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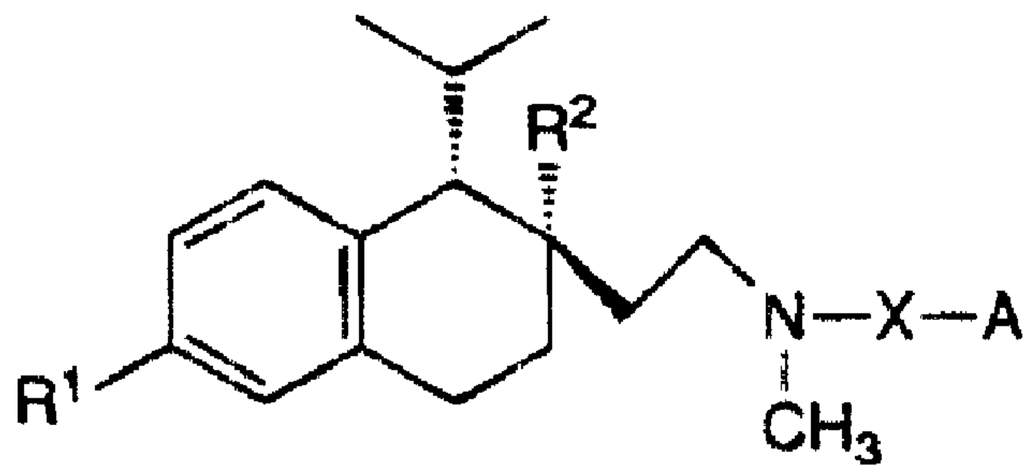
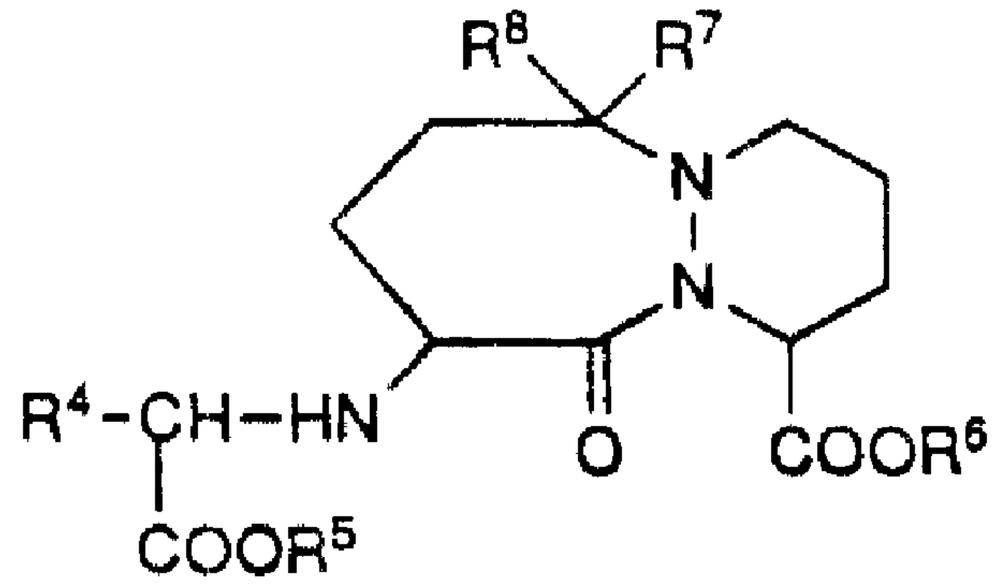
(54) Title: ANTIHYPERTENSIVE COMBINATION



(I)



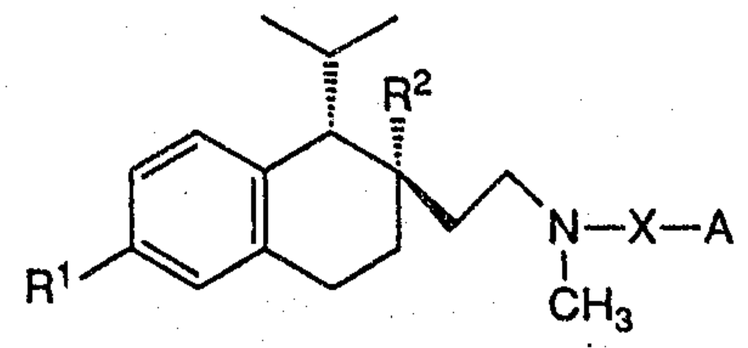
(II)

(57) Abrégé/Abstract:
Antihypertensive combination preparation containing a tetrahydronaphthalene derivative of the general formula (see formula I) wherein R^1 signifies halogen, R^2 signifies lower-alkoxy-lower-alkylcarbonyloxy, X signifies C^2-C^8-alkylene and A signifies benzimidazolyl optionally substituted at the N atom by alkyl with 1 to 12 C atoms, and a pyridazodiazepine of the general formula (see formula II) wherein R^4 signifies aralkyl with 1 to 6 C atoms in the alkyl residue and phenyl, which is optionally mono-substituted by halogen, alkoxy with 1 to 6 C atoms or phenyl, as the aryl residue, R^5 and R^6 each independently signify hydrogen or alkyl with 1 to 6 C atoms and R^7 and R^8 each signify hydrogen or together signify an oxo group, in the form of their free bases, their hydrates or their pharmaceutically usable salts for the simultaneous, separate or planned stepwise use.

2074039
RAN 4019/117

Abstract

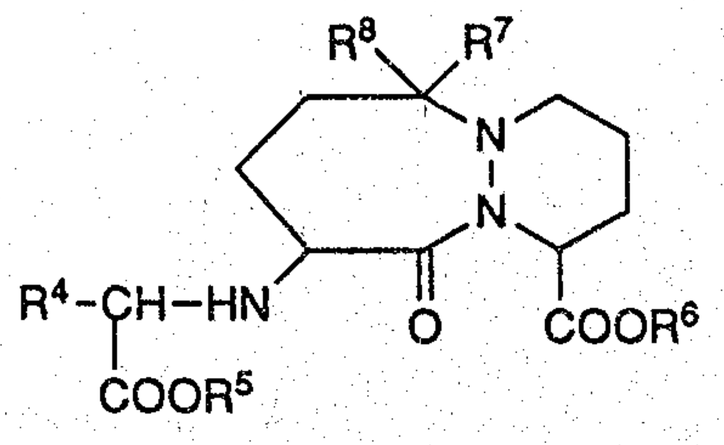
Antihypertensive combination preparation containing a tetrahydronaphthalene derivative of the general formula



I

wherein R^1 signifies halogen, R^2 signifies lower-alkoxy-lower-alkylcarbonyloxy, X signifies C_2-C_8-alkylene and A signifies benzimidazolyl optionally substituted at the N atom by alkyl with 1 to 12 C atoms,

and a pyridazodiazepine of the general formula



II

wherein R^4 signifies aralkyl with 1 to 6 C atoms in the alkyl residue and phenyl, which is optionally mono-substituted by halogen, alkoxy with 1 to 6 C atoms or phenyl, as the aryl residue, R^5 and R^6 each independently signify hydrogen or alkyl with 1 to 6 C atoms and R^7 and R^8 each signify hydrogen or together signify an oxo group,

in the form of their free bases, their hydrates or their pharmaceutically usable salts for the simultaneous, separate or planned stepwise use.

RAN 4019/117

The present invention is concerned with pharmaceutical combination preparations, which are suitable for the treatment of hypertension, containing certain tetrahydronaphthalene derivatives and pyridazodiazepines.

The said tetrahydronaphthalene derivatives are calcium antagonists [EP-A 0,268,148] and are suitable for the treatment of hypertension [Clozel et al., Cardiovasc. Drug Rev. 9, 4-17 (1991)].

The said pyridazodiazepines are known angiotensin converting enzyme (ACE) inhibitors and are accordingly suitable for the treatment of hypertension [EP-A 0,094,095].

The treatment of hypertension by the simultaneous administration of the blood pressure-lowering calcium antagonist nitrendipine and the ACE inhibitor captopril [J.Cardiovasc. Pharmacol. 7, S88-S91 (1985)] has shown that the patients treated with nitrendipine and captopril with the simultaneous administration of the two active substances have a better and, respectively, overall response than with the sole administration of captopril or nitrendipine, whereby in these trials both of the individual components were used in the dosages conventional for the respective monotherapy.

However, there still exists the need to provide a pharmaceutical combination the administration of which leads to a lowering of the blood pressure, in which the dosages of the individual components are significantly reduced and undesired side effects, which appear in each case using the necessary dosages in monotherapy, can be suppressed.

In the scope of the present invention it has been established that with the administration of the combination in accordance with the invention of a tetrahydronaphthalene derivative with a pyridazodiazepine the blood pressure lowering-properties of the individual components are not only additive, but are surprisingly

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potentiated, whereby the effective dosages of the two individual components can be decreased significantly.

The antihypertensive combination in accordance with the invention accordingly has the following advantages:

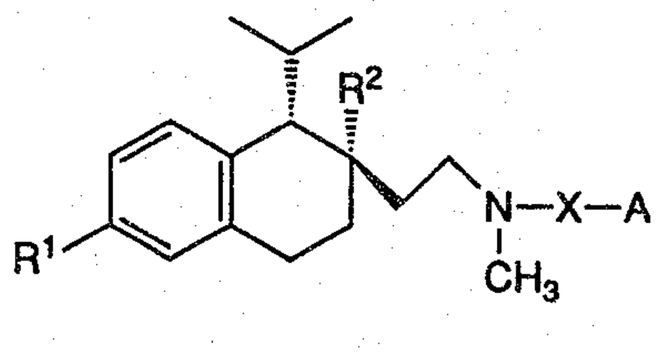
a) The amounts of active ingredients to be administered are reduced significantly;

b) undesired side effects are eliminated or greatly reduced;

c) both individual components have a similar long biological half life of 10-12 hours in the treatment of hypertension in human beings. The course of the effect is therefore expected to be equivalent;

d) both individual components have a high bioavailability (for the most preferred tetrahydronaphthalene derivative [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate dihydrochloride (referred to as Compound A hereinafter) e.g. 80-100% and for the most preferred pyridazodiazepine 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid (referred to as cilazapril hereinafter) e.g. 70%).

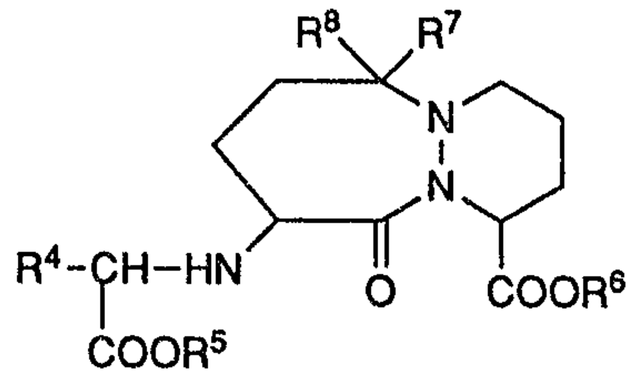
The invention is accordingly concerned with novel pharmaceutical combination preparations for the simultaneous, separate or planned stepwise use in the treatment of hypertension, containing a tetrahydronaphthalene derivative of the general formula



I

wherein R^1 signifies halogen, R^2 signifies lower-alkoxy-lower-alkylcarbonyloxy, X signifies C_2-C_8-alkylene and A signifies benzimidazolyl optionally substituted at the N atom by alkyl with 1 to 12 C atoms,

and a pyridazodiazepine of the general formula



II

wherein R^4 signifies aralkyl, R^5 and R^6 each independently signify hydrogen or alkyl with 1 to 6 C atoms and R^7 and R^8 each signify hydrogen or together signify an oxo group,

whereby the active substances can be present either in the form of their free bases, their hydrates or their pharmaceutically usable salts.

The aryl residue in aralkyl is a phenyl group which can be mono-substituted by halogen (i.e. fluorine, chlorine, bromine or iodine), alkoxy with 1 to 6 C atoms or phenyl. The alkyl residue in aralkyl has 1 to 6 C atoms. Benzyl, 2-phenylethyl, 3-phenylpropyl, 2-(4-chlorophenyl)ethyl, 2-(4-methoxyphenyl)ethyl and the like are examples of aralkyl groups.

The weight ratio of tetrahydronaphthalene derivative to pyridazodiazepine is conveniently 100:1 to 1:1, preferably 20:1 to 2:1.

Advantageously, the dosage of a combination to be administered per day is 5 to 100 mg of a tetrahydronaphthalene derivative and 1 to 5 mg of a pyridazodiazepine. In general, the total amount of a tetrahydronaphthalene derivative and a pyridazodiazepine derivative to be administered daily is a maximum of 55 mg. When a hydrate or a pharmaceutically usable salt is used, then the above values have to be altered appropriately.

Objects of the present invention are therefore

- a combination of a tetrahydronaphthalene derivative and a pyridazodiazepine;

- a pharmaceutical preparation containing a tetrahydronaphthalene derivative and a pyridazodiazepine;

- the manufacture of a pharmaceutical preparation, which comprises bringing a mixture of a tetrahydronaphthalene derivative and a pyridazodiazepine into a galenical administration form;

- the use of a combination of a tetrahydronaphthalene derivative and a pyridazodiazepine and, respectively, of a pharmaceutical preparation containing a tetrahydronaphthalene derivative and a pyridazodiazepine for the control or prevention of illnesses, especially of circulatory disorders, particularly in the control or prevention of hypertension and disorders stemming therefrom.

Particularly preferred compounds of formula I are:

2-[2-[[3-(2-Benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthylmethoxy-acetate as well as Compound A.

Especially suitable pyridazodiazepines are those of formula II in which R^4 signifies aralkyl, R^5 signifies alkyl with 1 to 4 C atoms, R^6 signifies hydrogen and R^7 and R^8 each signify hydrogen or together signify an oxo group.

Particularly suitable pyridazodiazepines are those of formula II in which R^4 signifies phenyl-C_{1-4}-alkyl, R^5 signifies alkyl with 1 to 4 carbon atoms and R^6, R^7 and R^8 each signify hydrogen.

Cilazapril is the most suitable representative from the group of pyridazodiazepines of formula II.

A regular and long-lasting blood pressure-lowering effect can be achieved with the combination in accordance with the invention using low dosages of active substances.

The advantageous more than additive blood pressure-lowering effect of the combination in accordance with the invention vis-à-vis that of the two individual components will be evident having regard to the test described hereinafter.

The antihypertensive effect of the combination was investigated in conscious dogs having renal hypertension. The hypertension was produced in German sheepdogs (weight 23-30 kg) using known methods in which one kidney is wrapped with cellophane and a stenosis is formed in the renal artery of the contralateral kidney using an occluder. The blood pressure was measured with a catheter implanted in the abdominal aorta and connected to a transmitter in the abdominal cavity (telemetry).

Figure 1 illustrates the effect of cilazapril (10 mg/kg per os) and Compound A (30 mg/kg per os) alone as well as the effect of the simultaneous administration of the same dosages of the two substances (n = 3 dogs for cilazapril and the combination, n = 4 dogs for Compound A). Cilazapril alone was without effect and Compound A lowered the blood pressure (MAP) by 10-20 mmHg. The combination was substantially more active at all points in time.

The synergistic effect of the combination was also evident in a further series of experiments in which the dosages of the components were lower, namely 3 mg/kg per os for cilazapril and 10 mg/kg per os for Compound A (same number of test animals). The result obtained in this series of experiments is shown in Figure 2.

The advantageous more than additive effect of the combination in accordance with the invention vis-à-vis that of the two individual components in the known regression of the chronic hypertension-caused hypertrophy of the media in the large, muscular arteries by treatment of the hypertension with ACE inhibitors and other customary therapeutics [Hypertension 9, 178-187 (1987)] can be demonstrated with the aid of the test described hereinafter.

The influence of the individual compounds and their combination on the blood vessels was investigated in rats. Male rats, strain: RoRo (weight about 400 g; aged 4-5 months; Institut für Biologisch-Medizinische Forschung, Füllinsdorf, CH) were used. The animals were divided randomly into a control group and into treatment groups. The duration of the treatment was 15 days. Cilazapril was admixed with the feed in an amount such that the daily intake was on average 10 mg/kg and Compound A (30 mg/kg) was administered using a probang. The control animals received the same laboratory feed without additive.

After 15 days the rats were anaesthetized with ether and the carotid artery was fixed by perfusion with fixative agent (2.5% glutaraldehyde in 0.1 M phosphate buffer, pH 7.4). For this, a probe was passed through the left ventricle of the heart into the ascending aorta (inflow) and a second probe was pushed through the right ventricle into the auricle (discharge). The vascular system was firstly rinsed with 10 ml of buffered isotonic NaCl solution and then fixed for 15 minutes with fixative at a pressure of 11.7 kPa. Subsequently, the right carotid artery was dissected, freed from adhering tissue and placed in 2.5% glutaraldehyde for further fixation. Each artery was divided into five vascular segments from the distal end to the proximal end, dehydrated and embedded in EPON 12 (Registered Mark of Shell A.G.). The middle segment was used for the morphological investigations. Semi-thin cross-sections (1 µm thick) were coloured with toluidine blue and basic fuchsin. The cross-section surface of the media was measured with the morphometry system DIASYS (Datalab, Heinz Meyer, CH-3367 Thörigen).

The area of the media in the control animals was 89000 ± 5000 μm^2. The individual treatment was without effect (84000 ± 11000 μm^2 in the case of cilazapril and 87000 ± 4000 μm^2 in the case of Compound A). (See also Figure 3, the numbers in the columns relate to the number of experimental animals in the respective groups). The combination lowers the media area by 15% to 74000 ± 4000 μm^2 (statistically significant; $p < 0.05$ with the t-test according to Student).

The decrease in the media surface by the combination was confirmed in a second series of experiments.

A mechanistic interaction apparently exists between ACE inhibitors and calcium antagonists. It is known that by the administration of a calcium antagonist and the lowering of the blood pressure resulting therefrom a compensatory stimulation of the renin angiotensin system is effected. This compensation is suppressed by the use of the ACE inhibitor.

The foregoing results show the unexpected advantageous properties of the combinations in accordance with the invention. With a knowledge of the state of the art it could not be expected that just the combination of tetrahydronaphthalene derivatives, especially of Compound A, with pyridazodiazepines, especially with cilazapril, would show such an optimal blood pressure-lowering activity.

The combinations in accordance with the invention are generally administered orally, e.g. in the form of tablets, varnished tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

A combination in accordance with the invention can be processed with pharmaceutically inert, inorganic or organic excipients for the manufacture of tablets, varnished tablets, dragées and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used e.g. as such excipients for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc; depending on the nature of the active substance no excipients are generally required in the case of soft gelatine capsules.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose and the like.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

The following Examples illustrate the invention.

Example 1

Production of varnished tablets of the following compostion:

Tablet cores:

a.	Compound A	29.07 mg (= 25 mg of base)
b.	Cilazapril	1.25 mg
c.	Lactose anhydrous	70.18 mg
d.	Corn starch white	30.00 mg
e.	Polyvinylpyrrolidone	5.00 mg
f.	Talc	5.00 mg
g.	Sodium stearyl fumarate	1.50 mg
Weight per tablet core		142.00 mg

Varnish coating:

h.	Hydroxypropylmethylcellulose	4.00 mg
i.	Polyethylene glycol 6000	1.00 mg
j.	Titanium dioxide	1.60 mg
k.	Talc	1.40 mg
Varnish coating weight		8.00 mg
Total weight per varnished tablet		150.00 mg

Production procedure:

Production of the tablet core:

b is homogeneously mixed successively and portionwise with c and sieved. Then, a, d and e are added and the mixture is mixed briefly, sieved and moistened for a suitable period in a planetary mixer. The moist mass is granulated through a suitable sieve, dried and subsequently broken up in a suitable sieve. Thereto there are added the sieved f and g and the mixture is mixed homogeneously. The ready-to-press mixture is pressed to tablet cores of suitable size and form (with or without a break-bar) weighing 142.0 mg.

Production of the varnish coating:

An aqueous varnishing suspension is prepared from h to k and the tablet cores are coated with this in a suitable manner with the aid of a varnishing process in a coating kettle or another varnishing apparatus until the varnished tablets have achieved a final weight of 150 mg.

Example 2

Production of hard gelatine capsules of the following composition:

a.	Compound A	29.07 mg (= 25 mg of base)
b.	Cilazapril	2.50 mg
c.	Lactose powd.	26.93 mg
d.	Lactose cryst.	60.00 mg
e.	Microcrystalline cellulose	50.00 mg
f.	Talc	10.00 mg
g	Sodium stearyl fumarate	1.50 mg
Fill weight per capsule		180.00 mg

Production procedure:

b is homogeneously mixed successively and portionwise with c, sieved and the sieved a, d and e are added and mixed in a suitable manner. The sieved f and g are added thereto and mixed for a suitable period. The ready-to-fill final mixture is filled into hard gelatine capsules of suitable size and colour.

Example 3

Production of varnished tablets CR (controlled release) of the following composition:

CR tablet core:

a.	Compound A	58.13 mg (= 50 mg of base)
b.	Cilazapril	2.50 mg
c.	Lactose anhydrous	45.37 mg
d.	Methocel (Registered Mark of Dow Chemical Company)	10.00 mg
e.	Hydroxypropylcellulose	10.00 mg
f.	Talc	4.00 mg
g.	Sodium stearyl fumarate	2.00 mg
Weight per CR tablet core		132.00 mg

Varnish coating:

h.	Hydroxypropylmethylcellulose	4.00 mg
i.	Polyethylene glycol 6000	1.00 mg
j.	Titanium dioxide	1.60 mg
k.	Talc	1.40 mg
Varnish coating weight		8.00 mg

Total weight per CR varnished tablet 140.00 mg

Production procedure

Production of the CR tablet core:

b is homogeneously mixed successively and portionwise with c and sieved, and the sieved a, d and e are subsequently admixed and compacted on a rolling compactor in a suitable manner. The compacted material is sieved through a suitable sieve and subsequently mixed homogeneously with a sieved mixture of f and g and pressed to tablet cores of 132.0 mg in suitable size and form.

Production of the varnish coating:

An aqueous varnish suspension is produced from h to k and the tablet cores are coated with this in a suitable manner with the aid of a varnishing process in a coating kettle or another varnishing apparatus until the varnished tablets have achieved a final weight of 140 mg.

Example 4

Production of CR pellet formulations of the following composition in hard gelatine capsules:

Pellets:

a.	Compound A	58.13 mg (= 50 mg of base)
b.	Cilazapril	2.50 mg
c.	Microcrystalline cellulose	139.37 mg
Weight of pellet core per capsule		200.00 mg

CR pellet varnish:

d. Ethylcellulose (AQUACOAT dispers.)	16.00 mg
e. Dibutyl sebacate	4.00 mg
Wt. varnished pellet core/capsule	20.00 mg
Total weight CR pellets per capsule	220.00 mg

Production procedure:

Production of the pellet cores:

a, b and c are homogeneously mixed with one another in a suitable manner, moistened with the appropriate amount of water in a mixer and extruded through a suitable perforated disk. The extruded mass is broken up in a spheronizer, rounded-off and subsequently dried in a fluidized bed.

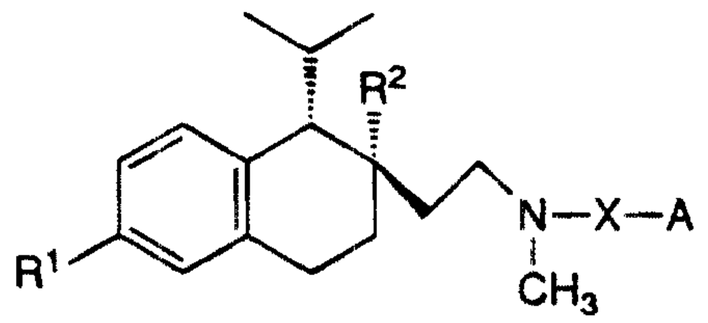
Production of the varnish coating:

The pellet cores are coated with the aqueous dispersion of d and e in a continuous process using a fluidized bed spray procedure under suitable conditions until the varnish coating amounts to 10% of the weight of the pellet cores. Subsequently, the varnished CR pellets are subjected to a heat treatment and

filled to 220 mg into hard gelatine capsules of suitable size and colour.

Claims

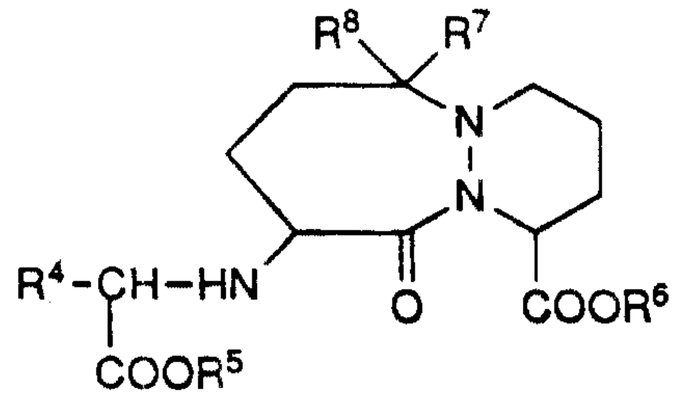
1. A pharmaceutical combination preparation, which contains a tetrahydronaphthalene derivative of the general formula



I

wherein R^1 signifies halogen, R^2 signifies lower-alkoxy-lower-alkylcarbonyloxy, X signifies C_2-C_8-alkylene and A signifies benzimidazolyl optionally substituted at the N atom by alkyl with 1 to 12 C atoms,

and a pyridazodiazepine of the general formula



II

wherein R^4 signifies aralkyl having an alkyl residue with 1 to 6 C atoms and having an aryl residue being phenyl, which is optionally mono-substituted by halogen, alkoxy with 1 to 6 C atoms or phenyl, R^5 and R^6 each independently signify hydrogen or alkyl with 1 to 6 C atoms and R^7 and R^8 each signify hydrogen or together signify an oxo group,

in the form of their free bases, their hydrates or their pharmaceutically usable salts.

2. A preparation according to claim 1, wherein the weight ratio of tetrahydronaphthalene derivative to pyridazodiazepine is 100:1 to 1:1 with respect to free bases.

3. A preparation according to claim 2, wherein the weight ratio is 20:1 to 2:1.

4. A preparation according to any one of claims 1 to 3, which contains 5 to 100 mg of a tetrahydronaphthalene derivative and 1 to 5 mg of a pyridazodiazepine or equivalent amounts of a hydrate or of a pharmaceutically usable salt.

5. A preparation according to any one of claims 1 to 4, wherein the total weight of tetrahydronaphthalene derivative and of pyridazodiazepine is a maximum of 55 mg with respect to free bases.

6. A preparation according to any one of claims 1 to 5, which contains 2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]-ethyl]-6-fluoro-1,2,3,4-tetrahydro-1α-isopropyl-2α-naphthyl-methoxyacetate or [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]-methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate dihydrochloride as the tetrahydro-naphthalene derivative of formula I.

7. A preparation according to claim 6, which contains [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxy-acetate dihydrochloride as the tetrahydronaphthalene derivative of formula I.

8. A preparation according to any one of claims 1 to 7, which contains a pyridazodiazepine of formula II in which R^4 signifies aralkyl wherein the alkyl residue is 1-4 C atoms, R^5 signifies alkyl with 1-4 C atoms, R^6 signifies hydrogen and R^7 and R^8 each signify hydrogen or together signify an oxo group.

9. A preparation according to claim 8, which contains a pyridazodiazepine of formula II in which R^4 signifies phenyl-C_{1-4}-alkyl, R^5 signifies alkyl with 1-4 carbon atoms and R^6, R^7 and R^8 each signify hydrogen.

10. A preparation according to claim 9, which contains 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-

oxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid as the pyridazodiazepine of formula II.

11. A preparation according to claim 10, wherein the 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid is present as a salt or hydrate.

12. A preparation according to claim 11, wherein the 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid is present as the hydrobromide or hydrate.

13. A preparation in accordance with any one of claims 1 to 12 for use in the control or prevention of hypertension and disorders stemming therefrom.

14. A preparation in accordance with any one of claims 1-12, for the simultaneous, separate or planned stepwise use in the control or prevention of circulatory disorders.

15. A preparation according to claim 14, wherein the circulatory disorder is selected from the group consisting of hypertension and disorders stemming therefrom.

16. A process for the manufacture of the preparation as defined in any one of claims 1 to 15, which process comprises bringing a mixture of the two active substances into a galenical administration form.

17. Use of the preparation as defined in any one of claims 1 to 14 for the control or prevention of circulatory disorders.

18. The use of a preparation according to claim 17, wherein the circulatory disorder is selected from the group consisting of hypertension and disorders stemming therefrom.

19. The use of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)-propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-iso-propyl-2-naphthylmethoxyacetate dihydrochloride in combination with 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1(S)-carboxylic acid for the manufacture of an antihypertensive.

20. Use of the preparation as defined in any one of claims 1-15, for the preparation of a medicament, for controlling or preventing hypertension and disorders stemming therefrom.

21. A pharmaceutical composition comprising [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate dihydrochloride and 9(S)-[1(S)-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1-(S)-carboxylic acid hydrate wherein the weight ratio of [1S,2S]-2-[2-[[3-(2-benzimidazolyl)propyl]methylamino]ethyl-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate dihydrochloride to 9(S)-[1-(S)-ethoxycarbonyl-3-phenylpropyl-amino]octahydro-10-oxo-6H-pyridazo[1,2-a][1,2]diazepine-1-(S)-carboxylic acid hydrate is about 3:1.

22. Use of the composition as defined in claim 21, for controlling or preventing hypertension and disorders stemming therefrom.

23. Use of the composition as defined in claim 21, for preparation of a medicament, for controlling or preventing hypertension or disorders stemming therefrom.

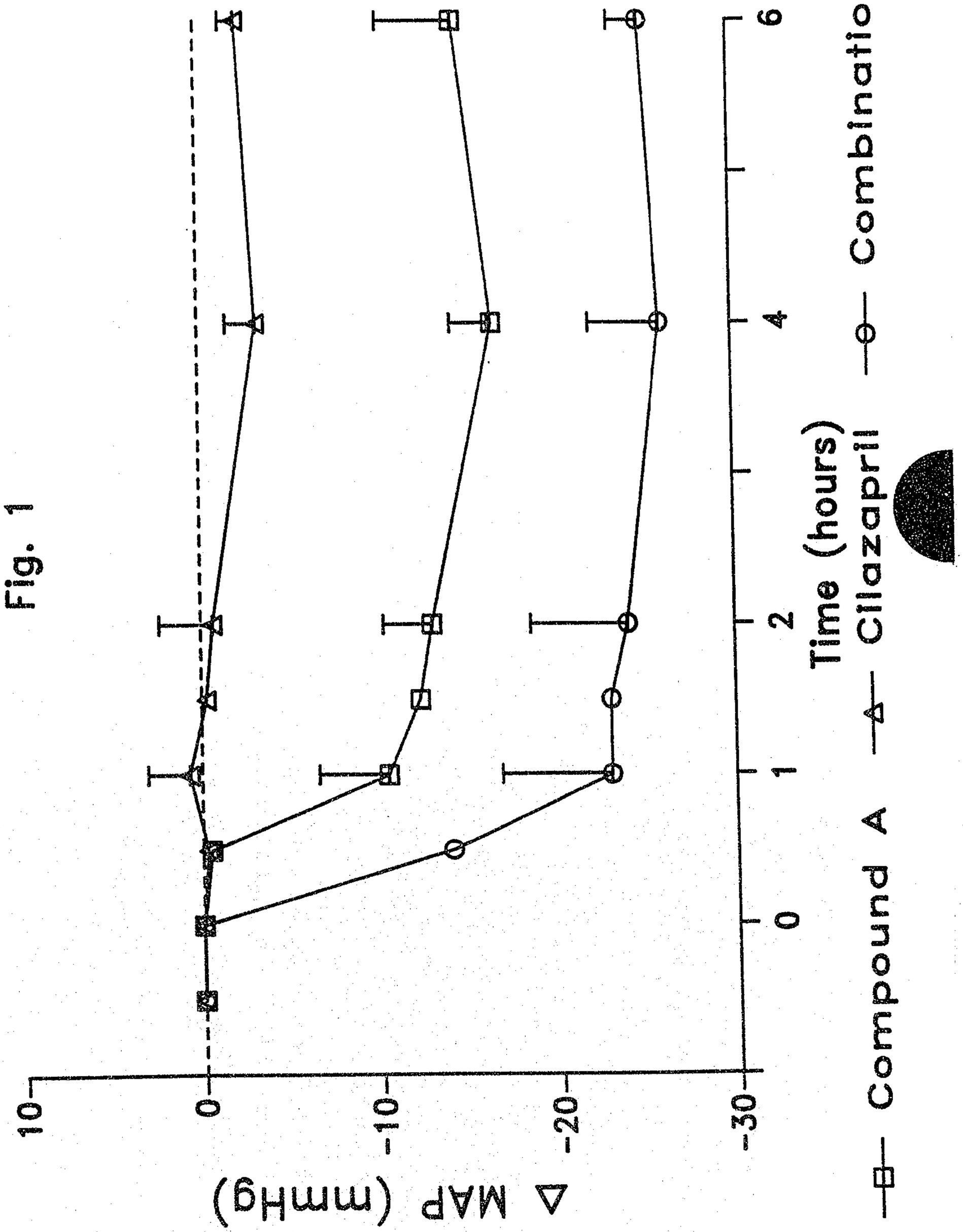

Δ MAP (mmHg)
10
0
-10
-20
-30
0
1
2
4
6
Time (hours)
Cilazapril
Compound A
Combination

Fig. 1

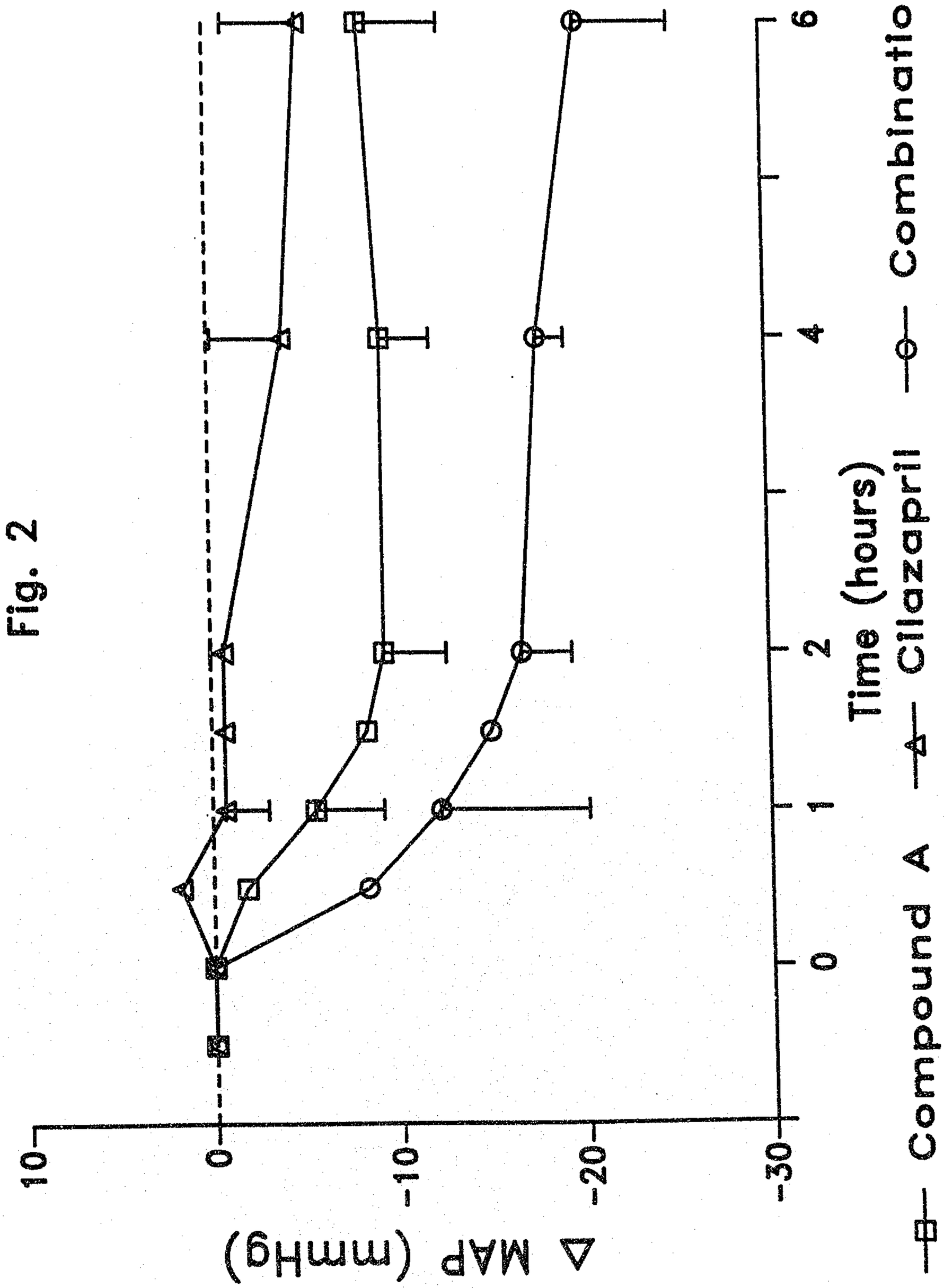

Δ MAP (mmHg)
10
0
-10
-20
-30
0
1
2
4
6
Time (hours)
Δ Compound A — Δ Cilazapril — Combination

Fig. 2

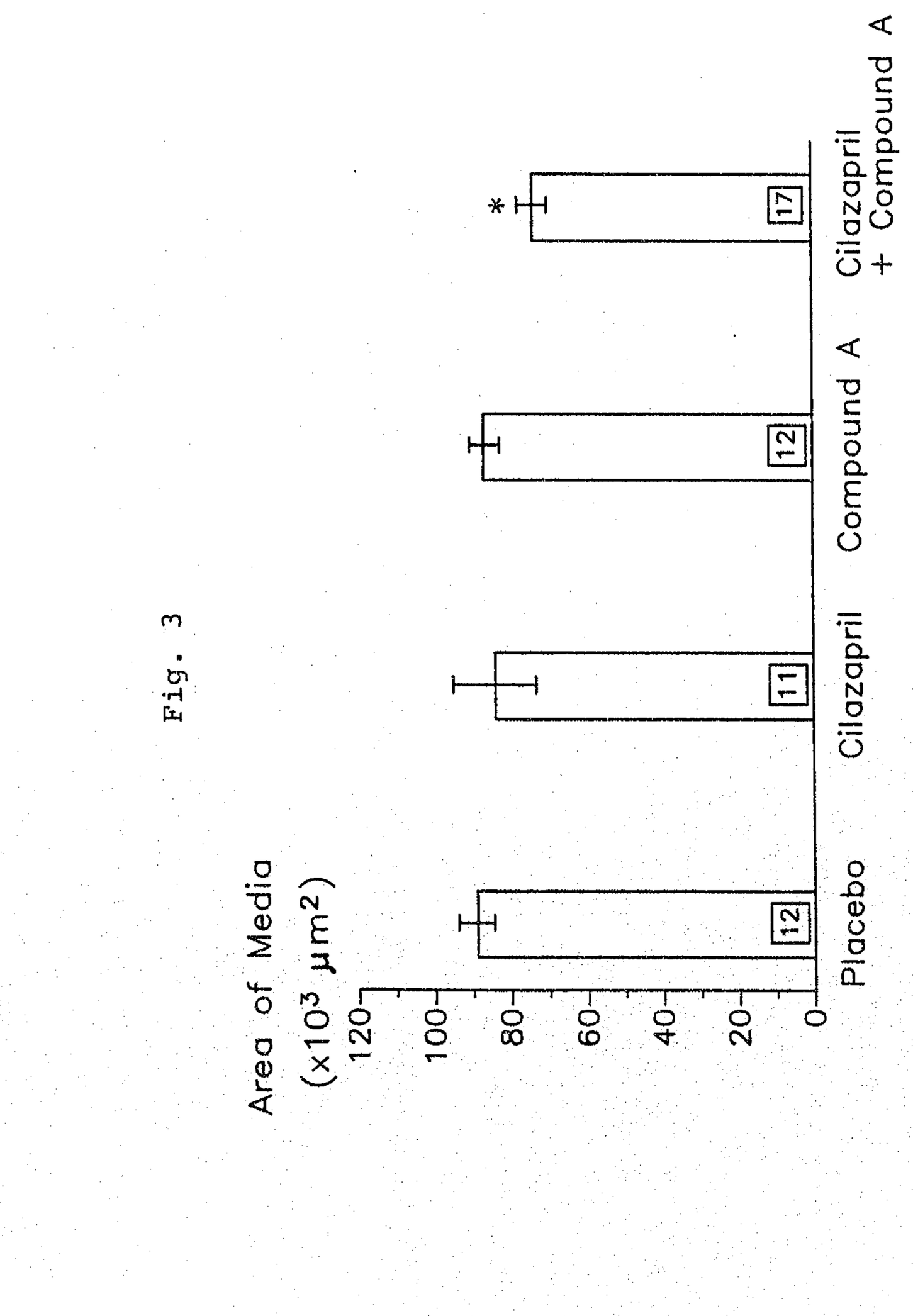
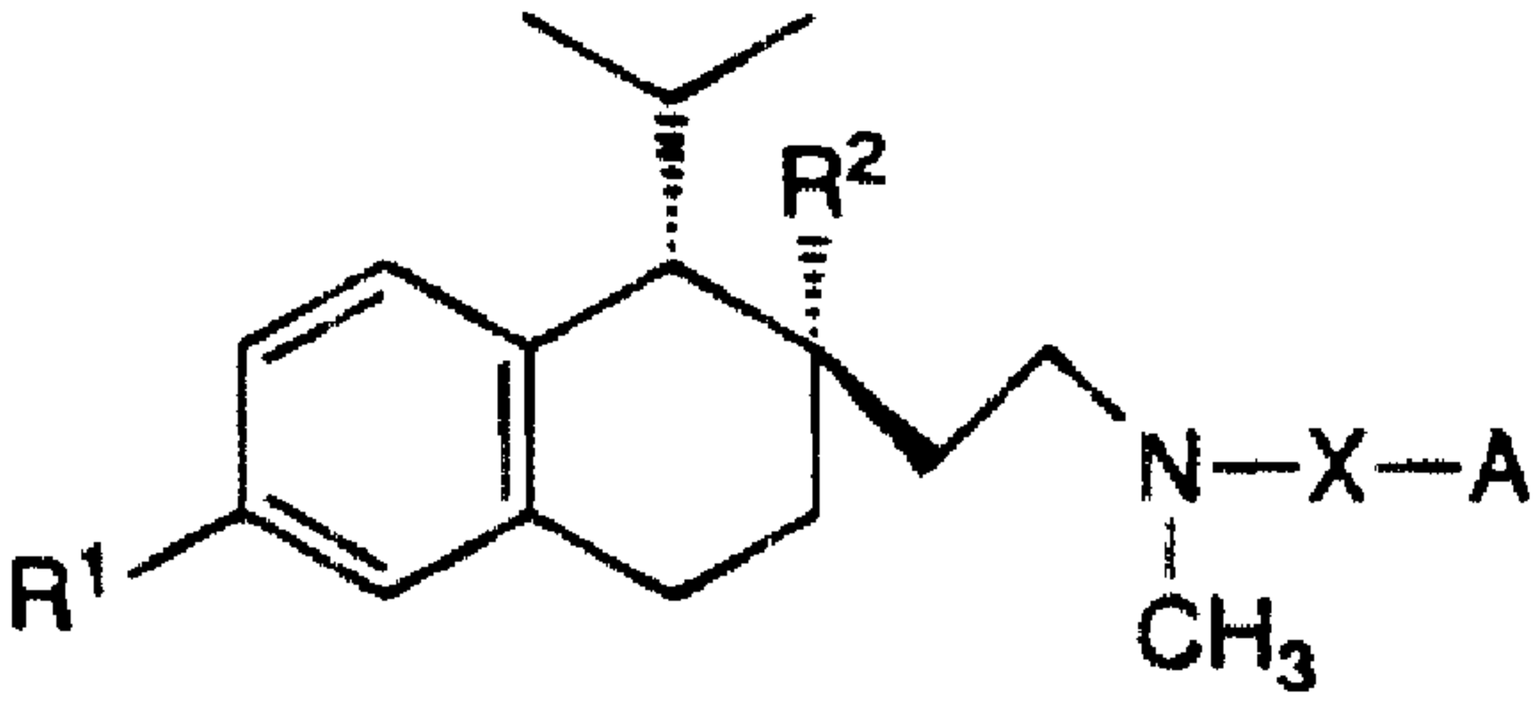
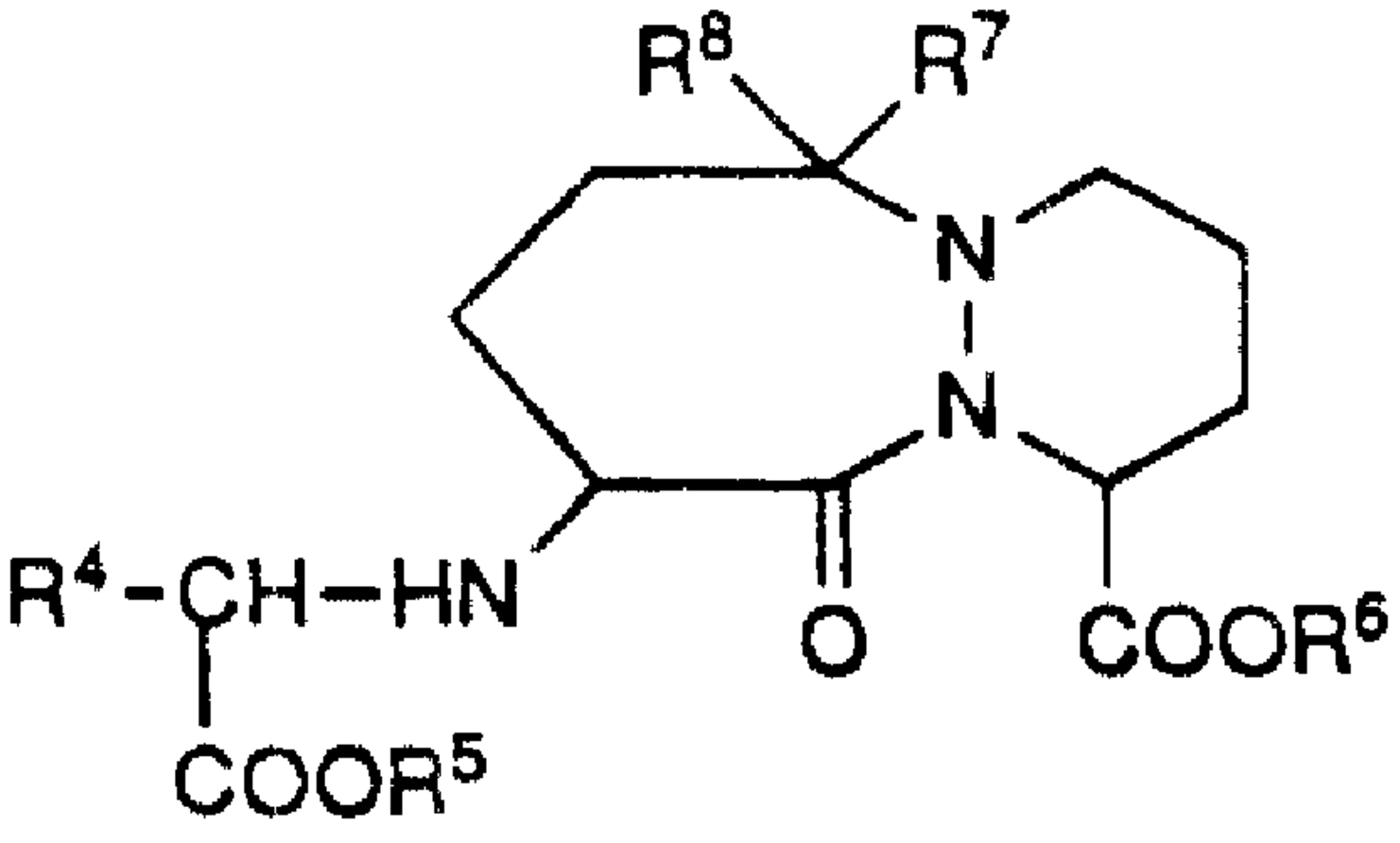

Area of Media
(x10³ μm²)
120
100
80
60
40
20
0
12
11
12
17
Placebo
Cilazapril
Compound A
Cilazapril
+ Compound A
*

Fig. 3



(I)



(II)