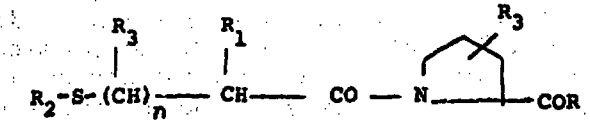
SPECIFICATION

Medicaments for treating hypertension

The present invention provides a composition for use in the treatment of hypertension i.e. for reducing or alleviating hypertension.

More specifically, the invention provides an oral antihypertensive composition comprising a compound of the formula



wherein R is hydroxy, lower alkoxy or $-NH_2$; R_1 and R_4 each is hydrogen, lower alkyl or phenyl-lower alkyl; R_2 is hydrogen or R_5CO-; R_3 is hydrogen, hydroxy or lower alkyl; R_5 is lower alkyl, phenyl or phenyl-lower alkyl; n is 0, 1 or 2; a diuretic compound; and a physiologically acceptable carrier therefor.

As used herein the terms "lower alkyl" and "lower alkoxy" mean respectively alkyl and alkoxy groups containing from 1 to 7 carbon atoms. Similarly the lower alkanoyl groups contain from 2 to 7 carbon atoms.

The compounds of formula I have been reported to be angiotensin converting enzyme inhibitors which intervene in the angiotensinogen→renin→angiotensin I→angiotension II mechanism and are effective in reducing or alleviating hypertension. See U.S. Patent 4,046,889, September 6, 1977; Science *196*, 441-443 (1977). It has been found that such compounds can be used in an oral dosage range of about 0.1 to 100 mg/kg per day and are most effective when provided at a total daily dosage of about 60 to 600 mg. Dosages within this range achieve a substantial reduction in arterial blood pressure and, in most instances, little, if any significant reduction is obtained by further increasing the dosage. Although certain peptides, teprotide (SQ20,881) for example, have been reported to have angiotensin converting enzyme activity, they are not of practical use for such an indication because of the cost and particularly since they are ineffective when orally administered [Rubin et al., *204*, Jour. Pharm, Exper. Ther. 271-280, 1978; Laffan et al., Jour. Pharm. Exper. Ther. *204*, 281-288, 1978; Brit. Med. Jour. *2(6141)*:866, 1978].

Hypertension is also frequently treated by the administration of a diuretic. Typically, treatment with an antihypertensive agent alone results in a compensatory retention of sodium and water which concomitant administration of a diuretic prevents (Wollam et al., Drugs *14*:420-460, 1977). However, administration of a compound of formula I does not result in sodium and water retention when administered alone and, in fact, may by itself cause natriuresis and diuresis (Bengis et al., Circulation Research, Vol. *43* I-45-I-53, 1978). Therefore, a diuretic would not be expected to enhance the antihypertensive action of compounds of formula I. However, it has been demonstrated tha the administration of a diuretic in combination with compounds of formula I is more effective than either drug alone. The combination of such compounds with a diuretic as described below results in a potentiation of the reduction in blood pressure significantly beyond that level which either substance can achieve itself at a dosage within the acceptable range and also at lower dosage levels.

This invention therefore provides a combination of a compound having formula I above and a diuretic which is preferably of the thiazide class, e.g., chlorothiazide hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlothiazide, trichlormethiazide, polythiazide or benzthiazide, as well as ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triamterene, amiloride and spironolactone, and salts of such compounds and, compositions comprising a combination of such compounds.

Preferred are those compounds of formula I wherein R is hydroxy or lower alkoxy, especially C_1-C_4 lower alkoxy; R_1 is hydrogen or lower alkyl, especially methyl, R_2 is hydrogen or lower alkanoyl, especially C_2-C_4 lower alkanoyl; R_3 is hydrogen or hydroxy, especially 4-hydroxy; R_4 is hydrogen or lower alkyl, especially C_1-C_4 lower alkyl; and n is 0 or 1. Especially preferred in this group are compounds of formula I wherein R is hydroxy; R_1 is hydrogen or methyl; R_2 is hydrogen or acetyl; R_3 is hydrogen; R_4 is hydrogen or methyl; and n is 0 or 1. The especially preferred embodiment includes a compound of formula I wherein R is hydroxy; R_1 is methyl; R_2 R_3 and R_4 each is hydrogen; and n is 1, most especially (D-3-mercapto-2-methylpropanoyl)-L-proline.

Preferred as the second component of the combination is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene, especially hydrochlorothiazide or furosemide.

The especially preferred embodiments are compositions comprising (D-3-mercapto-2-methylpropanoyl)-L-proline with either hydrochlorothiazide or furosemide.

The compounds of formula I can be produced as described in U.S. Patent 4,046,889, September 6, 1977. The diuretic members of the combination are known compounds which are produced by methods described in the literature.

A composition of this invention may be administered in an effective amount which comprises a total daily

dosage of 30 to 600 mg., preferably 30 to 300 mg. of a compound of formula I and 15 to 300 mg. preferably 15 to 200 mg. of the diuretic to a mammalian species which has elevated blood pressure. Such total daily dosages can be used in a single administration of the total amount or in divided doses two or four times daily. Generally, a t.i.d. or q.i.d. regimen is preferred. The preferred dosage is 10 to 100 mg. of the compound of formula I and 5 to 75 mg. of the diuretic three times daily or 5 to 125 mg. of the compound of formula I and 2.5 to 50 mg. of the diuretic four times daily. The preferred route of administration is oral.
mg. of a compound of formula I and about 15 to 300 mg. preferably 15 to 200 mg. of the diuretic to a mammalian species which has elevated blood pressure. Such total daily dosages can be used in a single administration of the total amount or in divided doses two to four times daily. Generally, a t.i.d. or q.i.d. regimen is preferred. This preferred dosage is about 10 to 100 mg. of the compound of formula I and 5 to 75 mg. of the diuretic three times daily or about 5 to 125 mg. of the compound of formula I and 2.5 to 50 mg. of the diuretic four times daily. The preferred route of administration is oral.

According to one preferred embodiment, the substances can be formulated in a single pharmaceutical dosage form for oral administration such as tablet, capsule, solution or suspension comprising an effective amount of each of the active ingredients in a physiologically acceptable carrier therefor.

The active substances in the dosage unit are generally present in a ratio of 1:2 to 12:1, preferably 2.5:1 to 10:1, of the compound of formula I with respect to the diuretic (by weight). Generally, 10 to 200 mg. of a compound of formula I and 2.5 to 100 mg. of the second component can be readily formulated in the composition.

Tablets of various sizes can be prepared, e.g., of 50 to 700 mg. in total weight, containing the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier or other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of the compound of formula I and the diuretic are more convenient and are preferred, expecially in tablet or capsule form for oral administration.

In formulating the compositions of this invention the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Many of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The following examples are illustrative of the invention and constitute especially preferred embodiments. They also serve as models for the preparation of other members of the group which can be produced by suitable substitution of ingredients as described above.

Example 1

6000 tablets each containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	100	mg.
Avicel (Trade Mark microcrystalline cellulose)	100	mg.
Hydrochlorothiazide	12.5	mg.
Lactose U.S.P.	113	mg.
Corn starch U.S.P.	17.5	mg.
Stearic acid U.S.P.	7	mg.
	350	mg.

are produced (from sufficient bulk quantities) by slugging the (D-3-mercapto-2-methylpropanoyl)-L-proline, Avicel and a portion of the stearic acid. The slugs are ground and passed through a #2 screen, then mixed with the hydrochlorothiazide, lactose, corn starch and remainder of the stearic acid. The mixture is compressed into 350 mg. capsule shaped tablets in a tablet press. The tablets are scored for dividing in half.

Example 2

10,000 tablets each containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	200	mg.
Corn starch U.S.P.	17.5	mg.
Lactose U.S.P.	215.4	mg.
Acacia U.S.P.	10.6	mg.
Water qs	(ca. 0.03	ml.)
Hydrochlorothiazide	25	mg.
Corn starch U.S.P.	17.5	mg.
Avicel	200	mg.
Stearic Acid	14	mg.
	700	mg.

are produced from sufficient bulk quantities as follows:

The acacia is dissolved in water. 17.5 mg. of corn starch, the (D-3-mercapto-2-methylpropanoyl)- L-proline and lactose are mixed thoroughly. The dry mixture is granulated using the aqueous solution of acacia. The granulation is wet screened, dried at 120°F. and reduced. The reduced, dry granulation is mixed with the hydrochlorothiazide and the remaining excipients are then added and mixed. The mixture is compressed into tables of 700 mg. each.

Example 3

Tablets each containing the following ingredients are made as described in Example 2:

(D-3-mercapto-2-methylpropanoyl)-L-proline	75	mg.
Corn starch U.S.P.	8	mg.
Lactose U.S.P.	120	mg.
Acacia U.S.P.	6	mg.
Water qs.	(ca. 0.03	ml.)
Chlorothiazide	50	mg.
Corn starch U.S.P.	8	mg.
Avicel	75	mg.
Stearic acid	8	mg.
	350	mg.

Example 4

1000 capsules, each containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	100	mg.
Lactose U.S.P.	211.8	mg.
Magnesium stearate	3.2	mg.
Hydrochlorothiazide	10	mg.
	325	mg.

are produced by dry blending the bulk materials (except the magnesium stearate) in a Hobart mixer, then passing the blend through a #20 screen. The materials are mixed again in the Hobart mixer with the magnesium stearate. The mixture is then filled into #2 two-piece gelatin capsules.

Example 5

By substituting 10 mg. of furosemide for the hydrochlorothiazide in Example 4, capsules containing furosemide and (D-3-mercapto-2-methylpropanoyl)-L-proline are similarly produced.

Example 6

By following the procedure of Example 2 but substituting 20 mg. of furosemide for the hydrochlorothiazide and using 220.4 mg. of lactose, 700 mg. tablets each containing 20 mg. of furosemide and 200 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline are similarly produced.

Example 7

By substituting 10 mg. of furosemide for the hydrochlorothiazide and using 115.5 mg. of lactose in the procedure of Example 1, 350 mg. scored tablets each containing 10 mg. of furosemide and 100 mg. of (D-3-mercapto-2-methylpropanoyl)-L-proline are similarly produced.

Example 8

6000 scored tablets of 400 mg. each and containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	125	mg.
Corn starch	8	mg.
Lactose U.S.P.	95	mg.
Acacia	7	mg.
Water qs.	(ca. 0.03	ml.)
Triamterene	50	mg.
Corn starch U.S.P.	8	mg.
Avicel	100	mg.
Stearic acid	7	mg.
	400	mg.

are produced as described in Example 2.

Example 9

6000 scored tablets of 350 mg. each and containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	100	mg.
Avicel	100	mg.
Triamterene	25	mg.
Lactose U.S.P.	100	mg.
Corn starch U.S.P.	17	mg.
Stearic acid	8	mg.
	350	mg.

are produced as described in Example 1.

Example 10

5000 scored tablets of 180 mg. each and containing the following ingredients:

(D-3-mercapto-2-methylpropanoyl)-L-proline	10	mg.
Avicel	50	mg.
Hydrochlorothiazide	5	mg.
Lactose U.S.P.	101	mg.
Corn starch U.S.P.	10	mg.
Stearic acid	4	mg.
	180	mg.

are produced as described in Example 1.

Example 11

By substituting the same amount of ticrynafen for the hydrochlorothiazide in Example 1, tablets containing 100 mg. of (D-3-mercapto-2-methylpropanoyl)- L-proline and 12.5 mg. of ticrynafen are similarly obtained.

Representative of the results obtained with combinations of agents of this invention are data obtained from studies in spontaneously hypertensive rats and two kidney renal hypertensive rats.

A) In an acute study with spontaneously hypertensive rats, ten to fourteen week old male Wistar-Kyoto spontaneously hypertensive rats (190-210 gm.) of the Okamoto-Aoki strain (obtained from Taconic Farms, Germantown, N.Y.) were given food and water ad libitum and intubated according to the method of Weeks and Jones, Proc. Soc. Exp. Biol. Med. *104*, 646-648 (1960), to prepare them for blood pressure and heart rate determination by implanting indwelling abdominal aortic catheters under sodium pentobarbital anesthesia.

Three weeks later their direct blood pressure and heart rate were recorded by the method of Laffan et al, Cardiovasc. Res. *6*, 319-324 (1972), modified as follows. The signal from the transducer was digitized in a 10 bit A/D converter and input to a PDP 11/05 computer. The computer was programmed to sense and store samples at a rate of 125/sec for each rat, as well as the number of pressure pulses during 10 sec. of each scan on each rat. These parameters were averaged and stored as the MBP (mean blood pressure, mm Hg) and heart rate (beats/min.) for that time. Data were acquired form each rate every five minutes. Six such sets of data were averaged to give a mean value representing a 30 minute sample and this 30 minute figure was stored for subsequent analysis. Each time a 48 hour cycle was completed (or sooner if demanded) the data were transferred serially to a host computer (PDP 11/40) for further analysis and the data were printed out on a Versatec Printer/Plotter for at least 16 hours after each dose.

The spontaneously hypertensive rats were segregated into four groups of five rats each (except group 3 which included six rats). The following was administered to the rats in the respective groups:

1. (Control) Agar - 5 ml./kg + agar - 5 ml./kg
2. Water - 5 ml./kg + Compound A* - 30 mg./kg
3. Compound F** - 50 mg./kg + Agar - 5 ml./kg
4. Compound F** - 50 mg./kg + Compound A* - 30 mg./kg

* Compound A = (D-3-mercapto-2-methylpropanoyl)- L-proline

** Compound F = Furosemide

Compound F was suspended in 0.25% agar and Compound A was in aqueous solution. All substances were administered by gavage and there was a one hour interval between drugs. Test results were evaluated 2.5 hours after single oral doses.

The following results were obtained:

Table I

Mean Blood Pressure (mm/Hg)	Before	2.5 hours after single oral dose
(1)	173	169
(2)	175	158
(3)	184	172
(4)	177	128

In these studies Compound F alone, 50 mg./kg. p.o., produced a 9.7% decrease in SHR blood pressure. Compound A alone, 30 mg./kg., produced 6.5% decrease in blood pressure. The combination of Compound A, 30 mg./kg., p.o., + Compound B, 50 mg./kg., p.o., reduced blood pressure in SHR rats by 27.7%.

B) In chronic studies with renal hypertensive rats, male rats (115-150 g.) of the Charles River Sprague Dawley (COBS-CO) strain were anesthetized with ether and a silver clip (0.22 mm i.d.) was placed on the left renal artery through a flank incision. The controlateral kidney was left intact (two-kidney Goldblatt model: 2-K RHR). Each rat was fitted with a tail cuff for air inflation and a Korotkoff sound microphone for the detection of arterial pulsation. An oscilloscope was used for a visual appearance and disappearance of the pulse. Blood pressure measurements were determined after a minimum of six inflations with systolic pressures observed on a Narco physiograph manometer. Blood pressures were determined initially just prior to dosing and twice weekly at 4 hours after dosing.

The number of rats in each group was 15. Single daily treatments were made by gavage with crossover treatments as indicated in the table below. The control group received distilled water. Compound A was administered in distilled water, 30 mg./kg. Compound H was administered in 0.25% methylcellulose. The mean blood pressure (mm/Hg.) for each group before dosing and on day 119 (4 hours after dosing) and the number of survivors on day 120 is shown in the table.

Table II

Group	Treatment	Crossover Treatment*	Mean Blood Pressure		No. of Survivors (%)
			Initial	Day 119	
1	H_2O	H_2O	198±4.9	207±6.6	10 (66.7)
2	H_2O	H_2O + A	198±4.9	206±5.2	10 (66.7)
3	H_2O	H_2O + H	206±7.5	207±4.8	11 (73.3)
4	A	A	197±5.3	167±4.6	14 (93.3)
5	A	H_2O	197±6.2	176±5.1	14 (93.3)
6	A	A# + H#	202±6.6	140±4.6	15 (100)
7	H	H	197±5.8	202±8.4	8 (53.3)

*Crossover took place on day 28 through day 33 and on day 91 through day 96 (except Group 6 - see below).

#Daily dosage of each maintained from day 109 on.

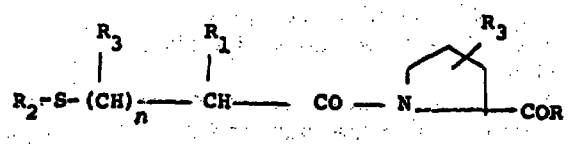
A = (D-3-mercapto-2-methylpropanoyl)-L-proline

H = Hydrochlorothiazide

The foregoing data show that on long term treatment compound H shows no significant decrease in blood pressure. Compound A alone shows approximately a 10 to 15% reduction in blood pressure. The combination dosing with Compound A and Compound H shows approximately a 30% reduction in blood pressure. Moreover, the combination is the only one showing a 100% survivor rate.

CLAIMS

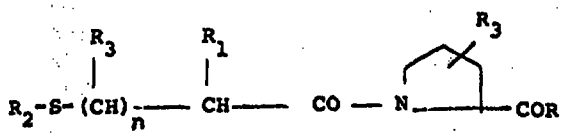
1. An oral anti hypertensive composition comprising a compound of the formula



wherein R is hydroxy, lower alkoxy or $-NH_2$; R_1 and R_4 each is hydrogen, lower alkyl or phenyl-lower alkyl; R_2 is hydrogen or R_5CO-; R_3 is hydrogen, hydroxy or lower alkyl; R_5 is lower alkyl, phenyl or phenyl-lower alkyl; n is 0, 1 or 2; a diuretic compound; and a physiologically acceptable carrier therefor.

2. A composition according to claim 1 wherein the diuretic is selected from chlorothiazide, hydrochlorothiazide, amiloride, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylclothiazide, trichlormethiazide, polythiazide, benzthiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triamterene, spironolactone and salts thereof.

3. An oral antihypertensive composition comprising 30 to 600 mg of a compound of the formula



wherein R, R_1, R_2, R_3, R_4 and n have the same meaning as in claim 1, 15 to 300 mg of a diuretic selected from chlorothiazide, hydrochlorothiazide, amiloride, flumethiazide, hydroflumethiazide, bendroflumethiazide,

B) In chronic studies with renal hypertensive rats, male rats (115-150 g.) of the Charles River Sprague Dawley (COBS-CO) strain were anesthetized with ether and a silver clip (0.22 mm i.d.) was placed on the left renal artery through a flank incision. The controlateral kidney was left intact (two-kidney Goldblatt model: 2-K RHR). Each rat was fitted with a tail cuff for air inflation and a Korotkoff sound microphone for the detection of arterial pulsation. An oscilloscope was used for a visual appearance and disappearance of the pulse. Blood pressure measurements were determined after a minimum of six inflations with systolic pressures observed on a Narco physiograph manometer. Blood pressures were determined initially just prior to dosing and twice weekly at 4 hours after dosing.

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3	H_2O	H_2O + H	206±7.5	207±4.8	11 (73.3)
4	A	A	197±5.3	167±4.6	14 (93.3)
5	A	H_2O	197±6.2	176±5.1	14 (93.3)
6	A	A# + H#	202±6.6	140±4.6	15 (100)
7	H	H	197±5.8	202±8.4	8 (53.3)

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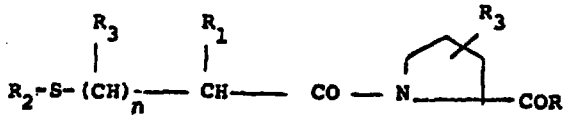
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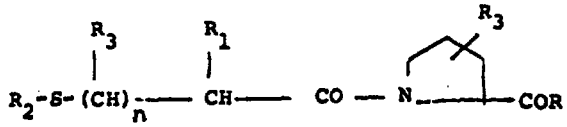
1. An oral anti hypertensive composition comprising a compound of the formula



wherein R is hydroxy, lower alkoxy or $-NH_2$; R_1 and R_4 each is hydrogen, lower alkyl or phenyl-lower alkyl; R_2 is hydrogen or R_5CO-; R_3 is hydrogen, hydroxy or lower alkyl; R_5 is lower alkyl, phenyl or phenyl-lower alkyl; n is 0, 1 or 2; a diuretic compound; and a physiologically acceptable carrier therefor.

2. A composition according to claim 1 wherein the diuretic is selected from chlorothiazide, hydrochlorothiazide, amiloride, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylclothiazide, trichlormethiazide, polythiazide, benzthiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triamterene, spironolactone and salts thereof.

3. An oral antihypertensive composition comprising 30 to 600 mg of a compound of the formula



wherein R, R_1, R_2, R_3, R_4 and n have the same meaning as in claim 1, 15 to 300 mg of a diuretic selected from chlorothiazide, hydrochlorothiazide, amiloride, flumethiazide, hydroflumethiazide, bendroflumethiazide,

methylclothiazide, trichlormethiazide, polythiazide, benzthiazide, ethacrynic acid, ticrynafen, chlorthalidone, furosemide, bumetanide, triameterene, spironolactone and salts thereof, and a physiologically acceptable carrier therefor.

4. A composition as claimed in claim 3 comprising 30 to 300 mg of the compound of the formula and 15 to 200 mg of the diuretic.

5. A composition as claimed in any one of claims 1-4 wherein the compound of the formula has R as hydroxy or lower alkoxy; R_1 as hydrogen or lower aklyl; R_2 as hydrogen or lower alkanoyl; R_3 as hydrogen or hydroxy; R_4 as hydrogen or lower alkyl; and n as 0 or 1.

6. A composition as claimed in any one of claims 1-5 wherein lower alkoxy is C_1-C_4 alkoxy, lower alkyl is C_1-C_4 alkyl and lower alkanoyl is C_2-C_4 alkanoyl.

7. A composition as claimed in claim 5 or 6 wherein the compound of the formula has R as hydroxy; R_1 as hydrogen or methyl; R_2 as hydrogen or acetyl; R_3 as hydrogen; R_4 as hydrogen or methyl; and n as 0 or 1.

8. A composition as claim in any one of claims 1-7 wherein the diuretic is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene.

9. A composition as claimed in claim 8 wherein the diuretic is hydrochlorothiazide or furosemide.

10. A composition as claimed in any one of claims 1-4 wherein the compound of the formula has R as hydrogen or lower alkoxy; R_1 as hydrogen or lower alkyl; R_2 as hydrogen; R_3 as hydrogen or hydroxy; R_4 as hydrogen or lower alkyl; and n as 0 or 1; and the diuretic is chlorothiazide, hydrochlorothiazide, furosemide, ticrynafen or triamterene.

11. A composition as claimed in claim 10 wherein lower alkoxy is C_1-C_4 alkoxy, lower alkyl is C_1-C_4 alkyl and lower alkanoyl is C_2-C_4 alkanoyl.

12. A composition as claimed in any one of claims 1-4 wherein the compound of the formula is (D-3-mercapto-2-methyl-propanoyl)-L-proline and the diuretic is hydrochlorothiazide or furosemide.

13. A composition as claimed in claim 3 comprising 30 to 300 mg of (D-3-mercapto-2-methylpropanoyl)-L-proline and 15 to 200 mg of hydrochlorothiazide.

14. A composition as claimed in claim 3 comprising 30 to 300 mg of (D-3-mercapto-2-methylpropanoyl)-L-proline and 15-200 mg of furosemide.

15. A composition as claimed in claim 1 comprising 5 to 125 mg of (D-3-mercapto-2-methylpropanoyl)-L-proline and 2.5 to 50 mg of hydrochlorothiazide.

16. A composition as claimed in claim 1 comprising 5 to 125 mg of (D-3-mercapto-2-methylpropanoyl)-L-proline and 2.5 to 50 mg of furosemide.

17. A composition as claimed in claim 1 comprising 5 to 125 mg of (D-3-mercapto-2-methylpropanoyl)-L-proline and 5 to 75 mg of triamterene.

18. A composition as claimed in any one of claims 1-6 in the form of a tablet, capsule, solution, suspension, syrup or elixir.

19. A composition as claimed in any one of claims 1-7 including an excipient, binder, preservative, stabilizer, flavor, disintegrating agent, sweetener or lubricant.

20. A composition as claimed in claim 1, substantially as described in any of the Examples.

21. A composition comprising a compound of the formula given in claim 1 and a diuretic as defined in claim 1, for use in the treatment of hypertension.

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