PATENT SPECIFICATION

(11) 1 204 631

1 204 631

NO DRAWINGS

(21) Application No. 48134/68 (22) Filed 10 Oct. 1968

(31) Convention Application No. 674 753 (32) Filed 12 Oct. 1967 in

(33) United States of America (US)

(45) Complete Specification published 9 Sept. 1970

(51) International Classification A 61 k 27/00

(52) Index at acceptance

A5B 382 38Y 392 395 420 426 42Y 432 43Y 480 48Y 542 54Y 565 566 567 56Y 586 58Y 65X 65Y

C2C 17X—191—278 181—195—277 1Q11D 1Q11G 1Q3 1Q6B1 1Q7A 1Q8A 1Q8B 1Q8C 1Q9L 200 202 215 220 227 22Y 250 252 25Y 29X 29Y 313 314 31Y 320 327 328 338 677 703 744 746 74X 790 79Y NA NT



(72) Inventors JIRO KENNETH KODAMA, GEORGE RUFUS HAYNES and JAMES RICHARD ALBERT

(54) PHARMACOLOGICALLY ACTIVE BENZYLIDENEAMINO GUANIDINES AND THEIR USE

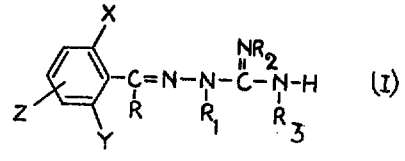
(71) We, SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ N.V., a Company organised under the Laws of the Netherlands, of 30 Carel van Bylandtlaan, The Hague, the Netherlands, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain pharmacologically active benzylideneaminoguanidines, compositions containing them, and their use.

In German patent specification No. 958,832 are described certain benzylideneaminoguanidines and their use as pharmaceuticals and therapeutic agents. Among these benzylideneaminoguanidines are those in which halogen is substituted on the phenyl ring; specifically, the benzylideneaminoguanidines which can be considered to be the derivatives of 4-chlorobenzaldehyde, 3,4 - dichlorobenzaldehyde and 3 - chlorobenzaldehyde. Generically, the said patent specification also discloses the benzylidene-aminoguanidines which can be considered to be the derivatives of the corresponding haloacetophenones. Despite the teachings of the German patent specification, it has been found that the benzylidene-aminoguanidines described in that specification and which do not have in their structure halogen substituted at an ortho position on the phenyl ring, exhibit little, if any, pharmacological activity.

In contrast, it has now been found that benzylidene-aminoguanidines having halogen substituted on at least one of the ortho carbon atoms of the phenyl ring exhibit very high pharmacological activity, particularly acting as depressants of the central nervous systems (CNS) and the cardivascular system, and as anti-depressants for overcoming psychic depression, in mammals including man.

Accordingly the present invention provides a method of treating a vendible mammal for the purpose of achieving a cardio-vascular response or/and inducing a central nervous system depressant response or/and combating psychic depression in such a mammal which comprises administering to the mammal an effective dosage of a benzylidene aminoguanidine of formula:—



(I)

wherein X is halogen or trifluoromethyl, Y and Z are hydrogen, halogen, trifluoromethyl or C_1—C_4 alkyl; R, R_1, R_2 and R_3 are hydrogen, C_1—C_4 alkyl, C_2—C_4 alkenyl or C_2—C_4 alkynyl, or R_2 and R_3 may together form an alkylene- or alkenylene-bridge of 2 to 4 carbon atoms, or physiologically acceptable acid addition salts thereof, or a composition containing such a compound or salt.

Suitable physiologically acceptable acid addition salts of these guanidines include their salts of such acids as hydrochloric acid, hydriodic acid, acetic acid, sulphuric acid, phosphoric acid, malic acid, ethionic acid, malonic acid, citric acid, benzoic acid and pamoic acid.

Preferred aminoguanidines are those wherein X and Y are chlorine or bromine, Z is hydrogen, chlorine or bromine and R_1, R_2, and R_3 are all hydrogen. Especially preferred is 1 - (2,6 - dichlorobenzylidene amino) - guanidine. Of the salts, the hydrochloride salts are preferred.

[*Price 5s. 0d. (25p)*]

Typical, illustrative species of this class of pharmaceuticals are set out in the Examples, as well as the following:

1 - (2 - chloro - 6 - (trifluoromethyl)benzylideneamino)guanidine
1 - (2 - chloro - 3,6 - bis(trifluoromethyl)-benzylideneamino)guanidine
1 - (2 - chloro - 6 - bromobenzylideneamino)guanidine
1 - (2,6 - dibromobenzylideneamino)guanidine
1 - (2 - bromo - 6 - methylbenzylideneamino)guanidine
1 - (2,3,6 - tribromobenzylideneamino)guanidine
1 - (2 - chloro - 6 - propylbenzylideneamino)guanidine
1 - (2,4,6 - trichlorobenzylideneamino)guanidine
1 - (2,6 - dichloro - 4 - methylbenzylideneamino)guanidine
1 - (2 - bromo - 6 - fluorobenzylideneamino)guanidine
1 - (2,6 - dichlorobenzylidene - amino) - 2 - propynylguanidine
1 - (2,6 - dichlorobenzylideneamino)-1,2,3-trimethylguanidine
1 - (2,6 - dichlorobenzylideneamino) - 2,3 - vinyleneguanidine
1 - (2,6 - dibromo - 4 - methylbenzylideneamino)guanidine
1 - (2 - chloro - alpha - methylbenzylideneamino)guanidine hydrochloride
1 - (2 - (trifluoromethyl) - alpha - methylbenzylidenamino)guanidine hydrochloride
1 - (2 - chlorobenzylideneamino)guanidine hydrochloride
1 - (2,4 - dichloro - alpha - methylbenzylideneamino)guanidine hydrochloride

The aminoguanidines for use in the method of the invention are in general crystalline solids. Many are slightly to sparingly soluble in most common organic solvents. Some are quite soluble in common pharmaceutical carriers, including water. The salts generally are more soluble in water than are the aminoguanidines *per se*.

The aminoguanidines are suitably administered orally, parenterally, intraperitoneally or intravenously. They can be formulated for these purposes as compositions using suitable carriers, the carriers, techniques of formulation, and administration being wholly conventional as appropriate to the intended mode of administration. In particular, it is well known that for parental, intraperitoneal or intravenous administration the composition should be formulated using a sterile carrier. The invention includes therefore within its scope compositions for use in the method of the invention comprising a benzylideneaminaguanidine of formula I, or acid addition salt thereof, together with a substantially sterile, physiologically acceptable carrier.

For ease of administration the compositions of the invention are suitably prepared in unit dosage form. The unit dosage or therapeutically effective quality of the active material may vary considerably. In general, a dosage of at least 0.01 mg active material per kg body weight of the patient is required while it will seldom be necessary to employ more than a dosage of 10 mg per kg body weight. The effective dosage will usually be from 0.1 to 5 mg per kg. body weight.

Methods for preparing these benzylideneaminoguanidines and their salts are shown in German Patent Specification No. 958,832. The preparation of particular compounds for use in the method of this invention is described in the following Examples, wherein "parts" means parts by weight, with parts by volume bearing the same relationship to parts by weight as does the litre to the kilogram. In each Example, the product is designated by a capital letter, to facilitate identification in a later Example.

EXAMPLE I

Preparation of 1-(2,6-dichlorobenzylideneamino)guanidine hydrochloride (A)

93 parts of 2,6-dichlorobenzaldehyde, 78 parts of aminoguanidine bicarbonate, 50 parts by volume of concentrated hydrochloric acid and 250 parts by volume of n-butanol were mixed and heated slowly to reflux (120°C). The by-product water was removed azeotropically over a period of 4 hours. The mixture was cooled and filtered to give 105 parts of a white solid melting at 223—224°C (uncorr.). The identity of the product was confirmed by elemental analysis.

Analysis (percent by weight):
Calculated: Cl—39.8; Cl^-—13.3; N—20.9
Found: Cl—39.3; Cl^-—13.0; N—20.6

EXAMPLE II

Preparation of 1-(2,6-dichlorobenzylideneamino)guanidine (B)

To 40 parts of the hydrochloride salt obtained in Example I in 600 parts by volume of water were added 130 parts by volume of 10% aqueous sodium hydroxide solution. The voluminous precipitate which formed was filtered and washed with water and acetone. Recrystallization from acetonitrile gave 23 parts

of a white solid which decomposes at 227—229°C (uncorr.). The product was identified as 1 - (2,6 - dichlorobenzylideneamino) guanidine by elemental and infrared spectrum analyses.

Analysis (percent by weight)
Calculated: Cl—30.7; Cl^-—0
Found: Cl—30.0; 30.1; Cl^-—0.1

EXAMPLE III

Preparation of 1-(2,6-dichlorobenzylideneamino)-2,3-ethyleneguanidine, hydroiodide and hydrochloride

a. *Hydroiodide salt* (C). 12.3 parts of 2,6 - dichlorobenzaldehyde and 16 parts of 2 - imidazolin - 2 - ylhydrazine hydroiodide were mixed in 100 parts by volume of absolute ethanol and refluxed at 80°C for 45 minutes. The mixture was cooled and filtered to give 24 parts of a light tan solid which decomposes at 275—278°C (uncorr.). The product was identified as the hydroiodide salt of 1 - (2,6-dichlorobenzylideneamino) - 2,3 - ethylene guanidine by elemental and infrared spectrum analyses.

Analysis (percent by weight)
Calculated: Cl—18.4; $I^\ominus$—33.0
Found: Cl—18.8; 19.0; $I^\ominus$—33.2, 33.3

b. *Hydrochloride salt* (D). To 10 parts of the HI salt from a. above in 100 parts by volume of water and 150 parts by volume of ethanol were added 50 parts by volume of 10% aqueous sodium hydroxide solution at 40°C. The mixture was cooled to 25°C and filtered. The solid was dissolved in 200 parts by volume of ethanol and treated with 13 parts of gaseous hydrogen chloride. The solvent was removed under water aspirator vacuum at 30° C. The residue was recrystallized from acetonitrile to give 5.6 parts of the hydrochloride salt melting at 232—233.5°C (uncorr.) identified by elemental and infrared spectrum analyses.

Analysis (percent by weight)
Calculated: $Cl^\ominus$ 12.1
Found: $Cl^\ominus$ 12.0

EXAMPLE IV

Preparation of 1-(alpha-methyl-2-chlorobenzylideneamino)guanidine hydrochloride (P)

8.8 parts of aminoguanidine carbonate, 20 parts by volume of concentrated hydrochloric acid and 150 parts by volume of n-butanol were refluxed to remove the formed water azeotropically. To the resultant solution, 10 parts of 2'-chloroacetophenone were added and refluxing continued for sixteen hours.

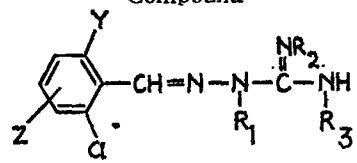
The solution was concentrated under water aspirator vacuum to give 18.7 parts of viscous orange liquid which by repeated crystallization gave 4.6 parts of a pink solid melting at 167—174°C identified by elemental analysis as 1 - (alpha - methyl - 2 - chlorobenzylideneamino)guanidine hydrochloride.

Analysis (percent by weight):
Calculated: N—22.7; Cl—28.8; Cl^-—14.4
Found: N—22.5; Cl—28.4; Cl^-—14.3

EXAMPLE V

Preparation of other (benzylideneamino)-guanidines and salts thereof

The following other benzylideneaminoguanidines and/or salts have been prepared from the appropriate aldehydes and guanidines according to the techniques demonstrated in Examples I—II. The table indicates the melting point of the product and comparison of the results of elemental analyses with the calculated values.

Compound 						Melting Point (°C)	Analysis (Percent by weight)	
							Calculated	Found
Y	Z	R_1	R_2	R_3	Salt			
(E) Cl	H	H	CH_3—	H	—	166.5—167.5	N — 22.9 Cl — 29.0	N — 22.3 Cl — 28.7
(F) Cl	H	H	CH_3—	H	HCl	207—208	$Cl^{\ominus}$ — 12.6	$Cl^{\ominus}$ — 12.4
(G) Cl	H	H	CH_2=$CHCH_2$—	H	HI	98—100	N — 14.0 Cl — 17.8 $I^{\ominus}$ — 31.8	N — 13.4 Cl — 17.8 $I^{\ominus}$ — 30.5
(H) Cl	J	H	CH_3—	CH_3—	HI	211.5—214.5	Cl — 18.3 N — 14.5 $I^{\ominus}$ — 32.8	Cl — 17.5 N — 14.2 $I^{\ominus}$ — 32.6
(I) Cl	H	H	CH_3—	i-C_3H_7—	HI	178+179	N — 13.5 Cl — 17.1 $I^{\ominus}$ — 30.6	N — 13.2 Cl — 17.4 $I^{\ominus}$ — 30.2
(J) Cl	H	H	CH_3—	i-C_3H_7	HCl	172—173.5	Cl — 32.9 $Cl^{\ominus}$ — 11.0	Cl — 32.5 $Cl^{\ominus}$ — 10.7
(K) Cl	H	CH_3	H	H	HCl	248—249 (Decomposition)	Cl — 37.8 $Cl^{\ominus}$ — 12.6	Cl — 36.5 $Cl^{\ominus}$ — 12.2
(L) F	H	H	H	H	HCl	208—209	Cl — 28.3 $Cl^{\ominus}$ — 14.1	Cl — 27.6 $Cl^{\ominus}$ — 13.7
(M) CH_3	H	H	H	H	HCl	176—177	N — 22.7 Cl — 28.4 $Cl^{\ominus}$ — 14.4	N — 22.4 Cl — 28.2 $Cl^{\ominus}$ — 14.7
(N) Cl	C—3l	H	H	H	—	210—211	N — 21.1 Cl — 40.2	N — 21.1 Cl — 40.2
(O) Cl	3—Cl	H	H	H	HCl	201.5—203	Cl — 47.0 $Cl^{\ominus}$ — 11.8	Cl — 46.5 $Cl^{\ominus}$ — 11.7

EXAMPLE VI

Effectiveness of the benzylideneamino-guanidines of Examples I to V as antidepressant agents

The antidepressant activity of a compound is shown by the absence of ptosis (defined as an eyelid closure of greater than one-half) after injection of reserpine into a treated animal. Following the reserpine challenge test of Chessin et al., J. Pharmac. Exp. Ther. *119*, 453 (1957), groups of five or ten mice are given graded doses of the chemical either orally or parenterally and then challenged with reserpine at 5.0 mg/kg i.p. One hundred and twenty minutes later the mice are assessed for their degree of ptosis. Ptosis of less than 50 percent is judged a positive response. Orally, the activity is assessed at the prohylactic time intervals of 1, 3, 5 and 16 hours. When administered intraperitoneally, the activity is determined at prophylactic intervals of 1, 2 and 4 hours. The effective dose required to prevent ptoses in 50 percent of the mice (ED_{50}) is calculated for each compound at its time of maximal effectiveness.

Following this procedure, the ED_{50} values for the compounds shown in Examples I to V are shown below along with the corresponding activity for known reference drugs.

Compound	Antidepressant activity I.p. $ED_{50} \pm$ S.E. (mg/kg.)
A	0.33 ± 0.08
B	0.12 ± 0.04
C	2.0 ± 0.5
D	3.3 ± 0.8
E	1.3 ± 0.4
F	2.2 ± 0.5
G	4.3 ± 1.3
H	2.4 ± 0.8
I	5.7 ± 2.0
J	4.2 ± 1.0
K	7.1 ± 2.3
L	2.2 ± 0.5
M	1.0 ± 0.2
N	1.6 ± 0.6
O	1.1 ± 0.6
P	7.2 ± 1.1
Q (1-(alpha-methyl-2-trifluoro-methylbenzyl-ideneamino)guanidine hydrochloride	7.6 ± 2.2
Tranylcypromine.SO_4	1.7 ± 0.4
Iproniazid.PO_4	42
Imipramine.HCl	24 ± 11

EXAMPLE VII

Effectiveness of benzylideneaminoguanidines as central nervous system (CNS) depressants

The presence of significant CNS depressant activity of drugs is demonstrated by the following two tests.

a. *Pernicious preening test*

Pernicious preening is elicited by painting the rear of the mouse with a pilocohesive dye. A violent, unremitting tearing of the stiff, cohering strands of hair constitutes the pernicious preening behaviour. The test procedure involves the intraperitoneal injections of the chemical to groups of 10 male mice (23—37 grams). Thirty minutes later, the pilocohesive dye was applied and the absence or presence of pernicious preening was noted for a 10-minute period. According to Wilfon and his co-workers, Fed. Proc. *19*, 21 (1960) both tranquilizers and potent analgesics effectively block this unusual behaviour in mice. Inhibitory effects have been elicited by other pharmacologic categories, such as sedatives, anti-convulsants, stimulants, amine oxidase inhibitors, anti-histamines, and miscellaneous compounds. With these agents, abolition of pernicious preening was generally accompanied by toxic manifestations.

b. *Phenylquinone writhing test*

The phenylquinone writhing test, as developed by Siegmund and associates (Proc. Soc. Exp. Biol. Med. *97*, 729 (1957), is most useful due to its simplicity, reproducibility, sensitivity and ability to assess a variety of psychotropic drugs. It involves the intraperitoneal injection of phenylquinone (2-phenyl-1,4-benzoquinone) to produce a writhing syndrome in mice. Ten male mice (23—27 grams) are used per dose. The writhing syndrome is characterized by the periodic twisting and turning of the lower half of the body, contractions of the muscles in the pelvic area, and extension of the hindlimbs with elevation of the base of the tail. The ability of the test drug in preventing this syndrome constitutes a positive pharmacological action.

Following these procedures, the effective dosages for the compounds were obtained. These dosages and those for reference drugs are shown in the following table.

TABLE II

Compound	Pernicious preening test (interperitoneal) ED_{50} (mg/kg)	Phenylquinone writhing test (intraperitoneal) ED_{50} (mg/kg)
A	0.79 ± 0.14	0.12
B	1.2 ± 0.2	not tested
D	3.0 ± 0.8	3.2
F	3	0.76 ± 0.26
J	8.0 ± 1.9	not tested
K	not tested	7.2 ± 1.8
L	4.6 ± 1.5	not tested
M	1.4 ± 0.3	0.21 ± 0.07
O	9	0.88 ± 0.21
Chlorpromazine. HCl	2.6	not tested
Amitriptyline.HCl	6.2 ± 1.6	not tested
d.Amphetamine.SO_4	2.7 ± 0.7	2.4
Tranylcypromine.SO_4	4.9	3.2
d-Propoxyphene.HCl	36	17.4 ± 4

CNS depressant effects mainly tranquilizing in nature were also noted when A, B, C and E were administered to cats and Rhesus monkeys in dosages as low as 0.30 mg/kg in some cases.

EXAMPLE VIII

Effectiveness of benzylideneaminoguanidines as cardiovascular agents

Procedure: classical anesthetized cat preparations were used to assess cardiovascular activities of the experimental drug when administered intravenously. Basal arterial blood pressure, heart-rate, electrocardiogram, respiratory rate and depth, intralumenal duodenal pressure, rectal temperature and nictitating membrane contraction were evaluated. In addition, the responses to standard doses of neurohumoral agents and nerve stimulation were measured.

Using these parameters, the following compounds were proven to possess unusually high cardiovascular activities as shown by a vasodepressor action on both the systolic and diastolic arterial blood pressures, a decrease in cardiac rate and an inhibition of the sympathetic nervous system, when given as a single intravenous injection as low as 0.01 mg/kg in some cases.

The most active compounds were:

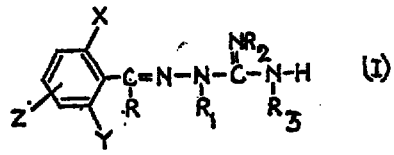
A, B, D, F, J, L, O,

R - 1 - (2 - chlorobenzylideneamino)-guanidine hydrochloride

S - 1 - (2,4 - dichloro - alpha - methylbenzylideneamino)guanidine hydrochloride

WHAT WE CLAIM IS:—

1. A method of treating a vendible mammal for the purpose of achieving a cardiovascular response or/and inducing a central nervous system depressant response or/and combating psychic depression in such a mammal which comprises administering to the mammal an effective dosage of a benzylideneaminoguanidine of formula:—



(I)

wherein X is halogen or trifluoromethyl, Y and Z are hydrogen, halogen, trifluoromethyl or C_1—C_4 alkyl; R, R_1, R_2 and R_3 are hydrogen, C_1—C_4 alkyl, C_2—C_4 alkenyl or C_2—C_4 alkynyl, or R_2 and R_3 may together form an alkylene- or alkenylene-bridge of 2 to 4 carbon atoms, or physiologically acceptable acid addition salts thereof, or a composition containing such a compound or salt.

2. A method as claimed in claim 1, in which is administered a benzylideneamino guanidine of formula I wherein X and Y are chlorine or bromine, Z is hydrogen, chlorine or bromine and R, R_1, R_2 and R_3 are all hydrogen, acid addition salts thereof or a composition containing such a compound or salt.

3. A method as claimed in claim 2 in which is administered the compound 1-(2,6-dichlorobenzylideneamino)guanidine or composition containing the same.

4. A method as claimed in 2 in which is administered the salt 1 - (2,6 - dichlorobenzylideneamino)guanidine hydrochloride or a composition containg the same.

5. A method as claimed in claim 1 substantially as herein before described with particular reference to Examples VI, VII, and VIII.

6. Vendible mammals when treated by a method as claimed in any one of the claims 1 to 5.

7. Compositions suitable for use in the method as claimed in claim 1 comprising a compound of formula I or acid addition salt thereof, together with a substantially sterile, physiologically acceptable carrier.

8. Compositions as claimed in claim 7 in unit dosage form.

9. Compositions as claimed in claim 7 or 8 substantially as hereinbefore described.

ROY C. ROGERS,
Chartered Patent Agent,
Shell Centre, London, S.E.1,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

CNS depressant effects mainly tranquilizing in nature were also noted when A, B, C and E were administered to cats and Rhesus monkeys in dosages as low as 0.30 mg/kg in some cases.

EXAMPLE VIII

Effectiveness of benzylideneaminoguanidines as cardiovascular agents

Procedure: classical anesthetized cat preparations were used to assess cardiovascular activities of the experimental drug when administered intravenously. Basal arterial blood pressure, heart-rate, electrocardiogram, respiratory rate and depth, intralumenal duodenal pressure, rectal temperature and nictitating membrane contraction were evaluated. In addition, the responses to standard doses of neurohumoral agents and nerve stimulation were measured.

Using these parameters, the following compounds were proven to possess unusually high cardiovascular activities as shown by a vasodepressor action on both the systolic and diastolic arterial blood pressures, a decrease in cardiac rate and an inhibition of the sympathetic nervous system, when given as a single intravenous injection as low as 0.01 mg/kg in some cases.

The most active compounds were:

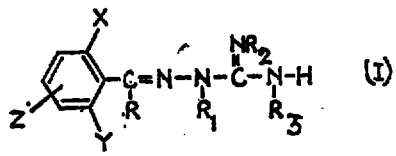
A, B, D, F, J, L, O,

R - 1 - (2 - chlorobenzylideneamino)-guanidine hydrochloride

S - 1 - (2,4 - dichloro - alpha - methylbenzylideneamino)guanidine hydrochloride

WHAT WE CLAIM IS:—

1. A method of treating a vendible mammal for the purpose of achieving a cardiovascular response or/and inducing a central nervous system depressant response or/and combating psychic depression in such a mammal which comprises administering to the mammal an effective dosage of a benzylideneaminoguanidine of formula:—



(I)

wherein X is halogen or trifluoromethyl, Y and Z are hydrogen, halogen, trifluoromethyl or C_1—C_4 alkyl; R, R_1, R_2 and R_3 are hydrogen, C_1—C_4 alkyl, C_2—C_4 alkenyl or C_2—C_4 alkynyl, or R_2 and R_3 may together form an alkylene- or alkenylene-bridge of 2 to 4 carbon atoms, or physiologically acceptable acid addition salts thereof, or a composition containing such a compound or salt.

2. A method as claimed in claim 1, in which is administered a benzylideneamino guanidine of formula I wherein X and Y are chlorine or bromine, Z is hydrogen, chlorine or bromine and R, R_1, R_2 and R_3 are all hydrogen, acid addition salts thereof or a composition containing such a compound or salt.

3. A method as claimed in claim 2 in which is administered the compound 1-(2,6-dichlorobenzylideneamino)guanidine or composition containing the same.

4. A method as claimed in 2 in which is administered the salt 1 - (2,6 - dichlorobenzylideneamino)guanidine hydrochloride or a composition containg the same.

5. A method as claimed in claim 1 substantially as herein before described with particular reference to Examples VI, VII, and VIII.

6. Vendible mammals when treated by a method as claimed in any one of the claims 1 to 5.

7. Compositions suitable for use in the method as claimed in claim 1 comprising a compound of formula I or acid addition salt thereof, together with a substantially sterile, physiologically acceptable carrier.

8. Compositions as claimed in claim 7 in unit dosage form.

9. Compositions as claimed in claim 7 or 8 substantially as hereinbefore described.

ROY C. ROGERS,
Chartered Patent Agent,
Shell Centre, London, S.E.1,
Agent for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1970.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

