene, and is straight-chain or branched and is in particular methylene, ethylene, propylene and butylene and also 1,2-propylene, 2-methyl-1,3-propylene and 2,2-dimethyl-1,3-propylene. C_1–C_5alkylene is preferred.

Alkylidene is in particular C_2–C_{10}alkylidene, such as ethylidene, 1,1- or 2,2-propylidene, also 1,1- or 2,2-butylidene or 1,1-, 2,2- or 3,3-pentylidene. C_2–C_5alkylidene is preferred.

Cycloalkylene is in particular C_3–C_7cycloalkylene and is, for example, 1,2-cyclopropylene, 1,2- or 1,3-cyclobutylene, 1,2- or 1,3-cyclopentylene, 1,2-, 1,3- or 1,4-cyclohexylene and 1,2-, 1,3- or 1,4-cycloheptylene. 1,3Ccyclopentylene and 1,4-cyclohexylene are preferred.

Lower alkoxy is in particular C_1–C_7alkoxy and is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy and also includes corresponding pentyloxy, hexyloxy and heptyloxy radicals. C_1–C_4alkoxy is preferred.

Lower alkoxy-lower alkyl is in particular C_1–C_4alkoxy-C_1–C_4alkyl, such as 2-methoxyethyl, 2-ethoxyethyl, 2-n-propyloxyethyl or ethoxymethyl. Lower alkoxy-lower alkenyl or -lower alkynyl is in particular C_1–C_5alkoxy-C_3–C_5alkenyl or —C_3–C_5alkynyl.

Lower alkoxycarbonyl is in particular C_2–C_8alkoxycarbonyl and is, for example, methoxy-, ethoxy-, propyloxy- or pivaloyloxy-carbonyl. C_2–C_5alkoxycarbonyl is preferred.

Phenyl-lower alkoxycarbonyl is in particular phenyl-C_1–C_4alkoxycarbonyl and is, for example, benzyloxy-, 1- or 2-phenylethoxy-, 3-phenylpropyloxy- or 4-phenylbutyloxy-carbonyl. Benzyloxycarbonyl is preferred. Lower alkenyloxycarbonyl is in particular C_3–C_5alkenyloxycarbonyl, preferably allyloxycarbonyl, while lower alkynyloxycarbonyl is in particular C_3–C_5alkynyloxycarbonyl, such as propargyloxycarbonyl.

Lower alkoxy-lower alkoxycarbonyl is in particular C_1–C_4alkoxy-C_1–C_4alkoxycarbonyl, preferably ethoxyethoxycarbonyl, methoxyethoxycarbonyl and isopropyloxyethoxycarbonyl.

Lower alkyleneoxy-lower alkylene is in particular C_1–C_4alkyleneoxy-C_2-C_4alkylene, preferably ethyleneoxyethylene.

Lower alkylamino is in particular C_1–C_7alkylamino and is, for example, methyl-, ethyl-, n-propyl- and isopropyl-amino. C_1–C_4alkylamino is preferred.

Lower alkenylamino is preferably C_3–C_5alkylamino, such as allyl- and methallylamino.

Lower alkynylamino is preferably C_3–C_5alkynylamino, such as propargylamino.

Phenyl-lower alkylamino is preferably phenyl-C_1–C_4alkylamino, in particular benzyl-, 1and 2-phenylethylamino.

Phenyl-lower alkenylamino is preferably phenyl-C_3–C_5alkenylamino, in particular 3-phenylallylamino and 3-phenylmethallylamino.

Phenyl-lower alkynylamino is preferably phenyl-C_3–C_5alkynylamino, in particular 3-phenylpropargylamino.

Di-lower alkylamino is in particular di-C_1–C_4alkylamino, such as dimethyl-, diethyl-, di-n-propyl-, methylpropyl-, methylethyl-, methylbutyl-amino and dibutylamino.

N-lower alkyl-N-phenyl-lower alkyl amino is in particular N-C_1–C_4alkyl-N-phenyl-C_1–C_4alkylamino, preferably methylbenzylamino and ethylbenzylamino.

Di-phenyl lower alkylamino is in particular di-phenyl-C_1–C_4alkylamino, preferably dibenzylamino.

Lower alkyleneamino is in particular C_2–C_6alkyleneamino, preferably pyrrolidin-1-yl or piperidin-1-yl.

Lower alkyleneoxy-lower alkyleneamino is in particular C_2–C_3-alkyleneoxy-C_2–C_3alkyleneamino, in particular morpholino.

Lower alkanoylamino is in particular C_1–C_5alkanoylamino, such as formyl-, acetyl-, propionyl-, butyryl- or pivaloylamino. C_2–C_5alkanoylamino is preferred.

Phenyl-lower alkanoylamino is in particular phenyl-C_2–C_5alkanoylamino, such as phenylacetyl- or phenylpropionylamino.

Lower-alkanesulfonylamino is in particular C_1–C_7alkanesulfonylamino, such as methane-, ethane-, propane- or butanesulfonylamino. C_1–C_4alkanesulfonylamino is preferred.

Lower alkenyloxy is in particular C_3–C_7alkenyloxy and is, for example, allyloxy or but-2-enyloxy or but-3-enyloxy. C_3–C_5alkenyloxy is preferred.

Phenyl-lower alkoxy is in particular phenyl-C_1–C_4alkoxy, such as benzyloxy, 1- or 2-phenylethoxy, 3-phenylpropyloxy or 4-phenylbutyloxy.

Lower alkenyloxy-lower alkyl is in particular C_3–C_5alkenyloxy-C_1–C_4alkyl, such as 2-allyloxyethyl, and lower alkenyloxy-lower alkenyl or-lower alkynyl is in particular C_3–C_5alkenyloxy-C_3–C_5alkenyl or —C_3–C_5alkynyl.

Extensive pharmacological investigations have shown that the compounds I and their pharmaceutically acceptable salts, for example, have pronounced angiotensin II antagonist properties.

As is known, angiotensin II has strong vasoconstrictor properties, additionally stimulates aldosterone secretion and thus causes distinct sodium/water retention. The consequence of angiotensin II activity is manifested, inter alia, in an increase in blood pressure. The importance of angiotensin II antagonists is in suppressing the vasoconstrictor and aldosterone secretion-stimulating effects caused by angiotensin II by competitive inhibition of the binding of angiotensin II to the receptors.

The angiotensin II antagonist properties of the compounds of the formula I and their pharmaceutically acceptable salts can be detected in the angiotensin II binding test. Rat smooth muscle cells from homogenized rat aorta are used here. The solid centrifugate is suspended in 50 mM tris buffer (pH 7.4) using peptidase inhibitors. The samples are incubated for 60 minutes at 25° C. with ^{25}I-angiotensin II (0.175 nM) and a varying concentration of angiotensin II or test substance. The incubation is then ended by addition of saline buffered with ice-cold phosphate, and the mixture is filtered through Whatman GF/F filters. The filters are counted using a gamma counter. The IC_{50} values are determined from the dose-effect curve. IC_{50} values from about 10 nM are determined for the compounds of the formula I and their pharmaceutically acceptable salts.

For the determination of angiotensin II-induced vasoconstriction, investigations on the isolated rabbit aorta ring can be used. For this purpose, aorta rings are dissected from each chest and fixed between two parallel clamps at an initial tension of 2 g. The rings are then immersed in 20 ml of a tissue bath at 37° C. and aerated with a mixture of 95% O_2 and 5% CO_2. The isometric reactions are measured: At 20-minute intervals, the rings are alternately stimulated with 10 nM angiotensin II (Hypertensin-CIBA) and 5 nM noradrenaline chloride. The rings are then incubated with selected concentrations of the test substances before treatment with the agonists. The data are analysed using a Buxco digital computer. The concentrations which cause a 50% inhibition of the initial control values are given as IC_{50} values. IC_{50} values from about 5 nM are determined for the compounds of the formula I and their pharmaceutically acceptable salts.

The fact that the compounds of the formula I and their pharmaceutically acceptable salts can reduce high blood pressure induced by angiotensin II can be verified in the normotensive anaesthetized rat test model. After

ml/kg i.v.), noradrenaline (1 μg/kg i.v.) or angiotensin II (0.3 μg/kg i.v.) in each case, increasing doses (3–6) of the test substance are intravenously injected by bolus injection, after which angiotensin II or noradrenaline is administered after each dose at 5 minute intervals. The blood pressure is measured directly in the carotid artery and recorded using an on-line data recording system (Buxco). The specificity of the angiotensin II antagonism is shown by the selective inhibition of the pressure effect produced by angiotensin II, but not that produced by noradrenaline. In this test model, the compounds of the formula I and their pharmaceutically acceptable salts show an inhibiting effect from a dose of about 0.3 mg/kg i.v.

The antihypertensive activity of the compounds of the formula I and their pharmaceutically acceptable salts may also be manifested in the renally hypertensive rat test model. High blood pressure is produced in male rats by constricting a renal artery according to the Goldblatt method. Doses of the test substance are administered to the rats by means of a stomach tube. Control animals receive an equivalent volume of solvent. Blood pressure and heart beat are measured indirectly at intervals in conscious animals by the tail clamp method of Gerold et al. [Helv. Physiol. Acta 24, (1966), 58] before administration of the test substances or of the solvent and during the course of the experiments. It was possible to detect the pronounced antihypertensive effect from a dose of about 30 mg/kg p.o.

The compounds of the formula I and their pharmaceutically acceptable salts can therefore be used, for example, as pharmaceutical active ingredients in antihypertensives which are employed, for example, for the treatment of high blood pressure and cardiac insufficiency.

The invention thus relates to the use of the compounds according to the invention and their pharmaceutically acceptable salts for the production of appropriate medicaments and to the therapeutic treatment of high blood pressure and cardiac insufficiency. The industrial production of the active substances is also included in the production of the pharmaceuticals.

The invention relates especially to compounds of the formula I and their salts in which R_1 is an aliphatic hydrocarbon radical which is unsubstituted or substituted by halogen or hydroxyl, or a cycloaliphatic or araliphatic hydrocarbon radical; X_1 is CO or SO_2; X_2 is a divalent aliphatic hydrocarbon radical which is unsubstituted or substituted by hydroxyl or a cycloaliphatic or aromatic radical, or is a divalent cycloaliphatic hydrocarbon radical, it being possible for a carbon atom of the aliphatic hydrocarbon radical to be additionally bridged by a divalent aliphatic hydrocarbon radical; R_2 is carboxyl which, if desired, is esterified or amidated, substituted or unsubstituted amino, formyl which, if desired, is acetalised, hydroxyl which, if desired, is etherified, $S(O)_m$—R where m is 0, 1 or 2 and R is hydrogen or an aliphatic hydrocarbon radical, alkanoyl, unsubstituted or N-substituted sulfamoyl or PO_nH_2 where n is 2 or 3; X_3 is a divalent aliphatic hydrocarbon; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or haloalkylsulfamoyl; and the rings A and B independently of one another are substituted or unsubstituted.

The invention relates in particular to compounds of the formula I and their salts in which R_1 is an aliphatic hydrocarbon radical which is unsubstituted or substituted by halogen or hydroxyl, or a cycloaliphatic or araliphatic hydrocarbon radical; X_1 is CO or SO_2; X_2 is a divalent aliphatic hydrocarbon radical which is unsubstituted or substituted by hydroxyl or a cycloaliphatic or aromatic radical; R_2 is carboxyl which, if desired, is esterified or amidated, substituted or unsubstituted amino, formyl which, if desired, is acetalised, hydroxyl which, if desired, is etherified, $S(O)_m$—R where m is 0, 1 or 2 and R is hydrogen or an aliphatic hydrocarbon radical, alkanoyl, unsubstituted or N-substituted sulfamoyl or PO_nH_2 where n is 2 or 3; X_3 is —CH_2—; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or haloalkylsulfamoyl; and the rings A and B independently of one another are substituted or unsubstituted.

The invention relates in particular to compounds of the formula I and their salts in which R_1 is lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, -lower alkenyl or -lower alkynyl, hydroxy-lower alkyl, -lower alkenyl or -lower alkynyl, cycloalkyl, cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl; X_1 is CO or SO_2; X_2 is alkylene or alkylidene which is unsubstituted or substituted by hydroxyl, a cycloalkyl or cycloalkenyl radical, a phenyl radical or a 5- or 6-membered, monocyclic heteroaromatic radical having up to four identical or different hetero atoms, where the cyclic radicals, for their part, are unsubstituted or substituted by carboxyl which is free or esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, carbamoyl in which the amino group is unsubstituted or monosubstituted or, independently of one another, disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or disubstituted by lower alkylene- or lower alkyleneoxy-lower alkylene, formyl, di-lower alkoxymethyl or oxy-lower alkyleneoxymethylene; R_2 is carboxyl which is free or esterified by an alcohol which is derived from lower alkyl, phenyl-lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl; carbamoyl in which the amino group is unsubstituted or monosubstituted or, independently of one another, disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or disubstituted by lower alkylene- or lower alkyleneoxy-lower alkylene; amino in which the amino group is unsubstituted or monosubstituted or, independently of one another, disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or disubstituted by lower alkylene- or lower alkyleneoxy-lower alkylene; lower alkanoyl-, phenyl-lower alkanoyl-, benzoyl-, lower alkanesulfonyl- or benzenesulfonyl-amino; formyl, di-lower alkoxymethyl, oxy-lower alkyleneoxymethylene, hydroxyl, lower alkoxy, lower alkenyloxy, phenyl-lower alkoxy, phenoxy, $S(O)_m$—R where m is 0, 1 or 2 and R is hydrogen, lower alkyl, lower alkenyl or lower alkynyl; lower alkanoyl, sulfamoyl in which the amino group is unsubstituted or monosubstituted or, independently of one another, disubstituted by lower alkyl, lower alkenyl, lower alkynyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl or disubstituted by lower alkylene- or lower alkyleneoxy-lower alkylene, or is PO_nH_2 where n is 2 or 3; X_3 is —CH_2—; R_3 is carboxyl, 5-tetrazolyl, SO_3H, PO_2H_2, PO_3H_2 or halo-lower alkylsulfamoyl; where (hetero)aromatic radicals including the rings A and B are independently of one another in each case

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