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PATENT SPECIFICATION

1 495 034

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(54) PHARMACEUTICAL COMPOSITIONS

(71) We, MERCK & CO INC, a corporation organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

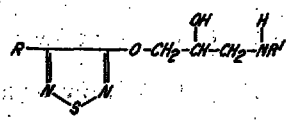
Diuretics such as the thiazides and certain pyrazines are useful as antihypertensive agents. However, these diuretics tend to increase circulating plasma resin levels. This increase in renin may be undesirable since it acts to reduce the antihypertensive effect of the diuretic.

β-adrenergic blocking agents are another class of drugs that are effective in long-term treatment of hypertension. Propranalol, a β-adrenergic blocking agent, has been found to inhibit renal renin secretion in man and in animals [New England Journal of Medicine *287*, 1209—1213 (1972)] Prindolol, another β-adrenergic blocking agent, has been found to have antihypertensive effect when administered alone and in combination with a thiazide diuretic [The Medical Journal of Australia *2*, 309—312, (1972)]. The effect on hypertension of a combination of large doses of 4 different β-blocking agents (including a substituted 1,2,5-thiadiazole) with a thiazide diuretic, has also been reported (Postgraduate Medical Journal *50*, 253—259, May 1974). U.S. Patent No. 3,832,470, issued August 27, 1974, discloses a mixture of a vasodilator and a β-adrenergic blocking agent. South African Patent No. 723,922 discloses a composition containing a β-adrenergic blocking agent, a vasodilator and a diuretic.

It has now been discovered that administration of a particular combination of a substituted 1,2,5 thiadiazole β-adrenergic blocking agent and said diuretic to a hypertensive animal (1) enhances the antihypertensive activity of the diuretic and (2) reduces the severity of potassium loss due to the diuretic.

The present invention provides compositions containing:

(A) as β-blocking agent, a compound having the formula



I

in which R is a hydrogen or halogen atom, a C_{3-6} cycloalkyl, C_{1-4} alkyl, C_{2-4} alkenyl, benzyl, phenyl, substituted phenyl, C_{1-5} alkoxy, heterocyclic, C_{1-4} alkylcarbamoyl or carbamoyl radicals or a group of formula $R^2—L—R^3—$ where R^2 is C_{1-3} alkyl, phenyl or substituted phenyl, L is oxygen or sulfur and R^3 is methyl or ethyl; and R' is a C_{1-10} alkyl, C_{2-6} alkynyl, C_{2-4} alkenyl, C_{1-4} alkylthio, C_{3-6} cycloalkyl or heterocyclic radical or a nontoxic pharmaceutically acceptable salt of such a compound, or a mixture containing two or more such compounds and/or salts; and

(B) as diuretic,

(a) a thiazide or a pharmaceutically acceptable salt thereof;

(b) a pyrazine diuretic compound as claimed in U.K. Patent No. 1,066,855 or as disclosed in U.S. Patent No. 3,781,430, e.g. amiloride or its pharmaceutically acceptable salts, or

(c) mixtures of (a) and/or (b).

The β-blocking agents of Formula I include the individual optical isomers as well as the racemate. More specific values of R in Formula I include hydrogen, chlorine, bromine, fluorine, methyl, ethyl, *n*-propyl, *t*-butyl, vinyl, allyl, methallyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, *n*-butylcarbamoyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *n*-pentoxy, phenyl, substituted phenyl in which the substituent(s) is/are one or more halogen atoms such as chlorine or fluorine, C_{1-3} alkyl groups and/or C_{1-3} alkoxy groups, aziridinyl, azetidinyl, pyrrolidyl, piperidyl, hexahydroazepineo, morpholino, piperidino, thiazolidinyl, *p*-thiazinyl, piperazinyl, thienyl, furyl or R^2—L—R^3— where L and R^3 are as defined above and R^2 is C_{1-3} alkyl such as methyl, ethyl or *n*-propyl, phenyl or substituted phenyl where the substituents(s) is/are halogen such as chlorine, bromine or fluorine, hydroxy, alkyl such as methyl, ethyl or *n*-propyl, or alkoxy such as methoxy, ethoxy, or *n*-propoxy.

More specific values of R' include isopropyl, *tert*-butyl, 2,2-dimethylpropyl, hexyl, allyl, vinyl methallyl, ethynyl, propynyl, butynyl, propargyl, hexynyl, cyclopropyl, cyclohexyl, cyclopentyl, pyrrolidinyl, piperazinyl, morpholino, thiazolidinyl, thienyl, furyl and thiazinyl.

Representative Formula I compounds and their salts which are useful in this invention are:

3 - chloro - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole

(+) - 3 - chloro - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

(–) - 3 - chloro - 4 - (3 - methylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

3 - bromo - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole

(+) - 3 - bromo - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

(–) - 3 - bromo - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride

3 - (4 - hydroxypiperidino) - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole

3 - morpholino - 4 - (3 - *n* - hexylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrogen maleate

(+) - 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrogen maleate

(–) - 3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrogen maleate

3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrochloride

3 - N - *t* - butylcarbamoyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole

(+) - 3 - N - *t* - butylcarbamoyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride

(–) - 3 - N - *t* - butylcarbamoyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride

3 - N - isopropylcarbamoyl - 4 - (3 - isopropylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole

(+) - 3 - N - isopropylcarbamoyl - 4 - (3 - isopropylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride

(–) - 3 - N - isopropylcarbamoyl - 4 - (3 - isopropylamino - 2 - hydroxypropoxy)-1,2,5 - thiadiazole hydrochloride

3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole benzoate

3 - chloro - 4 - (3 - isopropylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole

3 - bromo - 4 - (3 - isopropylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole

(+) - 3 - chloro - 4 - (3 - isopropylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole

3 - methyl - 4 - (3 - n - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole
3 - ethoxy - 4 - (3 - sec - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole
and the like.

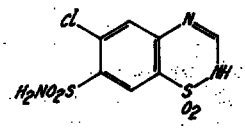
Preferred Formula I compounds are those in which R is halogen, alkyl, alkoxy, phenyl, benzyl, morpholino, piperazino of piperidino and R' is alkyl, preferably C_3—C_6. An especially preferred Formula I compound is one where R is morpholino, R' is *t*-butyl, more particularly the (–)isomer and pharmaceutically acceptable salts thereof, especially the hydrogen maleate.

The pharmaceutically acceptable salts of Formula I compounds are included as useful compounds in the present invention. Any non-toxic, pharmaceutically acceptable salt of Formula I compounds may be used. Representative examples of these pharmaceutically acceptable salts are the hydrohalides, e.g., hydrochlorides, hydrobromides, hydroiodides; the phosphates, sulfates, oxalates, lactates, malates, maleates, formates, acetates, succinates, tartrates, salicylates, citrates, phenylacetates, benzoates, p-toluenesulfonates and other salts such as those that provide relative insoluble products that afford a slow release of the active material, for example, a 1,1'-methylene-bis-(2-hydroxy-3-naphthoate).

The β-blocking agents of Formula I and methods for their preparation are described in U.S. Patents Nos. 3,655,663, 3,729,469, 3,657,237, 3,718,647 and 3,812,182.

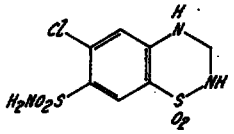
The thiazides used in the compositions of the present invention belong to a 1,2,4 benzothiazine a class of compounds. They include compounds such as flumethiazide, benzthiazide, cyclopenthiazide, cyclothiazide, trichloromethiazide, benzhydroflumethiazide, methylcyclothiazide, polythiazide and thiabutazide and their non-toxic, pharmaceutically acceptable salts.

Preferred thiazides are those having the following formulae:



II

and



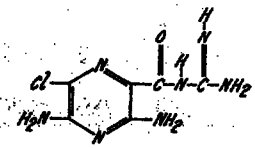
III

and their pharmaceutically acceptable salts.

The Formula II compound is chlorothiazide and the Formula III compound is hydrochlorothiazide. Salts of the Formula II and III compounds include those of alkali metals, especially sodium.

The thiazide diuretics, their use and methods for their preparation are described in U.S. Patents Nos. 2,809,184, 3,025,292, 2,937,169, 3,164,588 and 3,043,840.

The preferred pyrazine diuretic has the formula:



IV

The Formula IV compound is amiloride. The compound and its preparation are described in U.K. Patent No. 1,066,855 which also discloses analogous useful pyrazine derivatives. Amiloride is also useful in the form of a non-toxic pharmaceutically acceptable salt of an inorganic or organic acid, e.g. a hydrohalic acid, a phosphorus acid, sulfuric acid, or citric, tartaric, maleic, sulconic, phosphonic, malic or acetic acid. The hydrochloride dihydrate of amiloride is especially preferred.

Combinations containing thiazide and pyrazine diuretics are also useful. The weight ratios of the diuretics in these combinations can be varied. Generally weight ratios of pytazine: thiazide from 1:1 to 1:10 are useful and a weight ratio of 1:10 is particularly useful. In a preferred combination the diazine is amiloride hydrochloride (or its dihydrate) and the thiazide is hydrochlorothiazide: the weight ratio of amiloride to hydrochlorothiazide is preferably 1:10. These combinations are disclosed in Patent No. 3,781,430.

The compositions of the present invention are administered in dose quantities of β-adrenergic blocking agent: diuretic in weight ratio of from 1:15 to 24:1, preferably 1:12 to 4:1 and particularly 1:10 to 4:1 and most particularly about 1:1 to 1:1; a 1:5 to 1:1.25 ratio range is especially preferred. The amount of β-adrenergic blocking agent and diuretic administered is variable. Generally, the β-blocking agent is administered in quantities ranging from 1—12 mg. per kilogram of animal body weight while the diuretic is administered in quantities ranging from 0.5—15 mg. per kilogram of animal body weight. A preferable administration quantity range for the β-blocking agent is 1—8 mg./kg./day and for the diuretic 1—10 mg./kg./day. The present compositions are useful for treating hypertension in animals, including humans to effect a decrease in blood pressure. These compositions are administered in varying dosages and for various periods of time as the treatment requires.

It is to be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination and the severity of the disease undergoing therapy.

The compositions of the present invention may be administered in any acceptable and recognized manner. They are preferably administered orally in an acceptable dosage form. The compound may be combined in a capsule. The compositions may be provided in the form of tablets, which may include other ingredients ordinarily used to facilitate tablet formation, palatability, etc. The compositions may likewise be dissolved or dispersed in a pharmaceutically acceptable carrier for administration in a fluid form.

The following examples illustrate but do not limit the preparation of the various compositions of the invention.

TABLE I.

Ingredients	Parts by weight Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6
3-morpholino-4-(3-*t*-butylamino-2-hydroxy-propoxy)-1,2,5-thia-diazole	10	10	10	5	5	5
Hydrochlorothiazide	10	25	50	10	25	50
Starch USP Corn	124	114	109	99	84	80
Microcrystalline Cellulose	134	129	109	85	85	54
Magnesium Stearate	2	2	2	1	1	1
TOTAL (mg./tablet)	280	280	280	200	200	200

3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochlorothiazide, and part of the corn starch and microcrystalline cellulose are mixed together, milled and granulated with part of the corn starch as starch paste. The granulated mass is wet-sized, dried, dry milled, and blended with the remaining corn starch and microcrystalline cellulose, lubricated with magnesium stearate, and compressed into tablets.

Equivalent amounts of chlorothiazide or its sodium salt may be substituted for the hydrochlorothiazide in the Table I formulation to prepare corresponding compositions.

When other β-adrenergic blocking agents such as 3 - chloro - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - (4 - hydroxypiperidino) - 4 - (3-*t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - piperazino - 4 - (3 - *t*-butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - piperidino - 4 - (3 - *t*-butylamino - 2 hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - N - isopropylcarbamoyl - 4-

(3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - N - isopropylcarbamoyl - 4 - (3 - isopropylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - methyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, 3 - ethoxy - 4 - (3 - t - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole or representative salt thereof is substituted for 3 - morpholino - 4 - (3 - *t* - butylamino-2 - hydroxypropoxy) - 1,2,5 - thiadiazole, there is obtained the corresponding composition.

TABLE II.

Ingredients	Parts by weight Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12
3-morpholino-4-(3-*t*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate	10	10	10	5	5	5
Hydrochlorothiazide	10	25	50	10	25	50
Starch USP Corn	124	114	109	99	84	80
Microcrystalline Cellulose	134	129	109	85	85	54
Magnesium Stearate	2	2	2	1	1	1
TOTAL (mg./tablet)	280	280	280	200	200	200

3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, hydrochlorothiazide, and part of the corn starch and microcrystalline cellulose are mixed together, milled and granulated with part of the corn starch as starch paste. The granulated mass is wet-sized, dried, dry milled, and blended with the remaining corn starch and microcrystalline cellulose, lubricated with magnesium stearate, and compressed into tablets.

Corresponding compositions are prepared when an equivalent amount of amiloride or its hydrochloride dihydrate is substituted for hydrochlorothiazide in Table II.

When other optically active β-adrenergic blocking agents such as (–) - 3 - chloro - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (–) - 3 - (4 - hydroxypiperidino) - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (–) - 3 - piperidino) - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, (–) - 3 - N - *t*-butylcarbamoyl - 4 - (3 - t - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (–) - 3 - methyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrochloride, (–) - 3 - ethoxy - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride or (–) - 3 - chloro - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole is substituted for 3 - morpholino-4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate, there is obtained the corresponding composition.

TABLE III.

Ingredients	Parts by weight Ex. 13	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18
3-morpholino-4-(3-t-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate (racemate)	10	10	10	5	5	5
Hydrochlorothiazide	10	25	50	10	25	50
Starch USP Corn	124	114	109	99	84	80
Microcrystalline Cellulose	134	129	109	85	85	54
Magnesium Stearate	2	2	2	1	1	1
TOTAL (mg./tablet)	280	280	280	200	200	200

(3 - morpholino - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrogen maleate (racemate), hydralazine, and part of the corn starch and microcrystalline cellulose are mixed together, milled and granulated with part of the corn starch as starch paste. The granulated mass is wet-sized, dried, dry milled, and blended with the remaining corn starch and microcrystalline cellulose, lubricated with magnesium stearate, and compressed into tablets.

A mixture containing hydrochlorothiazide and amiloride hydrochloride dihydrate may be substituted for hydrochlorothiazide in Table III to prepare corresponding compositions.

When other optically active β-adrenergic blocking agents such as racemic 3 - chloro - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, (–) - 3 - (4 - hydroxypiperidino) - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole citrate, (+) - 3 - piperidino - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, racemic 3 - morpholino - 4-(3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrobromide, (+) - 3-N - *t* - butylcarbamoyl - 4 - (3 - t - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrochloride, (–) - 3 - methyl - 4 - (3 - *t* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole acetate, (+) - 3 - ethoxy - 4 - (3 - *t* - butylamino - 2-hydroxypropoxy) - 1,2,5 - thiadiazole phosphate, or (+) - 3 - chloro - 4 - (3 - t - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride is substituted for racemic 3 - morpholino - 4 - (3 - t - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole hydrogen maleate, with the hydrochlorothiazide or mixed hydrochlorothiazide/amiloride $HCl.2H_2O$ corresponding compositions are obtained.

The effect of the compositions of the present invention on blood pressure and plasma potassium was determined by an *in vivo* procedure utilizing adult beagle dogs in which hypertension was produced by surgical modification of the kidney. The blood pressure and plasma potassium level of these hypertensive dogs were measured over a number of days before and after (twice a day) oral administration (in gelatin capsules) of hydrochlorothiazide (HCTZ) and a combination of HCTZ and (–)-3-morpholino-4-(3-*t*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate (MTHM). The results obtained from a statistically designed set of experiments, using the aforesaid procedure, are tabulated below:

TABLE A.

EFFECT ON BLOOD PRESSURE AND PLASMA POTASSIUM

Test		Treatment	No. Of Dogs	Days Of Treatment	Plasma [1] Potassium	Blood [2] Pressure
A	1	Control	5	—	4.2	140
	2	HCTZ—10 mg/kg/day	5	2	3.4	122
	3	HCTZ—10 mg/kg/day	5	4	3.6	129
D	1	Control	5	—	4.3	132
	2	HCTZ—10 mg/kg/day + MTHM—2.0 mg/kg/day	5	2	4.1	114
	3	HCTZ—10 mg/kg/day + MTHM—2.0 mg/kg/day	5	4	4.1	105
B	1	Control (lactose)	4	—	—	126
	2	MTHM—1.0 mg/kg/day	4	2	—	128
		MTHM—1.0 mg/kg/day	4	4	—	133
	3	MTHM—4.0 mg/kg/day	4	2	—	137
		MTHM—4.0 mg/kg/day	4	4	—	141
C	1	Control	6	3	4.5	—
		MTHM—2.0 mg/kg/day	12	3	5.0	—

[1] millequivalents/liter

[2] mean arterial in mm/Hg

Comparable results were obtained when comparing effect on blood pressure and plasma potassium of 2.5 mg./kg/day HCTZ with 2.5 mg./kg/day HCTZ + 2 mg./kg/day MTHM and 2.5 mg./kg/day HCTZ + 8 mg./kg/day MTHM. The data presented in Table A, clearly show that the substituted thiadiazole substantially enhances (1) the antihypertensive effect of hydrochlorothiazide and (2) reduces the severity of potassium loss produced by hydrochlorothiazide.

Other combinations and dosages which have been studies are MTHM/HCTZ at 1.0/2.5, 4.0/10.0 and 8.0/10.0 mg/kg/day; and MTHM/HCTZ/amiloride hydrochloride dihydrate at 1.0/2.5/0.25, 4.0/10.0/1.0, 8.0/10.0/1.0, and 10.0/25/2.5 mg/kg/day.

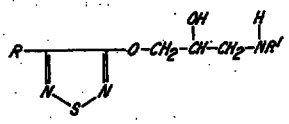
In addition to blood pressure reduction and plasma potassium level maintained the HCTZ/MTHM compositions were also found to reduce circulating renin levels.

Analogous results can be obtained for other compositions of the present invention as disclosed herein.

WHAT WE CLAIM IS:—

1. Compositions containing:

(A) as β-blocking agent, a compound having the formula



I

in which R is a hydrogen or halogen atom, a C_{3-6} cycloalkyl, C_{1-4} alkyl, C_{2-4} alkenyl, benzyl, phenyl, substituted phenyl, C_{1-5} alkoxy, heterocyclic, C_{1-4} alkylcarbamoyl or carbamoyl radical, or a group of formula $R^2—L—R^3—$ where R^2 is C_{1-3} alkyl, phenyl or substituted phenyl, L is oxygen or sulfur and R^3 is methyl or ethyl; and R′ is a C_{1-10} alkyl, C_{2-6} alkynyl, C_{2-4} alkenyl, C_{1-4} alkylthio, C_{3-6} cycloalkyl or heterocyclic radical or a non-toxic pharmaceutically acceptable salt of such a compound, or a mixture containing two or more such compounds and/or salts; and

(B) as diuretic,

(a) a thiazide or a pharmaceutically acceptable salt thereof;

(b) a pyrazine diuretic compound as claimed in U.K. Patent No. 1,066,855 or as disclosed in U.S. Patent No. 3,781,430, or

(c) a mixture of (a) and/or (b).

2. A composition as claimed in Claim 1, in which the thiazide is chlorothiazide, an alkali metal salt of chlorothiazide, or hydrochlorothiazide, and the pyrazine is amiloride or a pharmaceutically acceptable salt thereof.

3. A composition as claimed in Claim 1 or 2, in which R in the formula of the β-blocking agent is a halogen atom or a C_{1-4} alkyl, C_{1-5} alkoxy, phenyl, benzyl, morpholino, piperazino or piperidino radical and R′ is a C_{1-10} alkyl radical.

4. A composition as claimed in Claim 3, in which R is morpholino and R′ is C_{3-6} alkyl.

5. A composition as claimed in Claim 4, in which the diuretic is a pyrazine diuretic as claimed in U.K. Patent No. 1,066,855.

6. A composition as claimed in Claim 5, in which R′ is *t*-butyl and the β-blocking agent is a non-toxic pharmaceutically acceptable salt of the (–) isomer of the compound.

7. A composition as claimed in Claim 6, in which the salt is the hydrogen maleate.

8. A composition as claimed in any one of Claims 1 to 7, in which the diuretic is amiloride hydrochloride dihydrate.

9. A composition as claimed in Claim 4, in which the diuretic is a thiazide or a pharmaceutically acceptable salt thereof and R′ is *t*-butyl.

10. A composition as claimed in Claim 9, in which the β-blocking agent is a non-toxic pharmaceutically acceptable salt of the (–) isomer of the compound.

11. A composition as claimed in Claim 10, in which the salt is the hydrogen maleate and the diuretic is hydrochlorothiazide.

12. A composition as claimed in Claim 4, in which R′ is *t*-butyl, the β-blocking agent is a non-toxic pharmaceutically acceptable salt of the (–) isomer of the compound and the diuretic is a mixture of a pyrazine and a thiazide.

13. A composition as claimed in Claim 12, in which the salt is the hydrogen maleate and the diuretic mixture contains hydrochlorothiazide and amiloride hydrochloride dihydrate.

14. A composition as claimed in Claim 12, in which the ratio by weight of pyrazine to thiazide diuretic is in the range from 1:1 to 1:10.

15. A composition as claimed in Claim 12 or 13, in which the ratio by weight of pyrazine to thiazide diuretic is 1:10.

16. A composition as claimed in any preceding claim, in which the weight ratio of blocking agent to diuretic is in the range 1:12 to 4:1.

17. A composition as claimed in Claim 16, in which the weight ratio of blocking agent to diuretic is in the range 1:10 to 1:1.

18. A composition as claimed in any one of Claims 1 to 17 in orally administrable form.

19. A composition as claimed in Claim 18 in the form of a tablet.

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20. A composition as claimed in Claim 18 in the form of a capsule, solution or dispersion.

21. A composition as claimed in Claim 1, substantially as hereinbefore described in any one of Examples 1 to 18.

22. A method of treating a hypertensive non-human animal to reduce blood pressure which comprises co-administration of a pharmaceutically effective amount of a composition as claimed in any preceding claim.

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