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PHARMACEUTICAL COMPOSITION FOR USE AGAINST HYPERTENSION AND CONGESTIVE HEART FAILURE

This invention relates to novel pharmaceutical compositions effective against hypertension and congestive heart failure and to their production and use.

The present invention provides a pharmaceutical composition containing as active agents:

a) a Calcium-Antagonist

and

b) 7-(N-[1(S)-Ethoxycarbonyl-3-Phenylpropyl]-(S)-Alanyl)-1,4-Dithia-7-Azaspiro-[4,4]Nonane-8-(S)-Carboxylic Acid and its pharmaceutically acceptable salts.

The calcium antagonists comprise a class of physiologically active substances characterised by their calcium antagonistic or calcium channel blocking activity. A wide range of such compounds are now known and have found wide therapeutic application, in particular in the treatment of cardiovascular disturbances or disease, for example in the treatment of coronary insufficiency, disturbance in cerebral circulation, hypertension and in the treatment of other disturbances in peripheral circulation. Typically, the calcium antagonists are employed as vasodilators, e.g. in the treatment of hypertension.

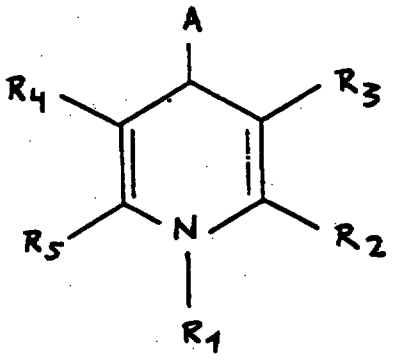
Component b) is an angiotensin-converting enzyme (ACE-) inhibitor. Little has been published on its pharmacological and biopharmaceutical properties. ACE inhibitors are known compounds that influence the transformation of angiotensin I in angiotensin II and that are useful in the lowering of elevated blood pressure when this is due to the action of angiotension II. ACE-blocking compounds when administered alone have to be used in relatively high amounts that may lead to unwanted side effects.

The pharmaceutical composition of the invention and also co-administration of component a) and component b) possess surprisingly and unexpectedly advantageous pharmaceutical properties with an especially favourable or improved pharmacological/therapeutic profile. In particular it has been found that co-administration of a component a) and a component b) as aforesaid in conjunction results in unexpected enhancement of antihypertensive activity and an surprisingly potent activity against congestive heart failure.

The component a) induces increase in central venous pressure and consequently the increase in cardiac output is blunted in component b) pretreated animals. The increase of central venous

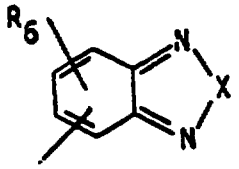
pressure in the absence of cardiac depression (cardiac contractility was accurately assessed with a strain gauge sewn onto the myocardium) indicates an increased venous return caused by arteriolar dilatation. The blunted effect of component a) hence indicates an increased venous compliance after ACE inhibition.

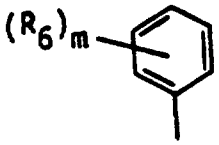
Preferred calcium antagonists for use in the compositions of the invention are those of the dihydropyridine class, e.g. of the formula I



(I)

wherein A is a residue of formula (a), (b) or (c)







(a) (b) (c)

R_1 is hydrogen, (C_{1-6})alkyl, hydroxy(C_{2-6})alkyl, (C_{3-6})alkoxyalkyl, (C_{3-6})alkenyl, (C_{3-6})alkinyl, (C_{3-7})cycloalkyl or (C_{4-8})cycloalkylalkyl, or (C_{7-9})phenylalkyl or (C_{9-12})phenylalkenyl, wherein the phenyl ring is unsubstituted or mono-, di- or tri-substituted by halogen, hydroxy, (C_{1-4})alkyl or (C_{1-4})alkoxy,

R_2 and R_5 are each independently hydrogen, (C_{1-6})alkyl, (C_{7-10})phenylalkyl, (C_{3-7})cycloalkyl or (C_{4-8})cycloalkylalkyl, whereby, when A is a residue b, one of R_2 and R_5 may also be (C_{1-4})hydroxyalkyl or cyano,

R_3 and R_4 are independently -CN, $-COOR_7$, $-COR_8$, $-S(O)_nR_9$ or $-COO-B-N\ R_{10}\ R_{11}$,

n is 0,1 or 2,

R_6 is hydrogen, halogen, (C_{1-4})alkyl, $(_{1-4})$alkoxy, (C_{1-4})alkyl thio, (C_{1-4})alkylsulfonyl, trifluoromethyl, nitro, hydroxy, azido, amino, (C_{1-4})alkylamino, di[$(C_{1-4}$alkyl]amino, (C_{1-5})

alkanoylamino, (C_{2-5})carbalkoxy, aminocarbonyl, trifluoromethoxy, cyano, sulfamoyl, (C_{1-4})alkylsulfamoyl or di[(C_{1-4})alkyl]sulfamoyl,

X is oxygen or sulphur,

m is 0, 1 or 2,

R_7, R_8 and R_9 are each independently (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkinyl, (C_{3-7})cycloalkyl, (C_{4-8})cycloalkylalkyl, hydroxy-(C_{2-6})alkyl, (C_{3-6})alkoxyalkyl, hydroxy (C_{4-8})alkoxyalkyl, amino-(C_{2-6})alkyl, (C_{1-4})alkylamino(C_{2-6})alkyl, di[(C_{1-4})alkyl]aminoalkyl, phenyl, (C_{7-10})phenylalkyl, a 5- or 6-membered heterocyclic ring, containing a nitrogen or oxygen or sulphur atom and which may also contain 1, 2 or 3 additional ring nitrogen atoms, or (C_{1-4})alkyl optionally substituted by a 5- or 6-membered heterocyclic ring containing a nitrogen or oxygen or sulphur atom as heteroatom and which may additionally contain 1, 2 or 3 further ring ntrogen atoms, whereby, when A is a residue b, R_7 may also be trifluoroethyl,

B is (C_{1-14})alkylene,

R_{10} and R_{11} are each independently (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkinyl, (C_{3-7})cycloalkyl, (C_{4-8})cycloalkylalkyl, hydroxy(C_{2-6})alkyl, (C_{3-6})alkoxyalkyl, hydroxy(C_{4-8})alkoxyalkyl, amino(C_{2-6})alkyl, (C_{1-4})alkylamino(C_{2-6})alkyl, di[C_{1-4})alkyl]-amino-(C_{1-4})alkyl, phenyl, or (C_{7-10})phenylalkyl, or

R_{10} and R_{11} form together with the nitrogenatom to which they are attached a 5-, 6- or 7-membered heterocyclic ring optionally

containing a further heteroatom selected from oxygen or sulphur or a group =N-R_{12} wherein R_{12} is (C_{1-4})alkyl, benzyl or bis- phenylmethyl, optionally mono- or independently disubstituted in the phenyl ring(s) by halogen of atomic number from 9 to 35 or alkoxy of 1 to 4 carbon atoms.

In formula I, (C_{1-6})alkyl groups preferably contain 1 to 4 carbon atoms, more preferably 1 or 2 carbon atoms, methyl groups being most preferred. (C_{1-4})-alkyl, -alkoxy, -alkylthio and -alkylsulfonyl groups preferably contain 1 or 2 carbon atoms. Hydroxy, alkoxy, hydroxyalkoxy, amino and alkylamino moieties of hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl, aminoalkyl and alkylaminoalkyl groups R_7 in residues -COOR_7 are preferably not attached at the α-carbon atom. Suitably they are in the terminal position. Preferred alkylene moities of hydroxyalkyl, alkoxyalkyl, hydroxyalkoxyalkyl, aminoalkyl and alkylaminoalkyl are ethylene and propylene. The alkylene moiety of cycloalkylalkyl groups is suitably methylene. Cycloalkyl moieties of cycloalkylalkyl groups are suitably cyclopropyl, cyclopentyl or cyclohexyl. By halogen is meant fluorine, chlorine or bromine, in particular chlorine.

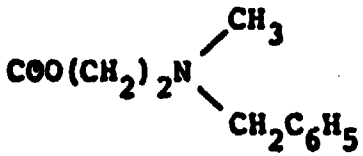
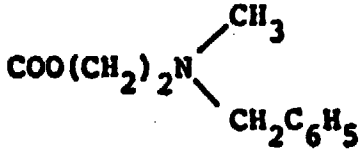
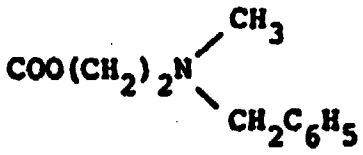
The multiple bond in alkenyl, alkinyl and phenylalkenyl groups R_1 or -COOR_7 is preferably not in the α,β-position. Alkenyl and alkinyl groups preferably have 3 to 5 carbon atoms. Alkenyl is suitably allyl or 2-methylallyl is suitably propionyl. Phenylalkenyl groups preferably have the trans-configuration and include, e.g. cinnamyl. When R_1 is phenyl this is preferably unsubstituted. When R_1 is di- or tri-substituted phenyl, the substituents are preferably the same and are halogene or alkyl. Hetrocyclic rings as R_7, R_8 and R_9 are, e.g. furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, piperidinyl, morpho-

linyl and triazinyl. Hetrocyclic rings comprised by R_{10} and R_{11} together with the nitrogen atom to which they are attached are preferably saturated and include pyrrolidine, piperidine, piperazine, N-alkylpiperazine and morpholine rings. Most preferred is however, di-phenyl-methyl-piperazine that can be substituted in the phenylring(s) as described above. R_2 and R_5 are preferably identical. R_6 is suitably halogen, alkyl, alkoxy, nitro or trifluoromethyl and is preferably in the o- or m-position with respect to the position of attachement of the dihydropyridine residue. When A is a residue a), R_6 is preferably hydrogen.

In $-COOBNR_{10}R_{11}$ B stands for an alkylene chain of 1 to 14 carbon atoms preferably of 5 to 14 carbon atoms especially of 10 carbon atoms.

Particularly suitable compounds of formula I, wherein A is a residue (a), for use in accordance with the present invention are those shown in the following table (the figure indicated under "y" represents the position of attachment of (a) to the dihydropyridine nucleus

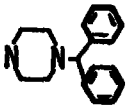
Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	X	y
1	H	CH_3	CN	COO-i-Bu	CH_3	H	O	4
2	H	CH_3	$COOC_2H_5$	SO_2CH_3	CH_3	H	O	4
3	H	CH_3	CN	$COOC_2H_5$	CH_3	H	O	4
4	H	CH_3	CN	$COOC_2H_5$	CH_3	H	S	4
5	H	CH_3	CN	$COOCH_2CH(CH_3)_2$	CH_3	H	S	4
6	H	CH_3	$COOCH_3$	COC_6H_5	CH_3	H	O	4
7	H	CH_3	$COO(CH_2)_2N(CH_3)(CH_2C_6H_5)$	$COOC_2H_5$	CH_3	H	O	4
8	H	CH_3	$COO(CH_2)_2N(CH_3)(CH_2C_6H_5)$	$COOC_2H_5$	CH_3	H	S	4
9	H	CH_3	$COO(CH_2)_2N(CH_3)_2$	$COO(CH_2)_2N(CH_3)_2$	CH_3	H	O	4

Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	X	y
10	H	CH_3	$COO(CH_2)_2N(CH_3)_2$	$COO(CH_2)_2N(CH_3)_2$	CH_3	H	S	4
11	H	CH_3	$COO(CH_2)_2N(CH_3)_2$	$COOC_2H_5$	CH_3	H	O	4
12	H	CH_3	$COO(CH_2)_2N(CH_3)_2$	$COOC_2H_5$	CH_3	H	S	4
13	H	CH_3		$COOC_2H_5$	CH_3	H	S	5
14	H	CH_3		$COOC_2H_5$	CH_3	H	O	5
15	H	CH_3		$COOCH_3$	CH_3	H	O	4
16	H		$COOC_2H_5$	$COOC_2H_5$	CH_3	H	O	4
17	H		$COOCH_3$	$COOCH_3$	CH_3	H	O	4
18	H		$COOCH_3$	$COOCH_3$		H	O	4

Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	X	y
19	H		$COOC_2H_5$	$COOC_2H_5$		H	O	4
20	H	CH_3	$COO(CH_2)_2-C_6H_5$	$COOCH_3$	CH_3	H	O	4
21	H	CH_3	$COOCH_3$	$COOCH_2C_6H_5$	CH_3	H	O	4
22	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	H	O	4
23	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	H	S	4
24	H	CH_3	$COOC(CH_3)_3$	$COOC(CH_3)_3$	CH_3	H	S	4
25	H	CH_3	$COOCH_3$	$COOCH_3$	CH_3	7-Cl	O	4
26	H	CH_3	$COOCH_3$	$COOCH_3$	CH_3	H	S	4
27	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	$5-OCH_3$	S	4
28	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	7-Cl	S	4
29	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	H	S	5
30	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	4-Cl	S	5

Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	X	y
31	H	CH_3	$COC(CH_3)_3$	$COC(CH_3)_3$	CH_3	H	S	4
32	H	CH_3	$COCH_3$	$COCH_3$	CH_3	7-Cl	O	4
33	H	CH_3	$COCH_3$	$COCH_3$	CH_3	H	S	4
34	H	CH_3	COC_2H_5	COC_2H_5	CH_3	5-OCH_3	S	4
35	H	CH_3	COC_2H_5	COC_2H_5	CH_3	7-Cl	S	4
36	H	CH_3	COC_2H_5	COC_2H_5	CH_3	H	S	5
37	H	CH_3	COC_2H_5	COC_2H_5	CH_3	4-Cl	S	5
38	H	CH_3	$COCH_3$	$COCH_3$	CH_3	H	O	4
39	H	CH_3	$COCH_3$	$COOC_2H_5$	CH_3	H	O	4
40	H	CH_3	$COCH_3$	$COOC_2H_5$	CH_3	H	S	4
41	H	CH_3	$COOCH_2CH(CH_3)_2$	$COOCH_3$	CH_3	H	O	4
42	H	CH_3	$COOCH_3$	$COOCH_3$	CH_3	H	O	4

Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	X	y
43	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	H	O	5
44	H	CH_3	$COOCH_2CH(CH_3)_2$	$COOC_2H_5$	CH_3	H	S	4
45	H	CH_3	$COOCH_2CH(CH_3)_2$	$COOC_2H_5$	CH_3	H	O	4
46	H	CH_3	$COOC(CH_3)_3$	$COOC(CH_3)_3$	CH_3	H	O	4
47	H	CH_3	$COOCH_2CH(CH_3)_2$	$COOCH_2CH(CH_3)_2$	CH_3	H	O	4
48	H	CH_3	$COO(CH_2)_2OC_2H_5$	$COOC_2H_5$	CH_3	H	O	4
49	H	CH_3	$COO(CH_2)_2OC_2H_5$	$COOC_2H_5$	CH_3	H	S	4
50	H	CH_3	$COO(CH_2)_2OC_2H_5$	$COOC_2H_5$	CH_3	H	S	5
51	H	CH_3	$COOCH(CH_3)_2$	$COOCH_3$	CH_3	H	O	4
52	H	CH_3	$COO(CH_2)_2OCH_3$	$COOCH_3$	CH_3	H	O	4
53	H	CH_3	$COO(CH_2)_2OCH(CH_3)_2$	$COOCH_3$	CH_3	H	O	4
54	H	CH_3	$COO(CH_2)_2OC_2H_5$	$COOCH_3$	CH_3	H	O	4
55	H	CH_3		$COOCH_3$	CH_3	H	O	4
56	H	CH_3	$COO(CH_2)_2OCH_3$	$COOCH(CH_3)_2$	CH_3	H	O	4

Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	X	y
57	H	CH_3	$COOCH_3$	$COOC_2H_5$	CH_3	H	O	4
58	CH_3	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	H	O	4
59	$n\text{-}C_3H_7$	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	H	O	4
60	H	CH_3	$COO(CH_2)_{10}$- 	$COOCH_3$	CH_3	H	O	4

Suitable compounds of formula I, wherein A is a residue (b), for use in accordance with the present invention are those shown in the following table:

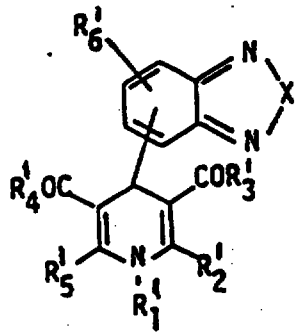
	R_1	R_2	R_3	R_4	R_5	R_6	x	y	m
61	H	CH_3	$COOCH_2CF_3$	$COOCH_3$	CH_3	o-Cl	-	-	1
62	H	CH_3	$COOCH_3$	$COOC_2H_5$	CH_3	2,3-di-Cl	-	-	2
63	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_2OH	$m\text{-}NO_2$	-	-	1
64	H	CH_3	$COOCH(CH_3)_2$	$COOCH_3$	-CN	$m\text{-}NO_2$	-	-	1
65	H	CH_3	$COO(CH_2)_2N(CH_3)(CH_2\text{-}C_6H_5)$	$COOCH_3$	CH_3	$m\text{-}NO_2$	-	-	1
66	H	CH_3	$COOCH_3$	$COOCH_3$	CH_3	$o\text{-}NO_2$	-	-	1
67	H	CH_3	$COO(CH_2)_2OC_3H_7$	$COO(CH_2)_2OC_3H_7$	CH_3	$m\text{-}NO_2$	-	-	1

Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	x	y	m
68	H	CH_3	$COO(CH_2)_2OCH_3$	$COOCH(CH_3)_2$	CH_3	m-NO_2	-	-	1
69	H	CH_3	$COOCH_3$	$COOCH_2CH(CH_3)_2$	CH_3	o-NO_2	-	-	1
70	H	CH_3	$COOC_2H_5$	$COOCH_3$	CH_3	m-NO_2	-	-	1
71	H	CH_3	$COOC_2H_5$	$COOC_2H_5$	CH_3	o-CF_3	-	-	1

A suitable compound of formula I, wherein A is a residue (c), for use in accordance with the present invention is compound No. 72 wherein:

R_1 = H, R_2 = CH_3, R_3 = $COOC_2H_5$, R_4 = $COOC_2H_5$, R_5 = CH_3, and R_6 = o-SCH_3 .

Especially prefered calcium-antagonists according to a) have the formula



Ia

wherein

R_1' is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl or alkinyl of 3 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, cycloalkylalkyl of 4 to 8 carbon atoms, phenylalkyl of 7 to 9 carbon atoms or phenylalkenyl of 9 to 12 carbon atoms, the phenyl ring being unsubstituted or mono-, di- or trisubstituted independently by halogen, hydroxy or alkyl or alkoxy of 1 to 4 carbon atoms.

R_2' and R_5, independently, are hydrogen or alkyl of 1 to 6 carbon atoms,

R_3' and R_4', independently, are alkyl of 1 to 6 carbon atoms, alkenyl or alkinyl of 3 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, cycloalkylalkyl of 4 to 8 carbon atoms, alkoxy of 1 to 6 carbon atoms, hydroxyalkoxy of 2 to 6 carbon atoms, alkoxyalkoxy of 3 to 6 carbon atoms, hydroxyalkoxyalkoxy of 4 to 8 carbon atoms, alkenyloxy or alkinyloxy of 3 to 6 carbon atoms, cycloalkyloxy of 3 to 7 carbon atoms or cycloalkylalkoxy of 4 to 8 carbon atoms, or R_3' has the significance $O\text{-}B'\text{-}R_7'$, wherin B' is an alkylene chain of 9 to 14 carbon

atoms and R_7' is piperidine or piperazine both substituted in the 4 position by methyl, benzyl or bis-phenylmethyl optionally mono- or independently disubstituted in the phenyl ring(s by halogen of atomic number from 9 to 53 or alkoxy of 1 to 4 carbon atoms and R'_4 has the significance cited above,

R_6' is hydrogen, halogen, alkyl or alkoxy or alkylthio or alkylsulfonyl, each of 1 to 4 carbon atoms, trifluoromethyl, nitro or hydroxy, and

X has the above significance.

The calcium antagonists used according to the invention are generally described together with their calcium antagonistic and i.a. antihypertensive activity in earlier published patents. In these Patents may also be mentioned that salt forms of the calcium-antagonists of formula I may be used instead of the free bases. Further it may be contemplated that when the substituents in the 2 and 6 positions and/or 3 and 5 positions of the 1,4-dihydropyridinyl moiety are different the calcium antagonists may exist in racemic form or in idividual enentiomer forms.

Particularly interesting calcium-antagonists of formula I or of formula Ia are 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester, hereinafter referred to as compound No 1;4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-3-methoxycarbonyl-pyridine-5-carboxylic acid isopropyl ester, hereinafter referred to as compound No 2,4-(2,1,3-benzoxathiadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester, hereinafter referred to as compound No 3 and (+)-(S)-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid-[10-[4-(diphenylmethyl)-

piperazin-1-yl]decyl]ester referred to as compound No 4; especially interesting are compounds No 2 and No 4.

7-(N-[1(S)-Ethoxycarbonyl-3-Phenylpropyl]-(S)Alanyl)-1,4-Dithia-7-Azaspiro[4,4]Nonane-8-(S)-Carboxylic Acid has the alternative chemical name [8S-[7[R*)],8R*]]-7-[2-[[1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid. It is also identified by SCHERING as SCH-33844 and has the generic name SPIRAPRIL. This compound is described in Example 3 of the US-Patent No 4,470,972. In this US-Patent it is also stated that the compound has antihypertensive activity. Pharmaceutical acceptable salt forms may be used. The hydrate may be used. In this US-Patent different salt forms are described that can be used instead of the free base e.g. the hydrochloride as described in Example 4 of this patent or the hemimaleate as described in Example 5 of this patent. The preferred form is the monohydrochloride monohydrate.

The co-administration of a calcium antagonist and component b) exhibits potent anti-hypertensive activity and activity against congestive heart failure as indicated in pharmacological experiments.

For example when a calcium antagonist especially a compound of formula I and a component b) are co-administered to animals, the natriuretic and diuretic activity of the calcium antagonists especially of the compounds of formula I may be surprisingly retained. Co-administering a calcium antagonist especially a compound of formula I with the above ACE-inhibitor thus reduces the need for further diuretics and/or beta-blockers. This is shown in the hydrated rat test (method of Flückiger et al., Schweiz. Med. Wochenschrift 93, No 35 [1963] 1232-7) described in the following:

Groups of 12 rats are used. Component a) at a diuresis inducing doses e.g. at 0.3 mg/kg p.o. to 3 mg/kg p.o. is investigated alone or in combination with component b) at a dosage of 3 mg/kg s.c. The compounds are administered at the same time. Urine is collected for 3 hours and its volume and sodium excretion measured.

This effect is confirmed in sodium-depleted rats. Rats are given furosemide (50 mg/kg/day) with drinking water for two days. Groups of 6 animals are used. The calcium antagonist is administered at diuresis dosages e.g. of 0.3 to 3 mg/kg p.o and component b) at dosages of 3 mg/kg s.c. The compounds are administered at the same time. Urine is collected for 3 hours and its volume and sodium excretion measured. Similar values as in the hydrated rat test are obtained.

It has thus been unexpectedly found that the diuretic and natriuretic activity is generally maintained .

This is surprising and makes the combinations of the invention particularly well-suited in the treatment of hypertension and congestive heart failure and reduces the need for diuretics.

The importance of this effect is highlighted by the increasing concerns in informed circles about the metabolic consequences of diuretics administration over extended periods. The antihypertensive effect of the co-administering a calcium antagonist and component b), is further supplemented by the renal effect.

Both components a) and b) may be - as discussed above - in the free base or where appropriate in salt, e.g. in acid addition salt form.

The new composition may be prepared by a process comprising formulating a calcium antagonist and component b) in a state of purity sufficient for pharmaceutical acceptability. Conventional pharmaceutical excipient including carrier and diluents, may also be formulated therewith.

The compositions of the invention are therefore indicated for use in the treatment of hypertension and congestive heart failure.

The calcium antagonist may be administered at e.g. one third to 100 percent of the normal dose for treating e.g. hypertension or congestive heart failure. An indicated oral daily dosage of compounds of formula I is from about 0.2 mg to about 350 mg, particularly from about 1 to 70 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.05 mg to about 175 mg e.g. to 20 mg of the compounds, or in sustained release form. The prefered compound is compound No. 2. An indicated dose is from about 2.0 to about 10 mg twice or once a day p.o.

An indicated preferred weight ratio of a calcium antagonist to the component b) calculated on the free base moiety thereof, may be from about 50:1 to about 1:10, particularly from about 10:1 to about 1:5, preferably from about 5:1 to about 1:3. Component b) may be administered at e.g. one third to 100 percent of the normal dose for treating hypertension or congestive heart failure. Contemplated dosage forms include 3 mg, 6 mg, 12 mg and 24 mg.

Thus for compound No 2 and the component b) preferred ratio is from about 50:1 to about 1:5, especially about e.g. 5:1 to 1.1 such as 1:1, 4:1, 3:1 or 2:1.

Conveniently, components a) and b) are administered in the form of a pharmaceutical composition in association with a pharmaceutical carrier or diluent. Such compositions may be formulated in conventional manner so as to be, for example, a solution such as an injectable solution or suspension, or preferably a solid form such as a tablet or capsule. If desired one or both of the components may be in sustained release form, e.g. in the case of compound No. 1 and 2 as described in GB 218 1 053 A or 216 0 100 A.

If desired the active agents may be arranged in a pack to facilitate administration of a particular dosage regimen, e.g. in a particular order in a blister pack.

A suitable form of administration may consist of a pack or dispenser device containing the composition of the invention together with instructions for use in hypertension or congestive heart failure.

A suitable composition may also consist of a pack containing separately a component a) and component b) required for concomitant administration, conveniently together with instructions for the concomitant administration of a predetermined amount of a component a) and of a predetermined amount of the component b).

The following Examples are illustrative of compositions for use in the invention.

EXAMPLE 1: Hard gelatine capsules for oral administration

Hard gelatine capsules containing the ingredients indicated below may be prepared by conventional techniques, and be administered once a day for the treatment of hypertension and congestive heart failure.

Ingredient	Weight
Compound No 2	10.0 mg
Component b)	2.0 mg
Lactose	167.0 mg
Sodium lauryl sulfate	5.5 mg
Corn starch	128.0 mg
Aerosil 200	1.5 mg
Polyethylenglycol 6000	8.0 mg
	322.0 mg

EXAMPLE 2: Tablets for oral administration

Sufficient amounts of the components are mixed in conventional manner and filled into gelatine capsules or compressed to tablets, which are administered once a day for the treatment of hypertension and congestive heart failure.

Ingredient	Weight
Compound No 2	10.0 mg
Component b)	2.0 mg
Lactose	224.0 mg
Sodium lauryl sulfate	2.0 mg
Polyvinylpyrrolidone	8.0 mg
Corn starch	13.0 mg
Magnesium stearate	2.6 mg
	262.0 mg

EXAMPLE 3: Separate Co-administration

Capsules of compound No. 2 may be made up with the following composition

Compound No 2	10	mg
Microcrystalline Cellulose (Avacel)	47	mg
Cetyl Palmitate	10	mg
Hydroxypropyl methylcellulose (Methocel E4M)	90	mg
Silica colloidal	1	mg
Magnesium stearate	2	mg
	160	mg

and Capsules of component b) may be made up with the following composition

Component b)	12	mg
Lactose	349	mg
Silica (colloidal)	8	mg
Maleic acid (ground)	5	mg
Stearic acid	16	mg
	400	mg

These may be arranged in calendar packs. If desired combined capsules containing both active agents may be produced.

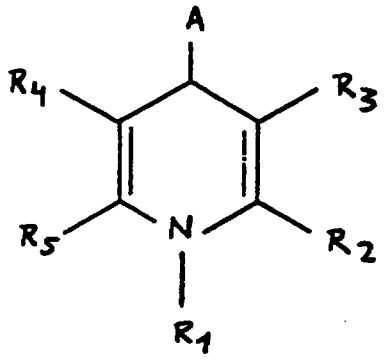
CLAIMS:

1. A pharmaceutical composition comprising

   a) A calcium antagonist and

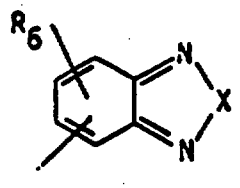
   b) 7-(N-[1(S)-Ethoxycarbonyl-3-Phenylpropyl]-(S)-Alanyl)-1,4-Dithia-7-Azaspiro-[4,4]Nonane-8-(S)-Carboxylic Acid and the pharmaceutically acceptable salts thereof.

2) A pharmaceutical composition according to claim 1 characterized in that the calcium-antagonists are those of formula I

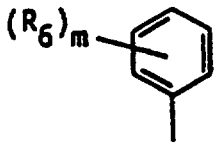


I)

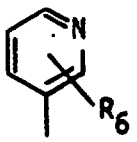
wherein A is a residue of formula (a), (b) or (c)



(a)



(b)



(c)

* C L M S *

R_1 is hydrogen, $(_{1-6})$alkyl, hydroxy(C2-6)alkyl, (C_{3-6})alkoxyalkyl, (C_{3-6})alkenyl, (C_{3-6})alkinyl, (C_{3-7})cycloalkyl or (C_{4-8})cycloalkylalkyl, or (C_{7-9})phenylalkyl or (C_{9-12})-phenylalkenyl, wherein the phenyl ring is unsubstituted or mono-, di- or tri-substituted by halogen, hydroxy, (C_{1-4})alkoxy,

R_2 and R_5 are each independently hydrogen, (C_{1-6})alkyl, (C_{7-10})-phenylalkyl, (C_{3-7})cycloalkyl or (C_{4-8})cycloalkylalkyl, whereby, when A is a residue b, one of R_2 and R_5 may also be (C_{1-4})hydroxyalkyl or cyano,

R_3 and R_4 are independently -CN, $-COOR_7$, $-COR_8$, $-S(O)_nR_9$ or $-COO-B-N\ R_{10}\ R_{11}$,

n is 0, 1 or 2,

R_6 is hydrogen, halogen, (C1-4)alkyl, $(C_{1-4}$alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylsulfonyl, trifluoromethyl, nitro, hydroxy, azido, amino, (C_{1-4})alkylamino, di[(C_{1-4})alkyl]-amino, (C_{1-5})alkanoylamino, (C_{2-5})carbalkoxy, aminocarbonyl, trifluoromethoxy, cyano, sulfamoyl, (C_{1-4})alkylsulfamoyl or di[(C_{1-4})alkyl]sulfamoyl,

X is oxygen or sulphur,

m is 0, 1 or 2,

R_7, R_8 and R_9 are each independently (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkinyl, (C_{3-7})cycloalkyl, (C_{4-8})cycloalkylalkyl, hydroxy-(C_{2-6})alkyl, (C_{3-6})alkoxyalkyl, hydroxy(C_{4-8})-alkoxyalkyl, amino-(C_{2-6})alkyl,(C_{1-4})alkylamino(C_{2-6})-

* C L M S *

alkyl,di[C_{1-4})alkyl]aminoalkyl, phenyl, (C_{7-10})-phenylalkyl, a 5- or 6-membered heterocyclic ring, containing a nitrogen or oxygen or sulphur atom and which may also contain 1, 2 or 3 additional ring nitrogen atoms, or (C_{1-4})alkyl optionally substituted by a 5- or 6-membered heterocyclic ring containing a nitrogen or oxygen or sulphur atom as heteroatom and which may additonally contain 1, 2 or 3 further ring nitrogen atoms, whereby, when A is a residue b, R_7 may also be trifluoroethyl,

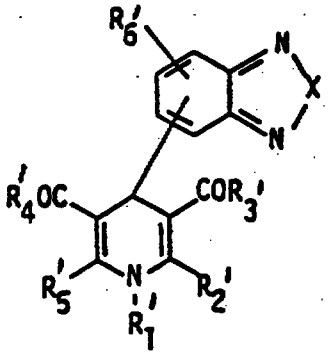
B is (C_{1-14})alkylene,

R_{10} and R_{11} are each independently (C_{1-6})alkyl, (C_{3-6})alkenyl, (C_{3-6})alkinyl, (C_{3-7})cycloalkyl, (C_{4-8})cycloalkylalkyl, hydroxy(C_{2-6})alkyl, (C_{3-6})alkoxyalkyl, hydroxy(C_{4-8})-alkoxyalkyl, amino(C_{2-6})alkyl, (C_{1-4})alkylamino(C_{2-6})-alkyl, di-[(C_{1-4})alkyl]amino-(C_{1-4})alkyl, phenyl, or (C_{7-10})phenylalkyl, or

R_{10} and R_{11} form together with the nitrogenatom to which they are attached a 5-, 6- or 7-membered heterocyclic ring optinally containing a further heteroatom selected from oxygen or sulphur or a group =N-R_{12}, wherein R_{12} is (C1-4)alkyl, benzyl or bis- phenylmethyl optionally mono- or independently disubstituted in the phenyl ring(s) by halogen of atomic number from 9 to 35 or (C_{1-4})alkoxy.

3. A pharmaceutical composition according to claims 1 and 2 characterized in that the calcium-antagonists are those of Formula Ia

* C L M S *



Ia

wherein

R_1' is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl or alkinyl of 3 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, cycloalkylalkyl of 4 to 8 carbon atoms, phenylalkyl of 7 to 9 carbon atoms or phenylalkenyl of 9 to 12 carbon atoms, the phenyl ring being unsubstituted or mono-, di- or tri-substituted independently by halogen, hydroxy or alkyl or alkoxy of 1 to 4 carbon atoms.

R_2' and R_5', independently, are hydrogen or alkyl of 1 to 6 carbon atoms,

R_3' and R_4', independently, are alkyl of 1 to 6 carbon atoms, alkenyl or alkinyl of 3 to 6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, cycloalkylalkyl of 4 to 8 carbon atoms, alkoxy of 1 to 6 carbon atoms, hydroxyalkoxy of 2 to 6 carbon atoms, alkoxyalkoxy of 3 to 6 carbon atoms, hydroxyalkoxyalkoxy of 4 to 8 carbon atoms, alkenyloxy or alkinyloxy of 3 to 6 carbon atoms, cycloalkoyoxy of 3 to 7 carbon atoms or cycloalkyl-alkoxy of 4 to 8 carbon atoms, or R_3' has the significance $O\text{-}B'\text{-}R_7'$, wherein B' is an alkylene chain of 9 to 14 carbon atoms and R_7 is piperidine or piperazine both substituted in

* C L M S *

the 4 position by methyl, benzyl or bis-phenylmethyl optionally mono- or independently disubstituted in the phenyl ring(s) by halogen of atomic number from 9 to 53 or alkoxy of 1 to 4 carbon atoms and R_4' has the significance cited above,

R_6' is hydrogen, halogen, alkyl or alkoxy or alkylthio or alkylsulfonyl, each of 1 to 4 carbon atoms, trifluoromethyl, nitro or hydroxy, and

X has the significance stated in claim 2.

4. A composition according to any of the claims 1 to 3, wherein component a) is selected from 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester; 4-(2,1,3)-benzoxadiazol-4-yl-1,4-dihydro-2,6-dimethyl-3-methoxycarbonyl-pyridine-5-carboxylic acid isopropyl ester; 4-(2,1,3-benzoxathiadiazol-4-yl)-2,6-dimethyl--1,4-dihydropyridin-3,5-dicarboxylic acid dimethyl ester and (+)-(S)-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxycarbonyl-2,6-dimethyl-3-pyridine carboxylic acid-[10[4-(diphenylmethyl)-piperazin-1-yl]decyl]ester.

5. A composition according to any of the claims 1 to 4 for use in the treatment of hypertension and congestive heart failure.

6. A composition according to claim 5 wherein the calcium antagonist is the 4-(2,1,3-Benzoxadiazol)-4-yl-1,4-dihydro-2,6-dimethyl-3-methoxycarbonyl-pyridine-5-carboxylic acid isopropylester.

7. A composition according to claim 5 wherein the calcium antagonist antagonist is the 4-(2,1,3-Benzoxadiazol-4-yl)-1,4-

* C L M S *

dihydro-2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl-ester.

8. A composition according to claim 5 wherein the calcium antagonist is the 4-(2,1,3-Benzoxathiadiazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethylester.

9. A composition according to claim 5 wherein the calcium antagonist is the (+)-(S)-4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-5-methoxy-carbonyl-2,6-dimethyl-3-pyridine carboxylic acid-[10-[diphenylmethyl)-piperazin-1-yl]decyl]ester.

10. A composition according to claim 5 wherein component b) is the 7-(N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl)-1,4-dithia-7-azaspiro-[4,4]nonane-8-(S)-carboxylic acid monohydrochloride monohydrate.

11. A composition according to any of the claims 1 to 10 characterized in that the weight ratio of component a) to component b) is from 5:1 to 1:3.

12. A composition according to claim 11 wherein the weight ratio is from 5:1 to 1:1.

13. A pack or dispenser device containing a pharmaceutical composition according to any one of the claims 1 to 12 together with instructions for use in hypertension or congestive heart failure.

* C L M S *

14. Use of a combination of component a) and component b) as defined in any of the claims 1 to 12 in the manufacture of a pharmaceutical composition for the treatment of hypertension a congestive heart failure.

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* C L M S *