

Combination of angiotensin-converting enzyme inhibitors with calcium antagonists as well as their use in drugs.

5 The present invention relates to a combination of angiotensin-converting enzyme inhibitors (ACE inhibitors) with calcium antagonists as well as their use in drugs, especially in hypotensive drugs. ACE inhibitors are compounds which prevent the conversion of angiotensin I into the pressor-active angiotensin II. Such compounds are, for example, described in the following patent
10 applications or patents:

US-PS 4,350,633, US-PS 4,344,949, US-PS 4,294,832, US-PS 4,350,704, EP-A 50,800, EP-A 31,741, EP-A 51,020, EP-A 49,658, EP-A 49,605, EP-A 29,488, EP-A 46,953 and EP-A 52,870.

15 They are also the subject of German Patent Applications P 3,226,768.1, P 3,151,690.4, P 3,210,496.0, P 3,211,397.8, P 3,211,676.4, P 3,227,055.0, P 3,242,151.6, P 3,246,503.3 and P 3,246,757.5.

20 Their hypotensive action is well documented. Calcium antagonists are compounds which influence the influx of calcium ions into cells, especially smooth muscle cells. Such compounds as well as their hypotensive activity are recorded in a large number of publications and patent applications.

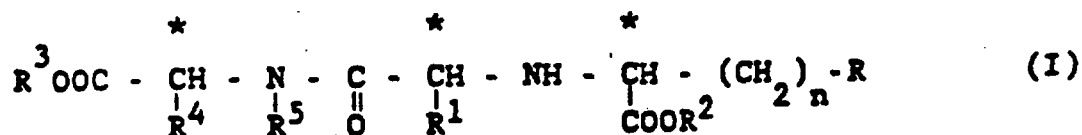
25 Since the two groups of substances act on different blood pressure-regulation systems, in combined use the effect of one combination partner is raised by the other partner. In combined use this leads to a reduction in the dose of the combination partners, compared with individual
30 use. Thus the appearance of side effects known for the two classes of substance can be reduced or avoided.

Combinations of enalapril with calcium antagonists from the dihydropyridine class of structures are described in EP-A-180,785; the combination of the ACE inhibitor enalapril with the nitrophenyl derivative nifedipine is disclosed by M.E. Vincent in Chemical Abstracts 102, January 1985, page 35, No. 372 x.

In addition, EP-A-0,257,485 describes combinations of ACE inhibitors with an inotropic dihydropyridine derivative.

The present invention relates to the combination of ACE inhibitors comprising a bicyclic or tricyclic system with specific calcium antagonists, this combination leading to a particularly strong hypotensive action.

The following compounds of the formula I or their physiologically acceptable salts can be considered as ACE inhibitors:



in which

n = 1 or 2,

R is (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₉)-cycloalkyl, amino-(C₁-C₄)-alkyl, (C₂-C₅)-acylamino-(C₁-C₄)-alkyl, (C₇-C₁₃)-aroylamino-(C₁-C₄)-alkyl, (C₁-C₄)-alkoxy-carbonylamino-(C₁-C₄)-alkyl, (C₆-C₁₂)-aryl-(C₁-C₄)-alkoxycarbonylamino-(C₁-C₄)-alkyl, (C₆-C₁₂)-aryl, which can be mono-, di- or tri-substituted by (C₁-C₄)-alkyl, (C₁-C₄)-alkoxy, hydroxy, halogen, nitro, amino, (C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino and/or methylenedioxy, or 3-indolyl, especially methyl, ethyl, cyclohexyl, tert.-butoxycarbonylamino-(C₁-C₄)-alkyl, benzyloxycarbonyl amino-(C₁-C₄)-

alkyl or phenyl, which can be mono- or di-substituted or, in the case of methoxy, trisubstituted by phenyl, (C₁-C₂)-alkyl, (C₁ or C₂)-alkoxy, hydroxy, fluoro, chloro, bromo, amino, (C₁-C₄)-alkylamino, di-(C₁-C₄)-alkylamino, nitro and/or methylenedioxy, is hydrogen or (C₁-C₈)-alkyl, which can be optionally substituted by amino, (C₁-C₆)-acylamino or benzoylamino, (C₂-C₆)-alkenyl, (C₃-C₉)-cycloalkyl, (C₅-C₉)-cycloalkenyl, (C₃-C₇)-cycloalkyl-(C₁-C₄)-alkyl, (C₆-C₁₂)-aryl or partially hydrogenated aryl, which can each be substituted by (C₁-C₄)-alkyl, (C₁ or C₂)-alkoxy or halogen, (C₆-C₁₂)-aryl-(C₁ to C₄)-alkyl or (C₇-C₁₃)-aroyl-(C₁-C₂)-alkyl, which can both be substituted as defined previously in the aryl radical, a mono- or bi-cyclic heterocyclic radical with 5 to 7 or 8 to 10 ring atoms respectively, of which 1 to 2 ring atoms represent sulfur or oxygen atoms and/or 1 to 4 ring atoms represent nitrogen atoms, or a side chain of a naturally occurring, optionally protected α-amino acid, but especially hydrogen, (C₁-C₃)-alkyl, (C₂ or C₃)-alkenyl, the optionally protected side chain of lysine, benzyl, 4-methoxybenzyl, 4-ethoxybenzyl, phenethyl, 4-amino-butyl or benzoylmethyl,

R² and R³ are the same or different and are hydrogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl or (C₆-C₁₂)-aryl-(C₁-C₄)-alkyl, but especially hydrogen, (C₁-C₄)-alkyl or benzyl, and

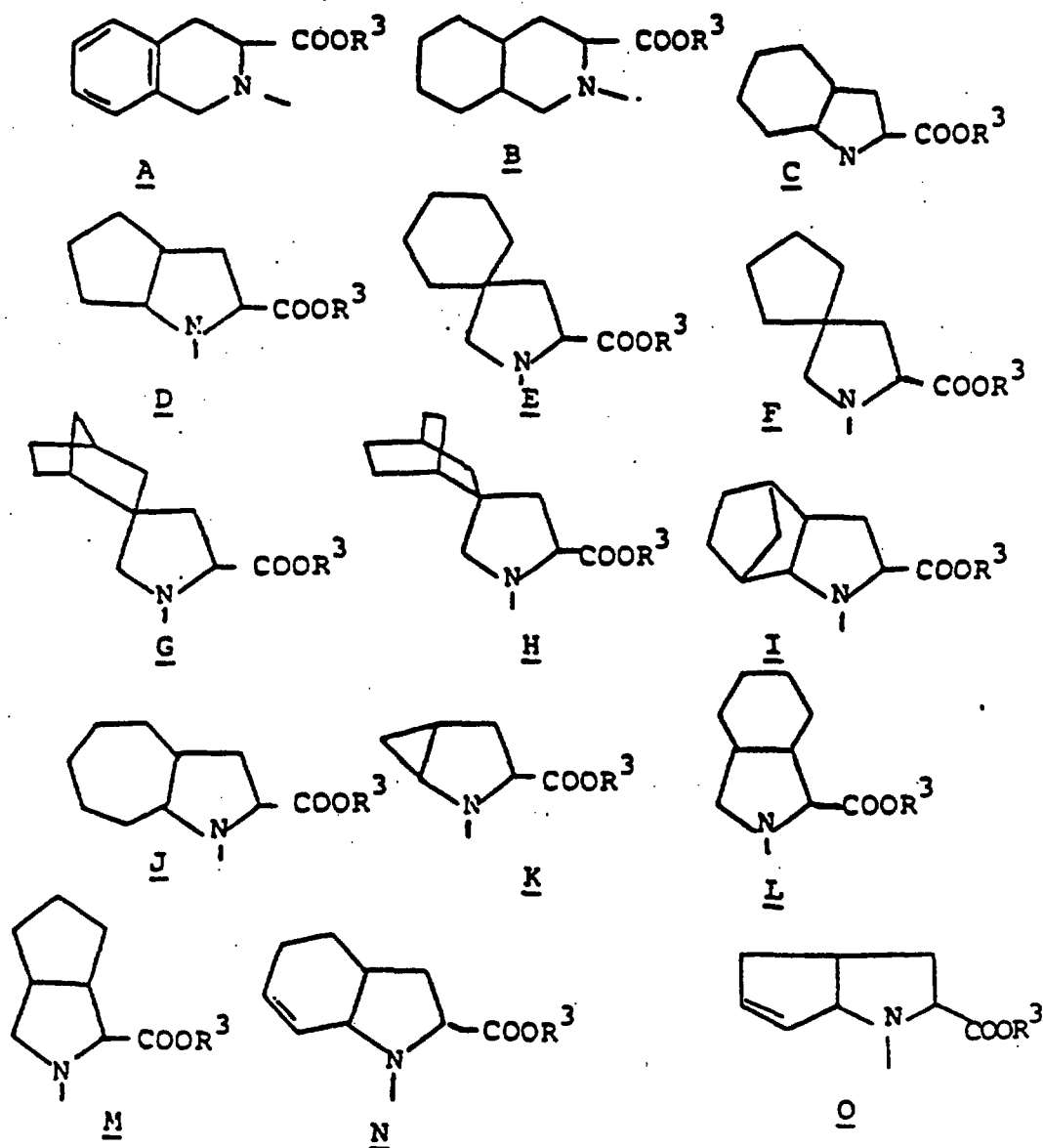
R⁴ and R⁵ together with the atoms carrying them form a ring system from the series

tetrahydroisoquinoline; decahydroisoquinoline; octahydroindole; octahydrocyclopenta[b]pyrrole; 2-azaspiro[4,5]decane; 2-azaspiro[4,4]nonane; spiro[(bicyclo[2,2,1]heptane)-2,3'-pyrrolidine]; spiro[(bicyclo)-[2,2,2]octane)-2,3'-pyrrolidine]; 2-azatricyclo-[4,3,0,1^{6,9}]decane; decahydrocyclohepta[b]pyrrole; octahydroisoindole; octahydrocyclopenta[c]pyrrole; 2,3,3a,4,5,7a-

hexahydroindole; 2-azabicyclo[3,1,0]-hexane and hexahydrocyclopenta[b]pyrrole, which can all be optionally substituted.

5 In the compounds which possess several chiral atoms all possible diastereomers, as racemates or as enantiomers, or mixtures of various diastereoisomers can be considered.

Esters of cyclic amino acids which can be considered exhibit the following structural formulae.



Aryl is to be understood here and also in the following as preferably optionally substituted phenyl, biphenyl or naphthyl. The same applies to aryl-derived radicals such as aryloxy, arylthio. Aroyl is understood as especially benzoyl. Aliphatic radicals can be straight-chain or branched.

A mono- or bi-cyclic heterocyclic radical with 5 to 7 or 8 to 10 ring atoms respectively, of which 1 to 2 ring atoms represent sulfur or oxygen atoms and/or of which 1 to 4 ring atoms represent nitrogen atoms, is to be understood, for example, as thienyl, benzo[b]thienyl, furyl, pyranal, benzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, indazolyl, isoindolyl, indolyl, purinyl, quinolizinyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolyl, cinnolyl, pteridinyl, oxazolyl, isoxazolyl, thiazolyl or isothiazolyl. These radicals can also be partially or completely hydrogenated.

Naturally occurring α -amino acids are described e.g. in Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], volume XV/1 and XV/2.

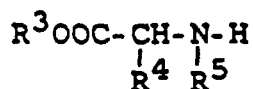
If R^1 represents a side chain of a protected naturally occurring α -amino acid, as e.g. protected Ser, Thr, Asp, Asn, Glu, Gln, Arg, Lys, Hyl, Cys, Orn, Cit, Hyr, Trp, His or Hyp, the groups usual as protective groups in peptide chemistry are preferred (see Houben-Weyl, volume XV/1 and XV/2). In the case where R^1 is the protected lysine side chain, the known amino-protecting groups and especially Z, Boc or (C_1-C_6) -alkanoyl are preferred. As O-protective groups for tyrosine (C_1-C_6) -alkyl is preferred, particularly methyl or ethyl.

Particularly preferred compounds are 2-[N-(1-S-ethoxycarbonyl-3-phenylpropyl)-S-alanyl]-(1S,3S,5S)-2-azabicyclo[3,3,0]octane-3-carboxylic acid (ramipril),

1-[N-(1-S-ethoxycarbonyl-3-phenylpropyl)-S-alanyl]-
(2S,3aR,7aS)octahydro[1H]indole-2-carboxylic acid
(trandolapril) as well as 2-[N-(1-S-ethoxycarbonyl-3-
phenylpropyl)-S-alanyl]-1,2,3,4-tetrahydroisoquinoline-
5 3-S-carboxylic acid (quinapril).

The ACE inhibitors of the formula I can be prepared by
reacting their fragments with one another in a suitable
solvent optionally in the presence of a base and/or a
coupling agent, optionally reducing resulting inter-
10 mediate unsaturated compounds, such as Schiff bases,
removing protective groups temporarily introduced for the
protection of reactive groups, optionally esterifying
compounds of the formula I with (a) free carboxyl
group(s) and optionally converting the compounds obtained
15 into their physiologically acceptable salts.

In the above manner, for example, compounds of the
formula V can be reacted with compounds of the formula
VI.



(V)

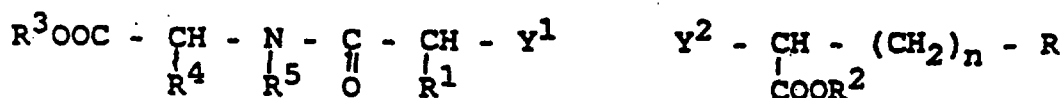


(VI)

The reaction of these compounds can be carried out, for
20 example, in analogy to known peptide coupling methods in
an organic solvent such as DMF, CH_2Cl_2 , DMA in the
presence of coupling agents, such as carbodiimides (e.g.
dicyclohexylcarbodiimide), diphenylphosphoaryl azide,
alkanephosphoric acid anhydrides, dialkylphosphinic acid
25 anhydrides or N,N-succinimidyl carbonates in a solvent
such as CH_3CN . Amino groups in compounds of the formula V
can be activated with tetraethyl diphosphite. The com-
pounds of the formula VI can be converted into active
esters (e.g. with 1-hydroxybenzotriazole), mixed

anhydrides (e.g. with chloroformates), azides or carbodiimide derivatives and thus activated (see Schröder, Lübke, The Peptides, volume 1, New York 1965, pages 76 - 136). The reaction is preferably performed between -20°C and the boiling point of the reaction mixture.

Likewise, compounds of the formula VII can also be reacted with compounds of the formula VIII with the formation of compounds of the formula I,



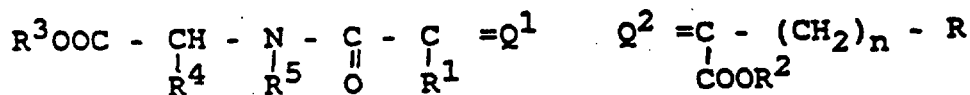
(VII)

(VIII)

wherein either Y¹ represents amino and Y² a leaving group or Y¹ represents a leaving group and Y² amino. Suitable leaving groups are e.g. Cl, Br, I, alkylsulfonyloxy or arylsulfonyloxy.

Alkylations of this type are suitably performed in water or an organic solvent such as a lower aliphatic alcohol (such as ethanol), benzyl alcohol, acetonitrile, nitromethane or a glycol ether at a temperature between -20°C and the boiling point of the reaction mixture in the presence of a base such as an alkali metal hydroxide or an organic amine.

In addition, compounds of the formula IX can be condensed with compounds of the formula X,



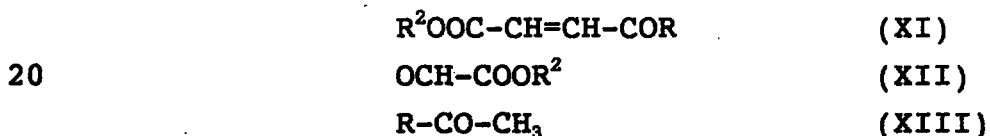
(IX)

(X)

wherein either Q¹ represents amino + hydrogen and Q² oxo or Q¹ represents oxo and Q² amino + hydrogen.

The condensation is suitably performed in water or an organic solvent, such as a lower aliphatic alcohol, at a temperature between -20°C and the boiling point of the reaction mixture in the presence of a reducing agent, such as NaBH_3CN , compounds of the formula I being directly obtained. The Schiff bases or enamines resulting as by-products can, however, also be reduced, after previous isolation, with formation of compounds of the formula II, for example by hydrogenation in the presence of a transition metal catalyst.

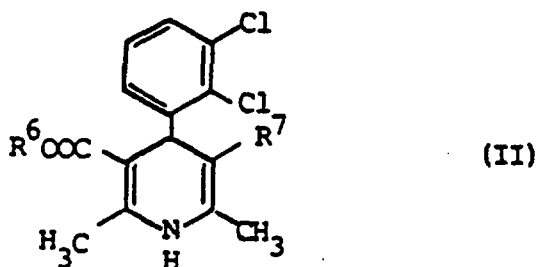
Finally, the reaction of compounds of the formula IX ($\text{Q}^1 = \text{H} + \text{NH}_2$) with compounds of the formula XI or their reaction with compounds of the formulae XII and XIII, suitably in the presence of a base, such as a sodium alkoxide, in an organic solvent, such as a lower alcohol, at a temperature between -10°C and the boiling point of the reaction mixture, also leads to compounds of the formula II ($n = 2$),



the resulting intermediate Schiff bases being reduced as described above and a carbonyl group being converted by reduction to methylene (for example with a complex hydride).

In the abovementioned formulae V - XIII, $\text{R} - \text{R}^5$ and n are as defined in formula I. Temporarily introduced protective groups for the protection of reactive groups not participating in the reaction are removed after the end of the reaction by a method known per se (see Schröder, Lübke, loc cit., pages 1 - 75 and 246 - 270; Greene, "Protective Groups in Organic Synthesis", New York 1981).

As calcium antagonists the compounds of the formula II can be considered



in which R⁶ is methyl, ethyl or isopropyl and R⁷ is methoxycarbonyl, ethoxycarbonyl or 1,2,4-oxidazol-3-yl, as well as their physiologically acceptable salts.

Particularly preferred are

4-(2,3-dichlorophenyl)-2,6-dimethyl-3-methoxycarbonyl-5-ethoxycarbonyl-1,4-dihydropyridine (felodipine, formula II); 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-(1,2,4-oxadiazol-3-yl)-5-isopropoxycarbonyl-1,4-dihydropyridine (formula II); as well as their physiologically acceptable salts with acids.

Of very particular interest are the following combinations:

Ramipril + felodipine or
ramipril + 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-(1,2,4-oxodiazol-5-yl)-5-isopropoxycarbonyl-1,4-dihydropyridine or
trandolapril + felodipine or
trandolapril + 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-(1,2,4-oxadiazol-3-yl)-5-isopropoxycarbonyl-1,4-dihydropyridine or
quinapril + felodipine or
quinapril + 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-(1,2,4-oxodiazol-5-yl)-5-isopropoxycarbonyl-1,4-dihydropyridine or
as well as the physiologically acceptable salts of each of the above single components, in so far as these form

salts.

The invention also relates quite generally to products, which contain:

- 5 a) an ACE inhibitor of the formula I or its physiologically acceptable salts and
- b) a calcium antagonist or its physiologically acceptable salts

10 as a combination preparation for simultaneous, separate or periodically regulated use in the treatment of high blood pressure.

The pharmaceutical compositions can be prepared, for example, either by intimately mixing the single components as powders, or by dissolving the single components in a suitable solvent such as, for example, a
15 lower alcohol and then removing the solvent.

The ratio of the active agents in the combinations and compositions according to the invention is preferably 1 - 15 parts by weight of ACE inhibitor to 15 - 1 parts by weight of calcium antagonist. The combinations and
20 compositions according to the invention contain altogether preferably 0.5 - 99.5% by weight, particularly 4 - 96% by weight, of these active agents.

As mentioned above, the compositions and combinations according to the invention can be used in drugs, particularly for the treatment of high blood pressure,
25 coronary insufficiency and coronary heart disease.

The compositions and combinations according to the invention can be orally or parenterally administered in a corresponding pharmaceutical composition. For oral use,
30 the active compounds are mixed with the additives usual

for this purpose, such as carriers, stabilizers or inert diluents, and converted by the usual methods into suitable forms for administration, such as tablets, dragees, cylindrical capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions. As inert carriers e.g. gum arabic, magnesium carbonate, potassium phosphate, lactose, glucose or starch, particularly maize starch, can be used. In this case, the composition can be formed both as dry or moist granules. Vegetable and animal oils, such as sunflower oil or cod liver oil for example, can be considered as oily carriers or solvents.

For subcutaneous or intravenous administration, the active substances or their physiologically acceptable salts are brought into solution, suspension or emulsion, optionally with the usually employed substances such as solubilizers, emulsifiers or other auxiliaries. As solvents for the active combinations and the corresponding physiologically acceptable salts there can be considered e.g.: water, physiological saline solutions or alcohols, e.g. ethanol, propanediol or glycerol, and in addition also sugar solutions such as glucose or mannitol solutions or else a mixture of the various solvents mentioned.

As salts of the compounds of the formulae I to IV there can be considered, depending on the acid or basic nature of these compounds, alkali or alkaline earth metal salts or salts with physiologically acceptable amines or salts with inorganic or organic acids such as e.g. HCl, HBr, H₂SO₄, maleic acid, fumaric acid, tartaric acid and citric acid.

The following examples serve to illustrate the present invention:

Example 1:

Preparation of an oral combination product from ramipril and felodipine

1,000 tablets, which contain 2 mg of ramipril and 6 mg of felodipine, are prepared as follows:

5	ramipril	2 g
	felodipine	6 g
	maize starch	140 g
	gelatine	7.5 g
10	microcrystalline cellulose	2.5 g
	magnesium stearate	2.5 g

The two active agents are mixed with an aqueous gelatine solution. The mixture is dried and ground to granules. Microcrystalline cellulose and magnesium stearate are mixed with the granules. The granules thus obtained are compressed into 1,000 tablets, each tablet containing 2 mg of ramipril and 6 mg of felodipine.

Example 2:

Preparation of an oral combination product from trandolapril and felodipine

1,000 tablets, which contain 3 mg of trandolapril and 5 mg of felodipine, are prepared as follows:

	trandolapril	3 g
	felodipine	5 g
25	maize starch	130 g
	gelatine	8.0 g
	microcrystalline cellulose	2.0 g
	magnesium stearate	2.0 g

The two active agents are mixed with an aqueous gelatine solution. The mixture is dried and ground to granules. Microcrystalline cellulose and magnesium stearate are mixed with the granules. The granules thus obtained are compressed into 1,000 tablets, each tablet containing 3 mg of trandolapril and 5 mg of felodipine.

Example 3:

Preparation of an oral combination product from quinapril and felodipine

1,000 tablets, which contain 2.5 mg of quinapril and 6 mg of felodipine, are prepared as follows:

5	quinapril	2.5 g
	felodipine	5 g
	maize starch	150 g
	gelatine	7.5 g
10	microcrystalline cellulose	2.5 g
	magnesium stearate	2.5 g

The two active agents are mixed with an aqueous gelatine solution. The mixture is dried and ground to granules. Microcrystalline cellulose and magnesium stearate are
15 mixed with the granules. The granules thus obtained are compressed into 1,000 tablets, each tablet containing 2.5 mg of quinapril and 5 mg of felodipine.



1. A pharmaceutical composition containing
 - a) an angiotensin-converting enzyme inhibitor (ACE inhibitor) of the formula I


$$n = 1 \text{ or } 2,$$

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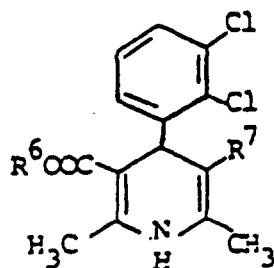
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30

5 aroyl-(C₁-C₂)-alkyl, which can both be substituted
 as defined previously in the aryl radical, a
 mono- or bi-cyclic heterocyclic radical with 5 to
 7 or 8 to 10 ring atoms respectively, of which 1
 to 2 ring atoms represent sulfur or oxygen atoms
 and/or 1 to 4 ring atoms represent nitrogen
 atoms, or a side chain of a naturally occurring,
 optionally protected α-amino acid, but especially
 hydrogen, (C₁-C₃)-alkyl, (C₂ or C₃)-alkenyl, the
 10 optionally protected side chain of lysine,
 benzyl, 4-methoxybenzyl, 4-ethoxybenzyl,
 phenethyl, 4-aminobutyl or benzoylmethyl,
 R² and R³ are the same or different and are hydrogen, (C₁-
 C₆)-alkyl, (C₂-C₆)-alkenyl or (C₆-C₁₂)-aryl-(C₁-C₄)-
 15 alkyl, but especially hydrogen, (C₁-C₄)-alkyl or
 benzyl, and
 R⁴ and R⁵ together with the atoms carrying them form a
 ring system from the series
 tetrahydroisoquinoline; decahydroisoquinoline;
 20 octahydroindole; octahydrocyclopenta[b]pyrrole;
 2-azaspiro[4,5]decane; 2-azaspiro[4,4]nonane;
 spiro[(bicyclo[2,2,1]heptane)-2,3'-pyrrolidine];
 spiro[(bicyclo)-[2,2,2]octane)-2,3'-pyrrolidine];
 2-azatricyclo-[4,3,0,1^{6,9}]decane; decahydrocyclo-
 25 hepta[b]pyrrole; octahydroisoindole; octahydro-
 cyclopenta[c]pyrrole; 2,3,3a,4,5,7a-hexahydro-
 indole; 2-azabicyclo[3,1,0]-hexane and hexahydro-
 cyclopenta[b]pyrrole, which can all be optionally
 substituted, or a physiologically acceptable salt
 30 thereof and

b) a calcium antagonist of the formula II



(II)

in which



R⁶ is methyl, ethyl or isopropyl and
R⁷ is methoxycarbonyl, ethoxycarbonyl or 1,2,4-oxadiazol-3-yl, or a physiologically acceptable salt thereof.

- 5 2. A composition as claimed in claim 1, containing 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-methoxy-carbonyl-5-ethoxycarbonyl-1,4-dihydropyridine or a physiologically acceptable salt thereof.
- 10 3. A composition as claimed in claim 1, containing ramipril + felodipine or
ramipril + 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-(1,2,4-oxodiazol-5-yl)-5-isopropoxycarbonyl-1,4-dihydropyridine or
trandolapril + felodipine or
15 trandolapril + 4-(2,3-dichlorophenyl)-2,6-dimethyl-3-(1,2,4-oxadiazol-5-yl)-5-isopropoxycarbonyl-1,4-dihydropyridine or
quinapril + felodipine or
quinapril + 4-(2,3-dichloro)-2,6-dimethyl-3-(1,2,4-oxodiazol-5-yl)-5-isopropoxycarbonyl-1,4-dihydro-
20 pyridine or in each case the physiologically acceptable salts of the above single components, in so far as these form salts.
- 25 4. A process for the preparation of a composition as claimed in claim 1, wherein
a) an ACE inhibitor or a physiologically acceptable salt thereof and
b) a calcium antagonist or a physiologically acceptable salt thereof
30 are combined in a suitable form for administration with a physiologically acceptable carrier and optionally further auxiliaries or additives.
5. A product, containing



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- a) an ACE inhibitor of the formula (I) as claimed in claim 1, or a physiologically acceptable salt thereof and
 - b) a calcium antagonist of the formula (II) or a physiologically acceptable salt thereof as claimed in claim 1
- as a combination preparation for simultaneous, separate or periodically regulated use in the treatment of high blood pressure.