1 565 686

PATENT SPECIFICATION (11) 1 565 686

(21) Application No. 47175/76 (22) Filed 12 Nov 1976
(31) Convention Application No. 14718/75
(32) Filed 13 Nov. 1975 in
(33) Switzerland (CH)
(44) Complete Specification published 23 April 1980
(51) INT CL³ A61K 31/495
(52) Index at acceptance
A5B 180 190 382 38Y 426 42Y 430 431 432 433 43Y 442 446 44Y 451 45Y 480 482 48Y 511 512 51X 51Y 521 522 523 52Y 551 552 55Y 576 57Y 586 587 58Y 596 597 59Y 650 651 652 65Y J



(72) Inventor ROLAND SALZMANN

(54) ANTI-HYPERTENSIVE COMPOSITIONS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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:—

The present invention relates to anti-hypertensive compositions.

The present invention provides a pharmaceutical composition incorporating as active agents:—

a) a hydrazino-pyridazine anti-hypertensive agent, and

b) N-amidino-2-(2,6-dichlorophenyl-acetamide.

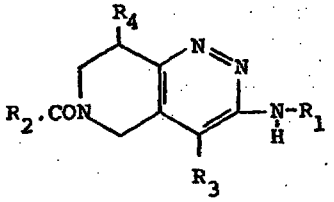
Active agents a) are in general known. They exhibit anti-hypertensive action by a peripheral vasodilator effect, but in general induce tachycardia.

Suitable active agents a) may have a bicyclic nucleus containing as one fused ring a pyridazine ring, and carrying on the pyridazine ring at least one hydrazino substituent.

Such compounds include the compounds of groups i), ii) and iii) below:—

i) 3-hydrazino-5,6,7,8-tetrahydro-pyrido[4,3-c]pyridazino derivatives, e.g. those such derivatives disclosed in formula I of U.K. Patent Specifications 1,392,474, 1,392,475 and 1,475,590.

Preferred active agents a) of group i) include those of formula I,



I

wherein

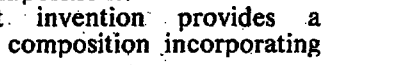
R_1 is amino or $—N=CR_5R_6$,

wherein

R_5 and R_6 are independently alkyl of 1 to 4 carbon atoms,

R_2 is alkyl or alkoxy of 1 to 6 carbon atoms,

alkenyl or alkenyloxy of 3 to 6 carbon atoms, or a group of formula:—



wherein

X is a direct bond or oxygen,

m is 0, 1 or 2, and

R_7 is hydrogen, fluorine, chlorine or bromine,

alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and

R_3 and R_4, are independently, hydrogen or methyl.

Preferably any alkyl containing group has 1 or 2 carbon atoms. Conveniently when R_2 is alkenyl or alkenyloxy the double bond is in the β,α-position.

Conveniently when R_7 is halogen, this is chlorine or preferably fluorine. R_1 is preferably isopropylidene-amino, or especially amino. R_2 is preferably ethoxy, phenylethyl, or phenyl or phenyl substituted by fluorine or alkoxy.

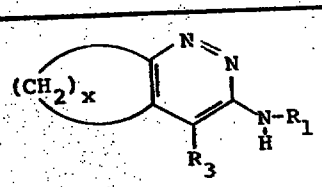
Especially preferred compounds include the following:—

6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine, and

3 - hydrazino - 5,6,7,8 - tetrahydro - 4,8 - dimethyl - 6 - pyrido[4,3 - c]pyridazine carboxylic acid ethyl ester.

ii) 3-Hydrazino-cycloalkane[c]pyridazine derivatives, e.g. those such derivatives disclosed in formula I of the above mentioned U.K Patent Specifications.

Preferred active agents of group ii) include those of formula II.



II

wherein

R_1 and R_3 are as defined above, and

x is 4, 5 or 6.

Preferred significances for R_1 and R_3 are as mentioned above with reference to formula I. x is preferably 5 or 6.

A preferred active agent is for example:— 3 - hydrazino - 5,6,7,8,9,10 - hexahydro - 4 - methylcycloocta[c]pyridazine.

iii) 1-Hydrazinophthalazine derivatives, e.g. 1-hydrazinophthalazine, 1 - [2 - (1,3 - dimethyl - 2 - butenylidene)hydrazino]phthalazine, 1,4-dihydrazinophthalazine or 1 - (N' - ethoxycarbonylhydrazino)phthalazine.

The peripheral vasodilator and tachycardia effects exhibited by active agents a) may be observed in standard animal tests. For example, the effects may be observed in the conscious, spontaneous hypertonic rat test, wherein a catheter is implanted in the rat aorta according to the principles of Weeks et al, Proc. Soc. Exp. Biol. Med. *104*, 646—648 (1960) and McIlreath et al, Arch. Int. Pharmacodyn. *157*, 330—338 (1965).

It has now been surprisingly found that the mixtures of active agents a) and b) per day advantageous anti-hypertensive activity involving reduced tachycardia.

Combinations of active agents a) and b) are therefore especially indicated for use as anti-hypertensive preparations.

The present invention therefore provides a composition for inducing an anti-hypertensive effect in an animal suffering from hypertension, which comprises active agents a) and b) as defined hereinbefore.

An indicated daily dose of active agent a) is from about 1 to 50 mg, preferably 2 to 30 mg.

An indicated weight ratio of active agent a) to active agent b) (based on the weight of the free base forms) is from 15:1 to 1:10, e.g. from 10:1 to 9:1 to 1:1, 3:7 or 1:9. A preferred weight ratio is from 15:1 to 2:1, e.g. 15:1 or 10:1 or 5:1.

The daily dosage may be conveniently administered 2 to 4 times a day, preferably 3 times a day, in divided doses, conveniently in unit dosage form, or in sustained release form.

Active agents a) and b) may be combined in one dosage form or retained separately until required for concomitant administration. Preferred weights of active agent a) in a unit dosage form are for example, 5 mg or conveniently 10 mg. Preferred weights of active agent b) are in a unit dosage form of 1 mg or 2 mg.

The present invention also provides a process for the production of a pharmaceutical composition as defined above including the step of bringing into admixture together active agents a) and b).

Processes used for the formulation of such pharmaceutical compositions are known in the art, e.g. as described in the Examples hereinafter. Pharmaceutical compositions containing active agents a) and b) separately are in general known. Pharmaceutical compositions containing both active agents a) and b) may be formulated using the same principles so as to be suitable for enteral or parenteral administration.

Depending on the compound used and composition contemplated the active agent a) and/or active agent b) may be in pharmaceutically acceptable acid addition salt form. Such forms are known and may be made from the free base form in conventional manner. Suitable salts for active agent a) include the hydrochloride. Suitable salts for active agent b) include the hydrochloride, methane-sulphonate, sulphate and fumarate.

Tablets, capsules, dragées, suppositories, suspensions and syrups may be used for enteral administration. Injectable suspensions or solutions may be used for parenteral administration. Preferably both active agent a) and active agent b) are administered orally, in the form of a unit dosage. Such a unit dosage may, if desired, have the active agents a) and b) separately encompassed therein, e.g. in separate layers in a mantle tablet.

Aside from the active agents the compositions may contain pharmaceutically inert organic or inorganic adjuvants, optionally granulating agents, binding agents, lubricants, dispersing agents, wetting agents and preservatives. Moreover, the pharmaceutical compositions may contain colouring, flavouring and sweetening substances, etc. Adjuvants for the production of tablets may be e.g. calcium carbonate, lactose, micro-crystalline cellulose, mannitol, or talc. Starch and alginic acid or micro-crystalline cellulose may be used as granulating and disintegrating agents, starch, polyvinylpyrrolidone and gelatine may be used as binding agents, and magnesium stearate, stearic acid, colloidal silica and talc as lubricants. Tablet formulations may be coated or uncoated, with the coating being applied in a manner known *per se* and having the purpose of delaying the disintegration and adsorption in the gastrointestinal tract, thus providing a retarded effect over a longer period. Suitable suspending agents for the production of liquid administration forms

are e.g. methyl cellulose, and sodium alginate. Suitable wetting agents are e.g. polyoxyethylene stearate and polyoxyethylene sorbitan-monooleate. Furthermore, preservatives such as p-hydroxy-benzoic acid alkyl ester may be used. Capsule formulations may contain the active agents a) and b) on their own or together with an inert solid diluent, for example calcium phosphate, calcium sulphate, corn-starch, lactose, mannitol, colloidal silica, magnesium stearate, and micro-crystalline cellulose.

Solid preparations are preferred, especially for active agent a), e.g. hard-gelatine capsules and tablets.

Insofar as the production of any compound or pharmaceutical composition is not particularly described herein, these may be made in known manner or analogous to known processes or analogous to processes described herein.

The following Examples are illustrative of compositions.

EXAMPLE 1

Tablets and Capsules Containing Active Agents a) and b) in Admixture

Tablets and capsules comprising the following constituents may be made in conventional manner.

Constituent	Weight (mg)
i) 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine methane sulphonate	6.875 (=5 mg base)
ii) N - amidino - 2 - (2,6 - dichlorophenyl)-acetamide	2.3 (=2 mg base)
iii) Lactose	90.8
iv) Corn starch	12.9
v) Polyvinylpyrrolidone	4.8
vi) Talc	1.125
vii) Magnesium stearate	1.2

EXAMPLE 2

Active agent a) given in Example 1 may be replaced by any other active agent a) mentioned hereinbefore.

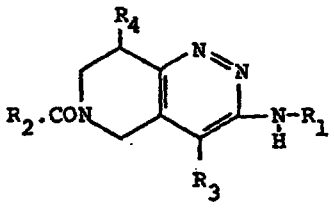
WHAT WE CLAIM IS:—

1. A pharmaceutical composition incorporating as active agents:—
   a) a hydrazino-pyridazine anti-hypertensive agent, and
   b) N - amidino 2 - (2,6 - dichloro-phenyl)acetamide.

2. A pharmaceutical composition according to Claim 1, wherein active agent a) is:—
   i) a 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine derivative,
   ii) a 3 - hydrazino - cycloalkane-[c]pyridazine derivative, or
   iii) a 1-hydrazinophthalazine derivative.

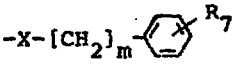
3. A pharmaceutical composition according to Claim 2, wherein active agent a) is a 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine derivative.

4. A pharmaceutical composition according to Claim 3, wherein active agent a) is of formula



I

wherein
R_1 is amino or $—N=CR_5R_6$,
wherein
R_5 and R_6 are independently, alkyl of 1 to 4 carbon atoms,
R_2 is alkyl or alkoxy of 1 to 6 carbon atoms,
alkenyl or alkenyloxy of 3 to 6 carbon atoms, or a group of formula:—



wherein
X is a direct bond or oxygen,
m is 0, 1 or 2, and
R_7 is hydrogen, fluorine, dioxane or bromine,
alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms, and
R_3 and R_4, are, independently, hydrogen or methyl.

5. A pharmaceutical composition according to Claim 4, wherein R_1 is amino or isopropylidene-amino and R_2 is ethoxy, phenethyl, or phenyl or phenyl substituted by fluorine or alkoxy.

6. A pharmaceutical composition according to Claim 4, wherein active agent a) is 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine.

7. A pharmaceutical composition according to Claim 4, wherein active agent a) is 3 - hydrazino - 5,6,7,8 - tetrahydro - 4,8 - dimethyl - 6 - pyrido[4,3 - c]pyridazine carboxylic acid ethyl ester.

8. A pharmaceutical composition according to Claim 2, wherein active agent a) is a 3-hydrazinocycloalkane[c]pyridazine derivative.

9. A pharmaceutical composition

are e.g. methyl cellulose, and sodium alginate. Suitable wetting agents are e.g. polyoxyethylene stearate and polyoxyethylene sorbitan-monooleate. Furthermore, preservatives such as p-hydroxy-benzoic acid alkyl ester may be used. Capsule formulations may contain the active agents a) and b) on their own or together with an inert solid diluent, for example calcium phosphate, calcium sulphate, corn-starch, lactose, mannitol, colloidal silica, magnesium stearate, and micro-crystalline cellulose.

Solid preparations are preferred, especially for active agent a), e.g. hard-gelatine capsules and tablets.

Insofar as the production of any compound or pharmaceutical composition is not particularly described herein, these may be made in known manner or analogous to known processes or analogous to processes described herein.

The following Examples are illustrative of compositions.

EXAMPLE 1

Tablets and Capsules Containing Active Agents a) and b) in Admixture

Tablets and capsules comprising the following constituents may be made in conventional manner.

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iii) Lactose	90.8
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v) Polyvinylpyrrolidone	4.8
vi) Talc	1.125
vii) Magnesium stearate	1.2

EXAMPLE 2

Active agent a) given in Example 1 may be replaced by any other active agent a) mentioned hereinbefore.

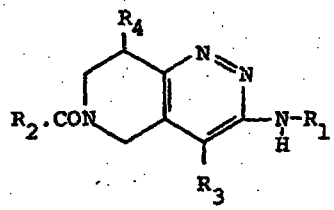
WHAT WE CLAIM IS:—

1. A pharmaceutical composition incorporating as active agents:—
   a) a hydrazino-pyridazine anti-hypertensive agent, and
   b) N - amidino 2 - (2,6 - dichloro-phenyl)acetamide.

2. A pharmaceutical composition according to Claim 1, wherein active agent a) is:—
   i) a 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine derivative,
   ii) a 3 - hydrazino - cycloalkane-[c]pyridazine derivative, or
   iii) a 1-hydrazinophthalazine derivative.

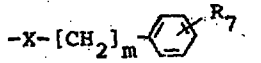
3. A pharmaceutical composition according to Claim 2, wherein active agent a) is a 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine derivative.

4. A pharmaceutical composition according to Claim 3, wherein active agent a) is of formula



I

wherein
R_1 is amino or $—N=CR_5R_6$,
wherein
R_5 and R_6 are independently, alkyl of 1 to 4 carbon atoms,
R_2 is alkyl or alkoxy of 1 to 6 carbon atoms,
alkenyl or alkenyloxy of 3 to 6 carbon atoms, or a group of formula:—



wherein
X is a direct bond or oxygen,
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R_7 is hydrogen, fluorine, dioxane or bromine,
alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms, and
R_3 and R_4, are, independently, hydrogen or methyl.

5. A pharmaceutical composition according to Claim 4, wherein R_1 is amino or isopropylidene-amino and R_2 is ethoxy, phenethyl, or phenyl or phenyl substituted by fluorine or alkoxy.

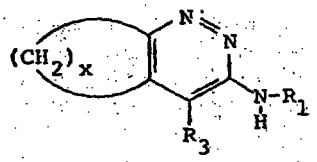
6. A pharmaceutical composition according to Claim 4, wherein active agent a) is 6 - benzoyl - 3 - hydrazino - 5,6,7,8 - tetrahydropyrido[4,3 - c]pyridazine.

7. A pharmaceutical composition according to Claim 4, wherein active agent a) is 3 - hydrazino - 5,6,7,8 - tetrahydro - 4,8 - dimethyl - 6 - pyrido[4,3 - c]pyridazine carboxylic acid ethyl ester.

8. A pharmaceutical composition according to Claim 2, wherein active agent a) is a 3-hydrazinocycloalkane[c]pyridazine derivative.

9. A pharmaceutical composition

according to Claim 8, wherein active agent a) is of formula,



II

wherein

R_1 and R_3 are as defined in Claim 4, and x is 4, 5 or 6.

10. A pharmaceutical composition according to Claim 9, wherein x is 5 or 6.

11. A pharmaceutical composition according to Claim 8, wherein active agent a) is 3 - hydrazino - 5,6,7,8,9,10 - hexahydro - 4 - methylcyclooct[c]pyridazine.

12. A pharmaceutical composition according to Claim 2, wherein active agent a) is a 1-hydrazinophthalazine derivative.

13. A pharmaceutical composition according to Claim 12, wherein active agent a) is 1-hydrazinophthalazine, 1 - [2 - (1,3 - dimethyl - 2 - butenylidene) - hydrazino]phthalazine, 1,4 - dihydrazinophthalazine or 1 - (N' - ethoxycarbonylhydrazino)phthalazine.

14. A pharmaceutical composition according to any one of the preceding claims, wherein the weight ratio of active agent a) to active agent b) is from 15:1 to 1:10.

15. A pharmaceutical composition according to Claim 6, wherein the weight ratio of active agent a) to active agent b) is from 15:1 to 2:1.

16. A pharmaceutical composition according to Claim 6, wherein the weight ratio of active agent a) to active agent b) is 15:1.

17. A pharmaceutical composition according to Claim 6, wherein the weight ratio of active agent a) to active agent b) is 10:1.

18. A pharmaceutical composition according to Claim 6, wherein the weight ratio of active agent a) to active agent b) is 5:1.

19. A pharmaceutical composition according to any preceding claim in unit dosage form.

20. A pharmaceutical composition according to Claim 19, wherein the weight of active agent a) is 10 mg.

21. A pharmaceutical composition according to Claim 19, wherein the weight of active agent b) is 1 or 2 mg.

22. A pharmaceutical composition substantially as hereinbefore described with reference to Example 1 or 2.

23. A process for the preparation of a pharmaceutical composition as claimed in any one of Claims 1 to 22 which comprises the step of bringing into admixture together active agents a) and b).

24. A pharmaceutical composition whenever produced by the process of Claim 23.

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Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.