

CONVENTION

AUSTRALIA

Patents Act

APPLICATION FOR A STANDARD PATENT

612137

✓ We E.R. Squibb and Sons Inc.

of Lawrenceville-Princeton Road,  
Princeton,  
New Jersey,  
UNITED STATES OF AMERICA.

hereby apply for the grant of a standard patent for an invention  
entitled:

METHOD FOR INHIBITING LOSS OF COGNITIVE FUNCTIONS  
EMPLOYING AN ACE INHIBITOR

which is described in the accompanying complete specification.

Details of basic application

Number of basic application: 043,127

Convention country in which  
basic application was filed: UNITED STATES OF AMERICA

Date of basic application : 27 April 1987

Address for Service:

PHILLIPS ORMONDE & FITZPATRICK  
Patent and Trade Mark Attorneys  
367 Collins Street  
Melbourne 3000 AUSTRALIA

Dated: 16 March 1988

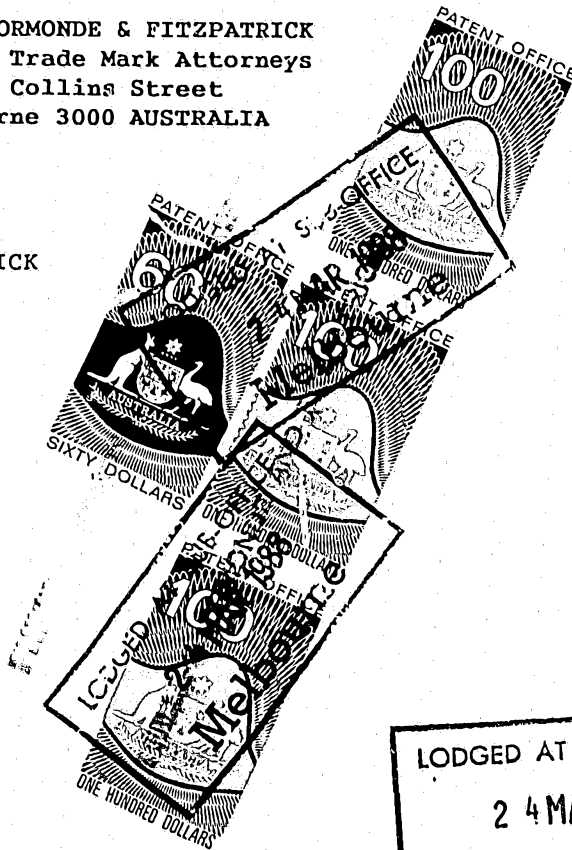
PHILLIPS ORMONDE & FITZPATRICK  
Attorneys for:  
E.R. Squibb and Sons Inc.

By:

Our Ref : 87862  
POF Code: 8448/43804

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MAIL OFFICER: V.D.

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LODGED AT SUB-OFFICE  
24 MAR 1988  
Melbourne

COMMONWEALTH OF AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS

- (a) Insert "Convention" if applicable
- (b) Insert FULL name(s) of applicant(s)
- (c) Insert "of addition" if applicable
- (d) Insert TITLE of invention
- (e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote)
- (f) Insert FULL name(s) AND address(es) of actual inventor(s)
- (g) Recite how applicant(s) derive(s) title (from actual inventor(s)) (See headnote)
- (h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application
- (i) Insert PLACE of signing
- (j) Insert DATE of signing
- (m) Signature(s) of declarant(s)

In support of the <sup>(a)</sup> convention application made by  
<sup>(b)</sup> E.R. SQUIBB & SONS, INC., a corporation duly organized and existing under the laws of the State of Delaware, United States of America, having its offices at Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, (hereinafter called "applicant" <sup>(c)</sup> for a patent <sup>(e)</sup> for an invention entitled <sup>(d)</sup>  
 METHOD FOR INHIBITING LOSS OF COGNITIVE FUNCTIONS EMPLOYING AN ACE INHIBITOR

I Nicholas P. Malatestinic of Princeton, New Jersey, United States of America,

do solemnly and sincerely declare as follows:

1. I am authorized to make this declaration on behalf of the applicant(s).
2. <sup>(f)</sup> ABRAHAM SUDILOVSKY, 712 Winchester Avenue, Lawrenceville, New Jersey, United States of America

is/are the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows:

- (a) The said E.R. SQUIBB & SONS, INC., is the assignee of the said ABRAHAM SUDILOVSKY by virtue of an assignment dated: June 24, 1987

3. The basic application(s) for patent or similar protection on which the application is based is/are identified by country, filing date, and basic applicant(s) as follows:

In: United States of America on: April 27, 1987

By: ABRAHAM SUDILOVSKY

4. The basic application(s) referred to in paragraph 3 hereof was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at <sup>(i)</sup> Princeton, New Jersey, U.S.A.,  
 Dated <sup>(j)</sup> March 17, 1988

<sup>(m)</sup> E.R. SQUIBB & SONS, INC.

By: Nicholas P. Malatestinic  
 Nicholas P. Malatestinic  
 Assistant Secretary

To: The Commissioner of Patents

Patent Declaration

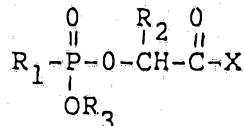
(SEAL)

Notes: No legalization or other witness required

(12) PATENT ABRIDGMENT (11) Document No. AU-B-13556/88  
 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 612137

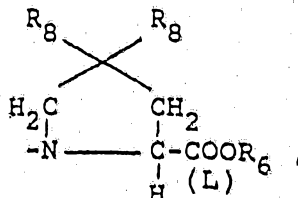
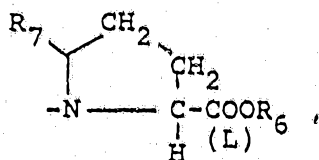
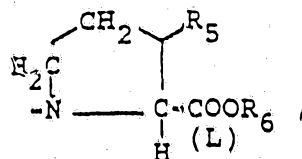
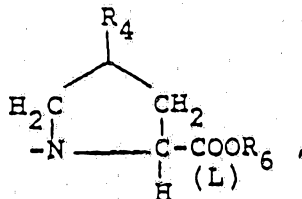
- (54) Title  
 METHOD FOR INHIBITING LOSS OF COGNITIVE FUNCTIONS EMPLOYING AN ACE INHIBITOR
- International Patent Classification(s)  
 (51)<sup>4</sup> A61K 031/675
- (21) Application No. : 13556/88 (22) Application Date : 24.03.88
- (30) Priority Data
- (31) Number (32) Date (33) Country  
 043127 27.04.87 US UNITED STATES OF AMERICA
- (43) Publication Date : 27.10.88
- (44) Publication Date of Accepted Application : 04.07.91
- (71) Applicant(s)  
 E.R. SQUIBB AND SONS, INC.
- (72) Inventor(s)  
 ABRAHAM SUDILOVSKY
- (74) Attorney or Agent  
 PHILLIPS ORMONDE & FITZPATRICK, 367 Collins Street, MELBOURNE VIC 3000
- (56) Prior Art Documents  
 AU 570202 13611/83 C07F 9/65 A61K 31/765 C07F 9/50  
 AU 51494/82 C07F 9/65 A61K 31/675 C07F 9/58  
 AU 82379/89 C07F 9/65 A61K 31/765 C07F 9/58
- (57) Claim

1. A method for inhibiting loss of cognitive function in a mammalian specie over a prolonged period of time, which comprises administering to a mammalian specie in need of such treatment an effective amount of an angiotensin converting enzyme inhibitor having the formula



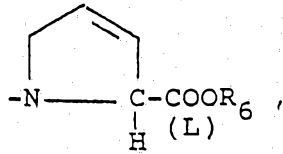
wherein:

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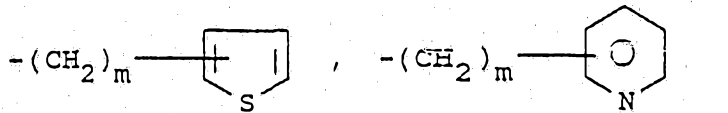
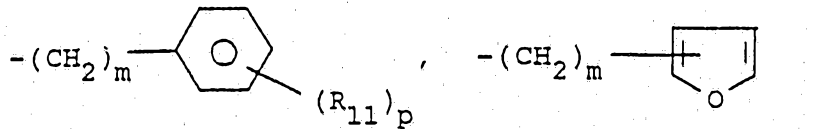
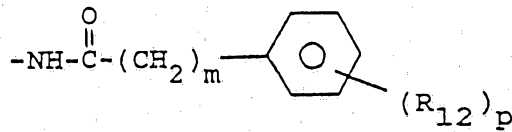


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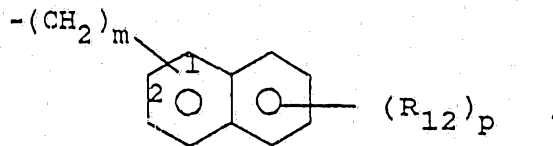
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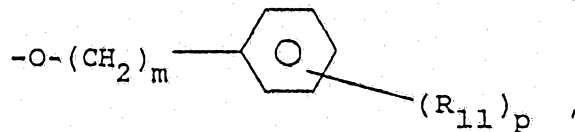
$R_4$  is hydrogen, lower alkyl, halogen, keto, hydroxy,  $-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{lower alkyl}$ , azido, amino,  $-\text{N} \begin{array}{l} \nearrow \text{R}_{17} \\ \searrow \text{R}_{18} \end{array}$ ,



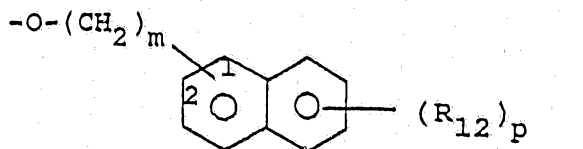
a 1- or 2-naphthyl of the formula



$-(\text{CH}_2)_m-\text{cycloalkyl}$ ,  $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N} \begin{array}{l} \nearrow \text{R}_{13} \\ \searrow \text{R}_{13} \end{array}$ ,  $-\text{O}-\text{lower alkyl}$ ,



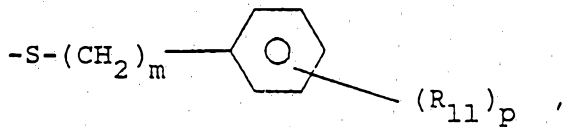
a 1- or 2-naphthyloxy of the formula



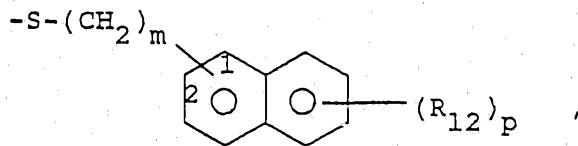
$-\text{S}-\text{lower alkyl}$ ,

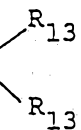
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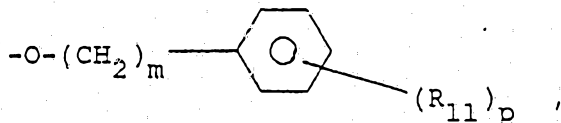
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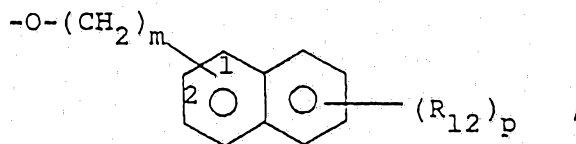
or a 1- or 2-naphthylthio of the formula



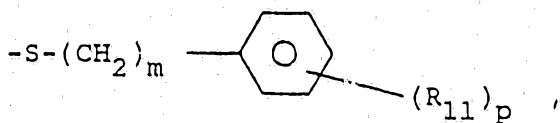
$\text{R}_5$  is keto, halogen,  $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}$  



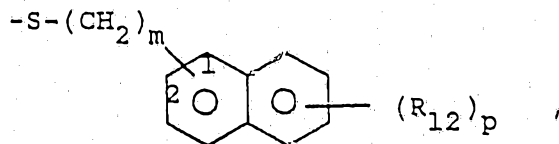
-O-lower alkyl, a 1- or 2-naphthyloxy of the formula



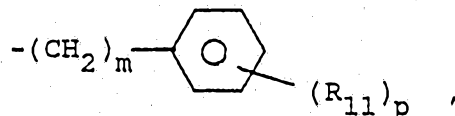
-S-lower alkyl,



or a 1- or 2-naphthylthio of the formula



$\text{R}_7$  is keto or



each  $\text{R}_8$  is the same or different and is halogen or  $-\text{Y}-\text{R}_{14}$ ;

$\text{R}_{11}$  is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, hydroxy, phenyl, phenoxy,

(11) AU-B-13556/88  
(10) 612137

-4-

phenylthio, or phenylmethyl;

$R_{12}$  is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl or hydroxy;

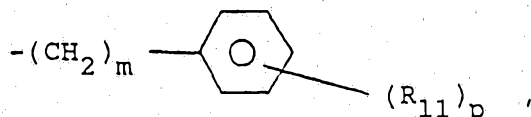
$m$  is zero, one, two or three;

$p$  is one, two or three provided that  $p$  is more than one only if  $R_{11}$  or  $R_{12}$  is hydrogen, methyl, methoxy, chloro or fluoro;

$R_{13}$  is hydrogen or lower alkyl of 1 to 4 carbons;

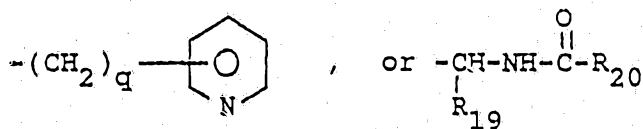
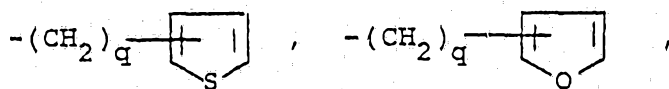
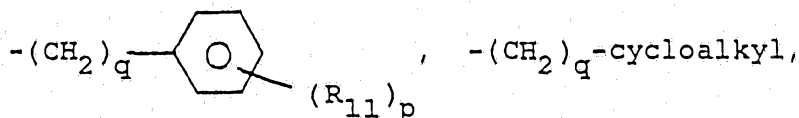
$Y$  is oxygen or sulfur.

$R_{14}$  is lower alkyl of 1 to 4 carbons,



or the  $R_{14}$  groups join to complete an unsubstituted 5- or 6-membered ring or said ring in which one or more of the carbons has a lower alkyl of 1 to 4 carbons or a di(lower alkyl of 1 to 4 carbons) substituent;

$R_1$  is alkyl of 1 to 10 carbons, aminoalkyl, haloalkyl,



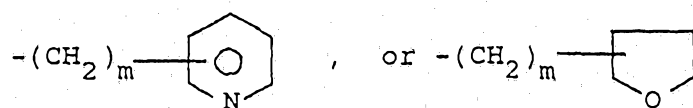
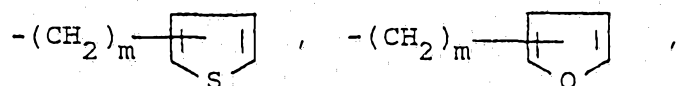
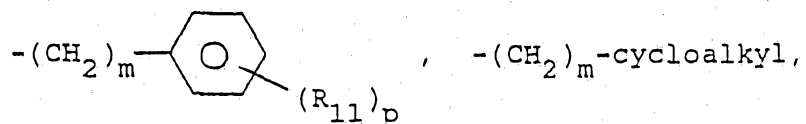
wherein  $q$  is zero or an integer from 1 to 7 and  $R_{11}$  and  $p$  are as defined above;

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(11) AU-B-13556/88  
 (10) 612137

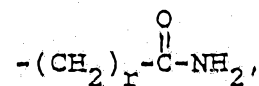
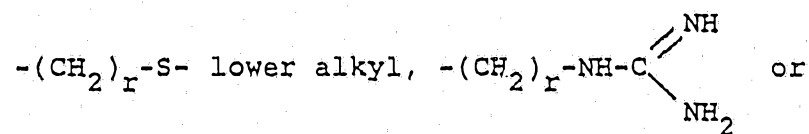
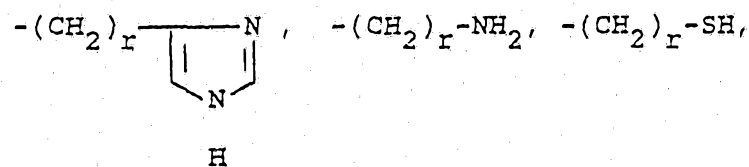
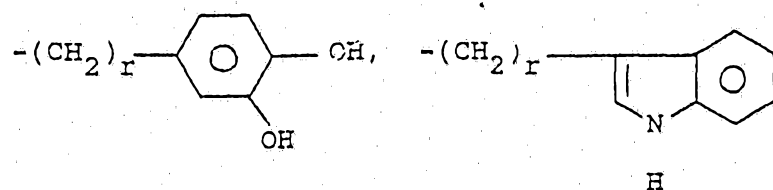
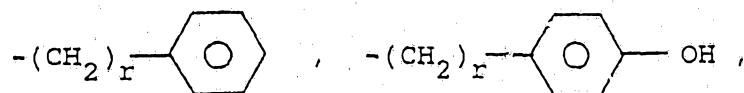
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$R_{19}$  and  $R_{20}$  are independently selected from hydrogen, lower alkyl, halo substituted lower alkyl,



wherein  $m$ ,  $R_{11}$ , and  $p$  are as defined above;

$R_2$  is hydrogen, lower alkyl, halo substituted lower alkyl,

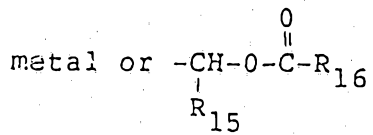


wherein  $r$  is an integer from 1 to 4;

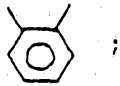
$R_3$  and  $R_6$  are independently selected from hydrogen, lower alkyl, benzyl, benzhydryl, alkali

(11) AU-B-13556/88  
(10) 612137

-6-



wherein  $\text{R}_{15}$  is hydrogen, lower alkyl, cycloalkyl or phenyl, and  $\text{R}_{16}$  is hydrogen, lower alkyl, lower alkoxy, phenyl, or  $\text{R}_{15}$  and  $\text{R}_{16}$  taken together are  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ ,  $-\text{CH}=\text{CH}-$ , or



$\text{R}_{17}$  is lower alkyl, benzyl, or phenethyl; and  
 $\text{R}_{18}$  is hydrogen, lower alkyl, benzyl or phenethyl or a pharmaceutically acceptable salt thereof to inhibit loss of cognitive function during such period of treatment.





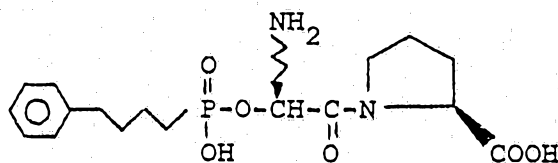
METHOD FOR INHIBITING LOSS  
OF COGNITIVE FUNCTIONS  
EMPLOYING AN ACE INHIBITOR

5           The present invention relates to a method for  
inhibiting loss of cognitive functions, including  
memory, which are associated with different types  
of dementias in mammalian species by  
administering an ACE inhibitor, which is a  
10   phosphonate substituted amino or imino acid or  
salt, such as SQ 29,852 over a prolonged period of  
time.

15           In accordance with the present invention, a  
method is provided for inhibiting loss of  
cognitive functions such as memory, attention span,  
concentration and ability to learn or for  
treating or delaying progression of Alzheimer's  
disease or other types of dementias, in mammalian  
20   species over a prolonged period wherein a  
therapeutically effective amount of an angiotensin  
converting enzyme inhibitor which is a phosphonate  
substituted amino or imino acid or salt thereof,  
which is systemically, such as orally or  
25   parenterally, administered over a prolonged period,  
to inhibit loss of cognitive function during such  
period.

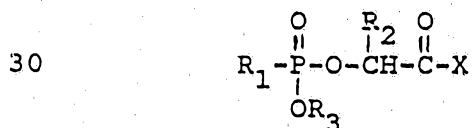
The method of the invention is useful in treating or delaying progression of primary degenerative dementias arising in the senium and presenium such as Alzheimer's disease, Pick's disease and Binswanger's disease, and vascular dementias such as arterialsclerotic dementias including multiple infarct dementia and Binswanger's disease.

The angiotensin converting enzyme inhibitor which may be employed herein includes any of the phosphonate substituted amino or imino acids or salts disclosed in U. S. Patent No. 4,452,790 with (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyl]oxy]-1-oxohexyl]-L-proline (SQ 29,852) being preferred.

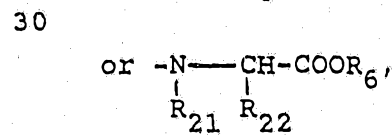
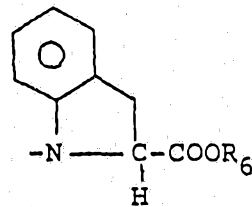
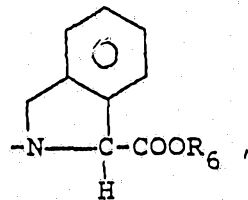
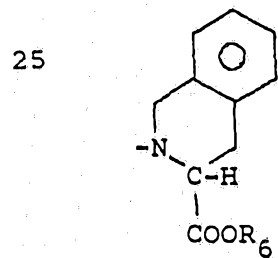
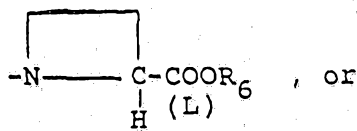
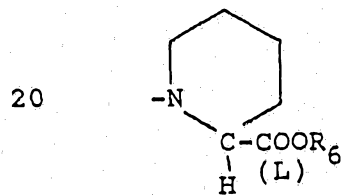
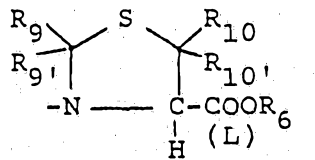
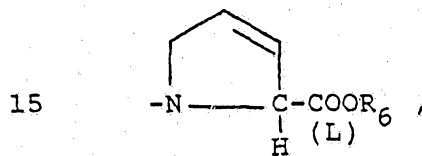
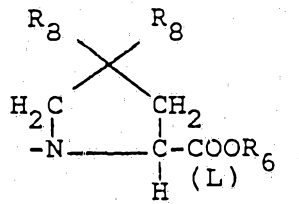
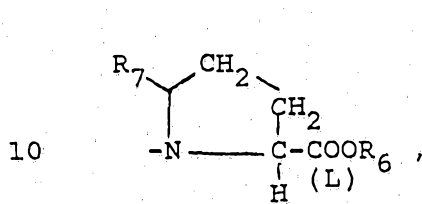
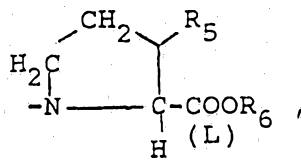
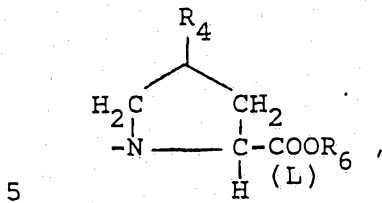


SQ 29,582

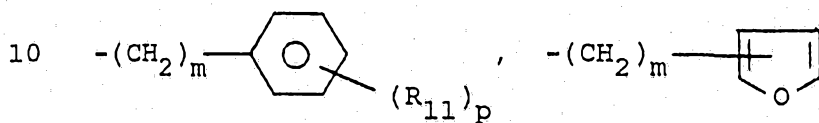
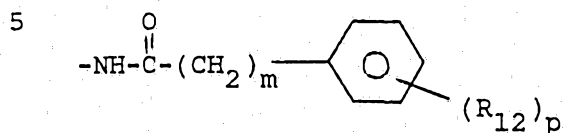
U. S. Patent No. 4,452,790 to Karanewsky et al is directed to angiotensin converting enzyme inhibitors which are phosphonate substituted amino or imino acids and salts thereof having the formula



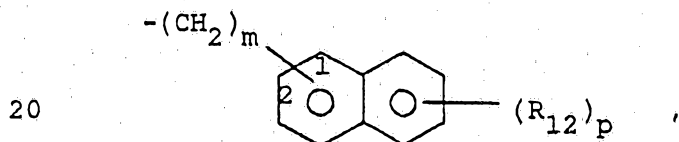
wherein X is an imino or amino acid of the formula



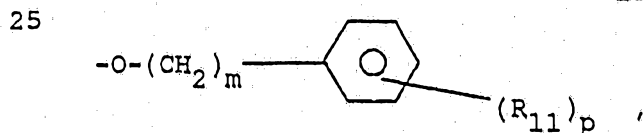
$R_4$  is hydrogen, lower alkyl, halogen, keto, hydroxy,  $-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-\text{lower alkyl}$ , azido, amino,  $-\text{N} \begin{matrix} \nearrow R_{17} \\ \searrow R_{18} \end{matrix}$ ,



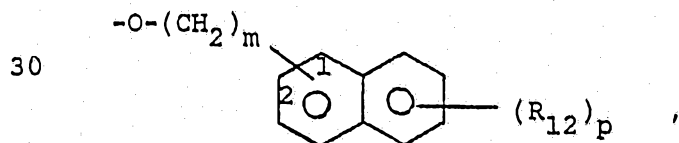
a 1- or 2-naphthyl of the formula



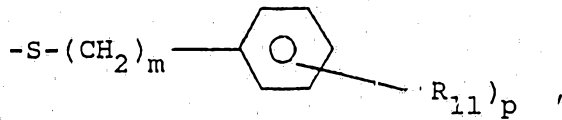
$-(\text{CH}_2)_m-\text{cycloalkyl}$ ,  $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N} \begin{matrix} \nearrow R_{13} \\ \searrow R_{13} \end{matrix}$ ,  $-\text{O}-\text{lower alkyl}$ ,



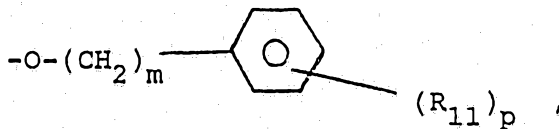
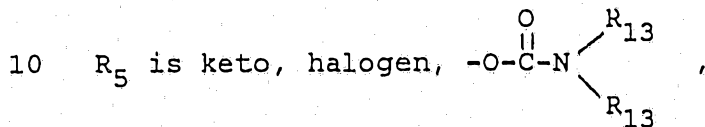
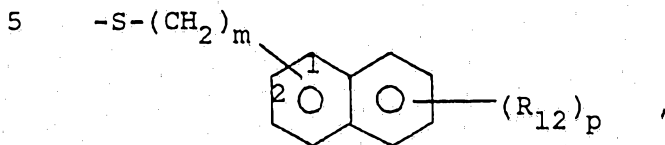
a 1- or 2-naphthyloxy of the formula



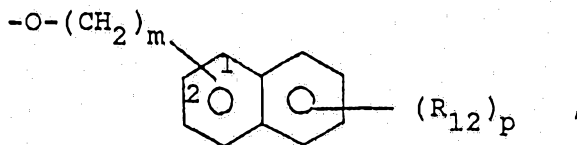
$-\text{S}-\text{lower alkyl}$ ,



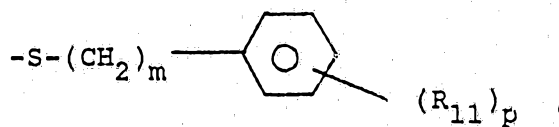
or a 1- or 2-naphthylthio of the formula



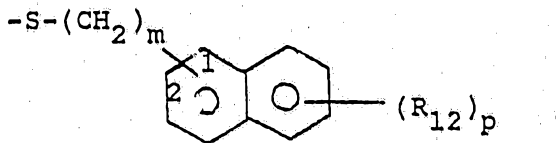
15 -O-lower alkyl, a 1- or 2-naphthyloxy of the formula



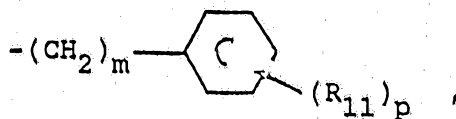
20 -S-lower alkyl,



25 or a 1- or 2-naphthylthio of the formula



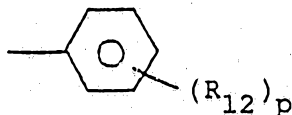
30 R<sub>7</sub> is keto or



Each  $R_8$  is independently halogen or  $-Y-R_{14}$ .

$R_9$ ,  $R_9'$ ,  $R_{12}$  and  $R_{10}'$  are independently selected from hydrogen and lower alkyl or  $R_9'$ ,  $R_{10}$  and  $R_{10}'$  are hydrogen and  $R_9$  is

5



$R_{11}$  is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, hydroxy, phenyl, phenoxy, phenylthio, or phenylmethyl.

$R_{12}$  is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl or hydroxy.

$m$  is zero, one, two or three.

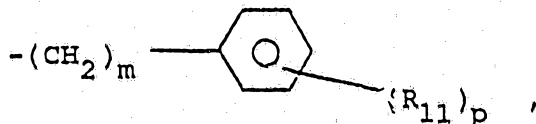
$p$  is one, two or three provided that  $p$  is more than one only if  $R_{11}$  or  $R_{12}$  is hydrogen, methyl, methoxy, chloro or fluoro.

$R_{13}$  is hydrogen or lower alkyl of 1 to 4 carbons.

$Y$  is oxygen or sulfur.

$R_{14}$  is lower alkyl of 1 to 4 carbons,

25

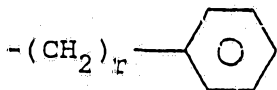


or the  $R_{14}$  groups join to complete an unsubstituted 5- or 6-membered ring or said ring in which one or more of the carbons has a lower alkyl of 1 to 4 carbons or a di(lower alkyl of 1 to 4 carbons) substituent.

30

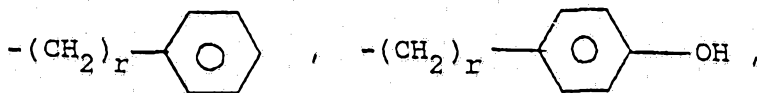
R<sub>21</sub> is hydrogen, lower alkyl, cycloalkyl, phenyl or

5

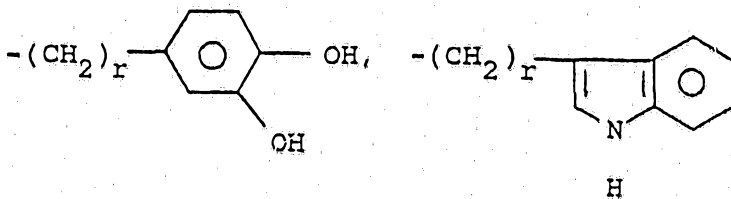


R<sub>22</sub> is hydrogen, lower alkyl,

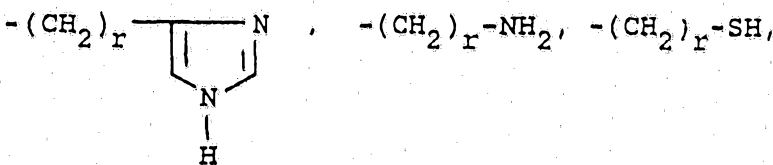
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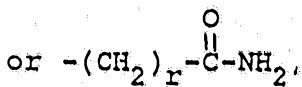
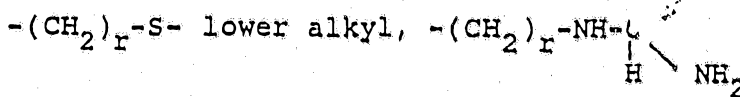
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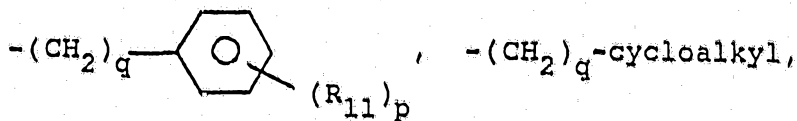
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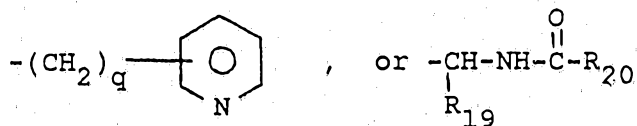
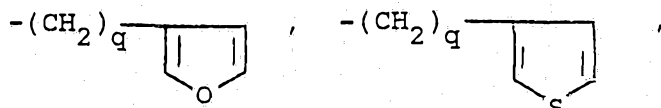
r is an integer from 1 to 4.

R<sub>1</sub> is alkyl of 1 to 10 carbons, aminoalkyl, haloalkyl,

30

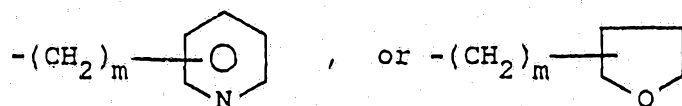
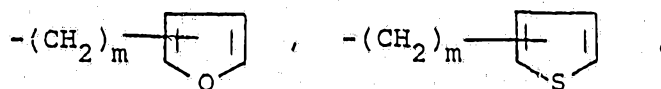
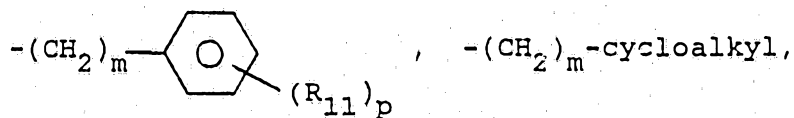






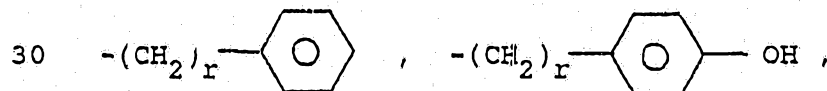
10 wherein q is zero or an integer from 1 to 7 and  $\text{R}_{12}$  and p are as defined above.

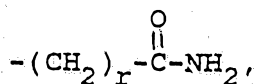
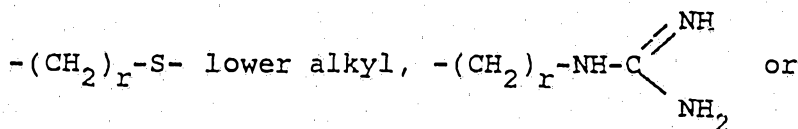
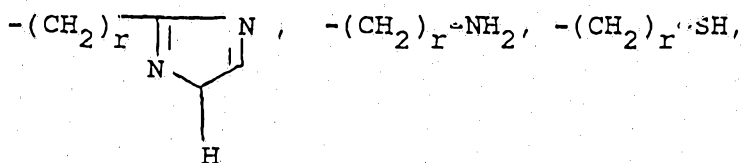
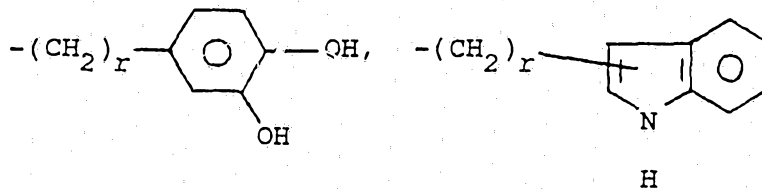
$\text{R}_{19}$  and  $\text{R}_{20}$  are independently selected from hydrogen, lower alkyl, halo substituted lower alkyl,



25 wherein m,  $\text{R}_{11}$ , and p are as defined above.

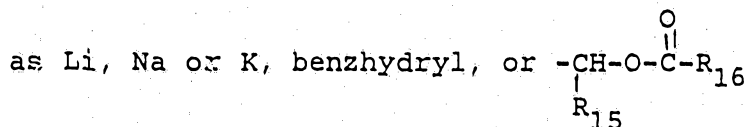
$\text{R}_2$  is hydrogen, lower alkyl, halo substituted lower alkyl,





wherein  $r$  is as defined above.

20  $R_3$  and  $R_6$  are independently selected from hydrogen, lower alkyl, benzyl, alkali metal such



25 wherein  $R_{15}$  is hydrogen, lower alkyl, cycloalkyl or phenyl, and  $R_{16}$  is hydrogen, lower alkyl, lower alkoxy, phenyl, or  $R_{15}$  and  $R_{16}$  taken together are  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ ,  $-\text{CH}=\text{CH}-$ , or



30  $R_{17}$  is lower alkyl, benzyl, or phenethyl.

$R_{18}$  is hydrogen, lower alkyl, benzyl or phenethyl.

The disclosure of the above-mentioned patent is incorporated herein by reference.

In carrying out the method of the present invention, the angiotensin converting enzyme inhibitor as defined above may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc. and as such may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

With regard to such systemic formulations, single or divided doses of from about 0.1 to about 500 mg, preferably from about 1 to 100 mg/one to four times daily, may be administered in systemic dosage forms as described above for a prolonged period, that is, for as long as inhibition of loss of cognitive function is to continue. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one week is required to achieve minimal benefit.

The accompanying Figure is a graph of mean percent of shuttle avoidance responding in male rats one hour after intraperitoneal administration of SQ 29,852 at 1 mg/kg, 10 mg/kg and 30 mg/kg and saline versus days of treatment.

The following Examples represent preferred embodiments of the present invention.

Example 1

5 An SQ 29,852 formulation suitable for oral administration in inhibiting loss of cognitive functions is set out below.

10 1000 tablets each containing 100 mg of (S)-1-[6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy-1-oxohexyl]-L-proline were produced from the following ingredients.

15	(S)-1-[6-Amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy-1-oxohexyl]-L-proline (SQ 29,852)	100 g
	Corn starch	50 g
	Gelatin	7.5 g
	Avicel (microcrystalline cellulose)	25 g
	Magnesium stearate	2.5 g

20 The SQ29,852 and corn starch are admixed with an aqueous solution of the gelatin. The mixture is dried and ground to a fine powder. The Avicel and then the magnesium stearate are admixed with the granulation. This is then compressed in a tablet to form 1000 tablets each containing 100 mg of active ingredient which is used for inhibiting loss of cognitive functions.

30 Example 2

By substituting 100 g of the ACE inhibitor ( $\pm$ )-1-[2-[[hydroxy(4-phenylbutyl)phosphinyl]oxy]-1-oxopropyl]-L-proline, dilithium salt for the SQ

29,852 in Example 1, 1000 tablets each containing 100 mg of such ACE inhibitor are produced which is useful in inhibiting loss of cognitive functions.

5

Example 3

1000 tablets each containing 200 mg of captopril are produced from the following ingredients:

10	1-[(S)-2-[[[(±)-1-Benzoylamino)-3-phenylpropyl]phosphinyl]oxy]-1-oxopropyl]-L-proline, dilithium salt (ACE inhibitor)	200 g
	Lactose	100 g
15	Avicel	150 g
	Corn starch	50 g
	Magnesium stearate	5 g

The ACE inhibitor, lactose and Avicel are admixed, then blended with the corn starch. Magnesium stearate is added. The dry mixture is compressed in a tablet press to form 1000 505 mg tablets each containing 200 mg of active ingredient. The tablets are coated with a solution of Methocel E 15 (methyl cellulose) including as a color a lake containing yellow #6. The resulting tablets are useful in inhibiting loss of cognitive functions.

30

Example 4

Two piece #1 gelatin capsules each containing 250 mg of ACE inhibitor are filled with a mixture of the following ingredients:

	(±)-1-[2-[[[(2,2-Dimethyl-1-oxopropoxy) methoxy](4-phenylbutyl)phosphinyl]-oxy]-1-oxopropyl]-L-proline	250 mg
	Magnesium stearate	7 mg
5	USP lactose	193 mg.

The resulting capsules are useful in inhibiting loss of cognitive functions.

10 Example 5

An injectable solution for use in inhibiting loss of cognitive functions is produced as follows:

	SQ 29,852	500 mg
15	Methyl paraben	5 mg
	Propyl paraben	1 mg
	Sodium chloride	25 g
	Water for injection qs.	5 l.

20 The SQ 29,852 preservatives and sodium chloride are dissolved in 3 liters of water for injection and then the volume is brought up to 5 liters. The solution is filtered through a sterile filter and aseptically filled into

25 presterilized vials which are then closed with presterilized rubber closures. Each vial contains 5 ml of solution in a concentration of 100 mg of active ingredient per ml of solution for injection.

30 Example 6

Tablets for use in inhibiting loss of cognitive functions are prepared as described in Example 1 except that (±)-1-[2-[[hydroxy(4-

phenylbutyl)phosphinyl]oxy]-1-oxopropyl]-L-proline, disodium salt is used in place of SQ 29,852.

5

Example 7

The following experiments were carried out to demonstrate the effectiveness of the ACE inhibitor SQ 29,852 to improve cognition and cognitive impairment.

10

Techniques used:

a) Ability to improve basic performance and to antagonize a scopolamine impairment in a mouse habituation test.

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b) Ability to improve basic performance and to antagonize a scopolamine impairment in a food reinforced alternation task in the rat using an elevated T maze.

20

c) Ability to improve discriminative and reverse learning in the mazzoni using the Wisconsin General Test Apparatus.

a) ABILITY TO IMPROVE BASIC PERFORMANCE  
AND TO ANTAGONIZE A SCOPOLAMINE  
IMPAIRMENT IN A MOUSE HABITUATION TEST

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Methods

The studies used a black:white test box procedure as described below. Male albino (BKW) mice were used, initially weighing 25-30 g. In their home cage, mice were housed in groups of 10 and given free access to food and water. The mice

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were kept on a 12 hour light and 12 hour dark cycle with lights off at 8:00 a.m. and on at 8:00 p.m.

The test box consisted of an open-topped  
5 box (45 x 27 x 27 cm), 40% of the area painted  
black and illuminated with a dim red light  
(1 x 60 W), the other painted white and brightly  
illuminated with white light (1 x 60W) located 17  
10 cm above the box. Access between the two areas  
was enabled by means of a 7.5 x 7.5 cm opening  
located at floor level in the center of the  
partition (which also served to prevent diffusion  
of light between the two compartments of the test  
box). The floor area was lined into 9 cm squares.

15 The habituation test was carried out daily  
by placing mice in the center of the white section  
of the test box (mice taken from dark home  
environment in a dark container, to the  
experimental room maintained in low red lighting,  
20 and would normally be averse to the bright white  
conditions). Testing was carried out between 8:30  
and 12:30 p.m. The test period was 5 minutes per  
day. Behavior was assessed via remote video  
recording, and the following measures taken:

- 25 1. Latency to move from the white to the  
black section (sec).
2. Numbers of exploratory rears in the  
white and black sections during the 5 minute test.
3. Numbers of line crossings (exploratory  
30 locomotion) in the white and black sections during  
the 5 minute test.
4. Time spent in the black section of the  
box during the 5 minute test.



5. Numbers of transitions between the black and white sections of the test box during the 5 minute test (since this parameter was not changed in any situation in the present studies, data for transitions is not given or commented on further).

Generally, as animals habituated to the test system, they would move into the black section of the box where behavioral exploration was exhibited as exploratory rears and line crossings.

Scopolamine was used at a dose of 0.25 mg/kg i.p. to disrupt habituation patterns. This could be achieved by a single acute challenge with scopolamine which disrupted the learning patterns on the day of treatment, with subsequent recovery, or by continued daily treatment with scopolamine 1 hour before test. The dose of scopolamine was carefully selected as one which did not cause autonomic disturbance (0.25 mg/kg i.p. methyl scopolamine failed to influence behavior). Under the influence of 0.25 mg/kg i.p. scopolamine mice would go to the door in the partition, investigate the opening and pass the head or body through, but without association of the dark environment with escape from the brightly-lit aversive environment.

#### Results

The normal learning curve for mice in the habituation test was 5-6 days as evidenced by reduced rearings and line crossings in the white compartment, increased in the black, reduced latency to move to the black and increased % of time spent in the black. Acutely administered

scopolamine causes impairment in control animals. Example data is given here for rears: mice had 'learned' to avoid the white aversive environment and by day 6 were carrying out most of their behavior in the black - this was prevented by scopolamine which caused an impairment characterized by increased activity in the white, decreased in the black. This impairment caused by scopolamine can be prevented by arecoline. The selection of dose and route for arecoline are critical to avoid unwanted autonomic disturbance. The arecoline is given continuously by intraperitoneal infusion from Alzet osmotic minipumps at a dose of 50 mg/kg/day. It is interesting that while the continuous treatment with this dose of arecoline inhibited the scopolamine impairment of habituation, the time course of the basic 'learning' or habituation was unaffected by the presence of arecoline. This contrasts with findings for the ACE inhibitor SQ 29,582.

Using the same procedure as described above, control mice and mice treated with SQ 29,852 were subject to the habituation procedure and challenged with scopolamine on days 6 and 10. Firstly, it was seen that the basal learning procedure was speeded by treatment with SQ 29,852 at doses as low as 0.0005mg/kg b.d. Secondly, the treatments with SQ 29,852 were shown to completely antagonize the impairments caused by scopolamine. SQ 29,852 doses were lowered on days 7-10 to 0.00005mg/kg i.p. b.d.: this is because an

anxiolytic potential was becoming apparent using the twice daily, continuous treatment regime.

Assessments of the potential of hydergine to improve cognitive function in the mouse habituation test utilized the same test protocol as described so far for arecoline and the ACE inhibitor. Hydergine was obtained as a proprietary product and the human dose titrated to mouse for single daily challenge, orally, 60 minutes before test. Treatment with hydergine was clearly shown to enhance 'learning' in the mouse habituation test. Rearing in the white section rapidly diminished as this behavior correspondingly increased in the black, and crossings in the white decreased significantly below control values by day 2 of testing, again with corresponding increases in the black and increased % of time in the black was significant on day 2 as were the reductions in latencies to move from the white to the black section on days 2, 3 and 4 of testing.

The treatment with hydergine was not associated with any anxiolytic potential and the dose regime was maintained constant at 0.1mg/kg p.o. daily. After 4 days some motor impairment and sedation developed in a small proportion of animals; this particularly influenced the latency to move from the white environment and data for such animals had to be excluded from analyses.

A very important observation was that while hydergine (like the ACE inhibitor but in contrast to arecoline) could enhance basal learning, it was not able to antagonize the

influence of scopolamine to impair performance whether measured as changed rearing, changed line crossings or changed % time in black, and latency to move out of the white, aversive environment.

5 This failure to antagonize, indeed, to any way influence the impairment caused by scopolamine contrasts with the marked antagonistic effects of arecoline and the ACE inhibitor SQ 29,852.

10 In a further series of experiments mice were allowed to habituate for 10 days and then were challenged daily with scopolamine, 0.25mg/kg. The habituation was impaired throughout the time of scopolamine challenge. If, after impairment with scopolamine was established, 15 mice were given arecoline (50mg/kg/day by intraperitoneal infusion from Alzet osmotic minipumps), or SQ 29,852 (0.5µg/kg i.p. b.d.) daily with the scopolamine treatment, then the scopolamine impairment was completely prevented.

20

b) ABILITY TO IMPROVE BASIC PERFORMANCE  
AND TO ANTAGONIZE A SCOPOLAMINE IMPAIRMENT  
IN A FOOD REINFORCED ALTERNATION TASK  
IN THE RAT USING AN ELEVATED T MAZE

25 Methods

The studies used male Lister hooded rats initially weighing 300-350 g. Rats were normally housed in groups of 5 in a room maintained at 23±1°C, on a 12 hour light:dark cycle with lights 30 or. at 8:00 a.m. and off at 8:00 p.m. The test room was maintained under identical conditions, and was sound-proofed.

The apparatus and technique used was essentially that of Salamone et al. (Behav. Brain Res. 13, 63-70, 1984) using a T maze constructed of wood and elevated 30cm from the ground with side arms measuring 60cm x 10cm and start arm measuring 80cm x 10cm. A small metal cup was placed towards the end of each side arm; these held the reward pellets as appropriate. A line was marked 20cm from the start of each side arm.

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Animals were food deprived excepting for 1 hour post-test, for 2 days prior to testing and throughout the 9 day test period, but water was available 'ad libitum'. Animals maintained 85% of normal body weight throughout testing. A few banana-flavored reward pellets were mixed with the food to habituate the rats to the taste of the pellets. Our rats showed clear preference for banana-flavored pellets as compared with their normal laboratory chow.

20  
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30  
Rats were allowed 10 minutes habituation to the T maze on day 1 (both arms baited with banana-flavored reward pellets, 4 x 45mg pellets in each cup) and were subject to a pretraining period of reinforced alternation on days 2-5 of test, with training on days 6-9. All training consisted of paired trials (each pair constituting a 'run'), the first being 'forced' in that one arm was blocked with a wooden barrier while the other was baited (for a positive response on the forced trial the rat must take the food). The second was a 'choice' trial in which reward pellets were placed in the arm opposite to that reinforced on the first trial of the pair. A correct choice was

when the rat entered the arm containing the food on the choice trial, crossing the point marked 20cm from the start of the side arm.

In addition, to correct/incorrect choice, latency to reward was recorded for both forced and choice trials. 4 runs/day were carried out on pretraining days (inter-trial interval 9 sec, inter-run interval 30 sec), 6 runs/day during training (inter-trial interval 30 sec, inter-run interval 60 sec).

6 groups of animals (n = 7 per group) were used as follows:

1. Control group - saline 1 ml/kg i.p. b.d.
2. Scopolamine group - scopolamine 0.25 mg/kg i.p. b.d.
3. Arecoline group - arecoline 30 mg/kg/day by intraperitoneal infusion from an Alzet osmotic minipump (carefully selected as maximum dose tolerated).
4. SQ 29,852 group - SQ 29,852 1.0 mg/kg i.p. b.d.
5. Scopolamine + arecoline group.
6. Scopolamine + SQ 29,852 group.

## 25 Results

Scopolamine was shown to impair performance in the food reinforced alternation task using an elevated T maze. This impairment was seen as delayed forced latencies, delayed choice latencies and reduced % correct responses. This impairment was evident both during the pretraining days (2-5) and training days (6-9). At no time was arecoline or SQ 29,852 treatment shown to enhance basal

performance in the T maze task. However, arecoline and SQ 29,852 were shown to antagonize the effects of scopolamine on days 2-5. The antagonism afforded by SQ 29,852 was less marked during days 6-9: that afforded by arecoline was more consistent.

Using the same strain of rats and the same doses of SQ 29,852 (1.0 mg/kg i.p.) assessment of anxiolytic action was carried out using an upscaled version of the black:white test box suitable for rat testing. Both compounds showed an anxiolytic profile and it is considered that this activity may have seriously interfered with responding on the T maze. Thus, while animals were challenged by a novel task on the first few days of training, this novelty was not apparent as learning progressed, and rats were noted to be 'nonchalant' to the test situation. However, the data obtained with SQ 29,852 shows that a scopolamine impairment in a food reinforced alternation task in the rat using an elevated T maze can be antagonized by SQ 29,852.

c) ABILITY TO IMPROVE DISCRIMINATIVE AND REVERSE LEARNING IN THE MARMOSET USING THE WISCONSIN GENERAL TEST APPARATUS

Methods

The studies used male and female marmosets aged 15-18 months (300-340 g) which had been bred at University of Bradford, England, or bought as weanlings, and had been regularly handled. All experiments were carried out by one experimenter since, while it is possible for two experimenters to work together for

double-blind dosing of animals, the relationship built between the experiment/marmoset makes it impossible to design the experiments for double-blind use of marmosets. Marmosets used in the present studies were coded 081, J59 and 025.

Shaping discrimination learning and training

The procedures followed for shaping and reverse learning were standard and would be applied to any marmoset when using the WGTA.

10 i) Shaping and discrimination learning

The animal is first presented with open, baited food wells and the stimuli are gradually moved over the wells on successive trials until they are completely covered. When the animal will respond to both stimuli (both are rewarded at this stage) and at both food wells, shaping is complete and discrimination learning, where the reward is always put under one and the same stimulus, can begin. For stimuli one can use small toy figures or 'junk' objects about 5 cm in the largest dimension (junk objects are pen-tops, bottle tops, etc.). Animals 081, J59 and 025 were generally nervous of the small toy figures presented to them (e.g. farm animals, cowboys and indians) and so the discriminative learning used a rubber bung (positive) and syringe needle cap (negative). Animals may meet different objects during its experimental career. However, a marmoset within our limited experience (and in the wider experience of others, Baker and Ridley) never forgets the first shaping and discriminative learning trials, and the first objects used, the rubber bung and needle cap for the marmosets used



in the present studies, can be used to help animals when they are later given very complex tasks, and lose confidence.

5 In order to ensure that the animal learns the discrimination on the basis of the stimulus association rather than because the reward is always on, say, the left, the left/right position of the stimuli is varied according to a "pseudo-random" schedule. In one such schedule, 10 described by Gellerman (1933; J. Genet. Psychol. 42, 206-208), the reward appears unpredictably on the left or right, though in each block of 10 trials it appears 5 times on each side. This schedule was used in the present experiment.

15 Marmosets are easily distracted by visual as well as auditory interference. The test cage therefore has opaque walls on all sides and a smoked Perspex panel facing the shutter. Sawdust should not be used on the floor of the cage otherwise the animal 20 may spend a considerable time sifting through it.

It was not necessary to maintain food deprivation during these training sessions. The procedure was to feed the animal its normal daily diet after the day's training session (sessions generally restricted to 8:30-11:30 a.m. and 12:00-3:00 p.m., feeding at 4:00 p.m.).

ii) Training on the Gellerman Schedule

Animals are tested usually on 4 or 5 consecutive days to gain 90/100 correct choices. They are then allowed a 1 week break before confirming a criterion of 18/20, and the 9/10. It is important that the experimenter knows the animals, and never makes them 'work' until bored or fail to concentrate. For 081, J59 and 025 the critical challenge was either 40 trials/days or 15 minutes of trials.

To prevent 'boredom' weekend breaks appeared very important and therefore generally experiments are carried out over a maximum 5 days. However, since there appeared to be a delay

in onset of the action of SQ 29,852, the test time was extended to 8 days.

SQ 29,852 was prepared in normal saline and was given twice daily (close to 7:00 a.m. and 7:00 p.m. for animals tested 12:00-3:00 p.m., 8:00 a.m. and 8:00 pm. for animals tested 8:30-11:30 a.m., but always 60 minutes before test).

iii) Reverse training

Objects used for the reverse training remained constant at yellow flask top/red pen top. Objects were presented until six correct consecutive trials were recorded, and the number of attempts before the 6 correct trials noted. Positive objects (with food reward) were alternated. For example, day 1 red pen top was first positive object, after 6 consecutive selections of the red pen top, the yellow flask top became the positive object, and was presented until it was selected on 6 consecutive attempts. The last positive object of each day (yellow flask top in this case) would be the first positive object of the following day.

On each day of testing, marmosets were subjected to a reverse learning task immediately after the discriminative task. For example, the objects used were yellow flask top/red pen top. If the yellow flask top was the last positive object of the previous day, it would be the first positive object of the test day and a marmoset would be expected to discriminate this from the red pen top by selecting the yellow flask top on 6 consecutive attempts. The number of attempts before this criterion was reached was determined

on each day and the mean numbers for days 1-4 (vehicle), 5-8 (vehicle or SQ 29,852) and 9-12 (vehicle or SQ 29,852) are given (termed D for first discriminative task). Marmosets were then  
5 subject to a reverse learning task, i.e., on completion of the 6 correct selections of the yellow flask top, the marmoset would be required to reverse to selecting the red pen top on 6 consecutive occasions (this now being the  
10 positive, food rewarded object). The mean number of attempts made in this reverse situation was determined for days 1-4, 5-8 and 9-12 as above, and indicated R.

#### 15 Results

During the first 4 days of the trials the three marmosets found reverse training more difficult than the initial discriminative learning (approximately 9 trials to criterion on  
20 discriminative learning, D, and 12 to criterion on reverse learning, R). Animal 081 was maintained on vehicle and he maintained responding on discriminative learning, continuing to find reverse learning difficult (on days 9-12 10 trials  
25 to criterion on discriminative learning but 18 on reverse learning).

The performance of animal J59 improved gradually over 8 days of treatment with SQ 29,852, 0.1 mg/kg s.c. b.d. (11>9>7 for discriminative  
30 learning, 13>9>7 for reverse learning), while animal 025 failed to improve during the first 4 days of treatment, but did improve over the

subsequent 4 day period (8>5 for discriminative learning, 12>9 for reverse learning).

These experiments were carried out double blind. However, the experimenter made full  
5 comments on the quality of behavior of these 3 marmosets during testing, all of which were well known in terms of their normal behavioral repertoire in the Wisconsin test. During treatment with SQ 29,852, the comment was consistently made  
10 that the animals appeared "too carefree to work". The dose of SQ 29,852 used is markedly anxiolytic in the marmoset, and it is our experience that animals fail to work well when undergoing full anxiolysis. Nevertheless, the size of improvement  
15 seen in J59 and 025 was important in that these animals have shown constant responding over many months. It is clear that SQ 29,852 is able to improve performance in both discriminative and reverse learning tasks in the marmoset.

20

#### CONCLUSIONS

##### ASSESSMENT OF ABILITY TO IMPROVE COGNITION AND COGNITIVE IMPAIRMENT

a) A mouse habituation test was used in which  
25 mice were repeatedly placed in the white compartment of a white:black test box. On repeated exposure to the test situation, mice 'learn' to avoid the aversive white, brightly-lit environment and move rapidly into the black where they spend a  
30 larger proportion of time and show most exploratory rearings and line crossings.

The habituation (learning) time is 5-6 days. This basic 'learning' time was not influenced by arecoline (50 mg/kg/day given by continuous intraperitoneal infusion: dose and route selected to avoid unwanted autonomic effects). However, this dose of arecoline successfully antagonised an impairment in habituation caused by acute challenge with scopolamine (0.25 mg/kg i.p., dose again carefully selected to avoid excessive peripheral autonomic disturbance, and particularly to avoid influence on vision which can influence performance in the test: lack of effect on vision was established by visual observation and by measurement of pupil function). Methyl scopolamine at a dose of 0.25 mg/kg i.p. failed to influence mouse habituation. The effect of scopolamine was marked: animals which had learned to avoid the white environment failed to enter the black, excepting for short periods of time, even though they easily found the door, and thus the rapid exit into the black and avoidance of the white environment was prevented by scopolamine treatment.

In contrast to arecoline, the speed of habituation was enhanced by treatment with low doses of SQ 29,852 (0.0005 mg/kg i.p. b.d.). Anxiolytic potential, which influenced the test procedure, generally developed on longer term treatment with these doses of the ACE inhibitor, and doses for use in the habituation test were subsequently lowered. SQ 29,852 was found to antagonize the impairment in habituation performance caused by acute challenge with

scopolamine. The dose which was fully effective against scopolamine was 0.0005 mg/kg i.p. b.d. SQ 29,852.

Hydergine (0.1 mg/kg p.o. once daily) was shown to speed the habituation process in a similar manner to the SQ 29,852 ACE inhibitor (both in contrast to the failure of arecoline), but hydergine treatment failed to influence the impairment in habituation caused by acute challenge with scopolamine (which contrasts with the actions of both the SQ 29,852 ACE inhibitor and the cholinomimetic agent).

Further studies allowed habituation to progress for 10 days before continuous impairment by scopolamine given daily for up to 14 days. This persistent impairment caused by scopolamine could be antagonized by arecoline (50 mg/kg/day by intraperitoneal infusion) and by SQ 29,852 (0.5 µg/kg i.p. b.d.).

b) In a food reinforced alternation task in the rat using an elevated T maze arecoline (30 mg/kg/day by intraperitoneal infusion) and SQ 29,852 (1.0 mg/kg i.p. b.d.) were shown to antagonize an impairment caused by scopolamine. This antagonism was particularly marked on pretraining days 2-5, but was less marked on training days 6-9. This may reflect the fact that the test becomes less challenging for the rats as training progresses, and that SQ 29,852 is anxiolytic at the dose used. Thus, it was observed that rats became increasingly 'nonchalant' about working on the test paradigm. Whatever, the data obtained with arecoline and

SQ 29,852 clearly indicates that a scopolamine impairment in learning in a rat test can be improved both by a cholinomimetic and SQ 29,852.

c) Marmosets were trained in a Wisconsin General Test Apparatus to discriminate between food rewarded and non-rewarded objects. After shaping to a criterion of 90/100, 18/20 and 9/10 correct responses (the 9/10 being repeated on several days), objects were changed and marmosets expected to select a new positive object on 6 consecutive occasions (discriminative learning), and then to change to selecting the second object (now positive in terms of food reward) on 6 consecutive occasions (reverse learning).

Marmosets used had shown constant responding over many months and there had been no improvement in either discriminative or reverse learning. However, after 8 days of treatment with 0.1 mg/kg s.c. b.d. SQ 29,852 marmosets showed clear improvement in both discriminative and reverse learning. The onset of action appeared to be delayed for some 4 days. It was also considered that the anxiolytic action of SQ 29,852 would interfere with testing, making the animals less inclined to work. However, it is clear that SQ 29,852 is capable of improving performance in established learning tasks in the common marmoset.



Example 8

The following experiments were carried out to demonstrate the effectiveness of the ACE inhibitor SQ 29,852 in inhibiting loss of cognitive functions.

Adult male Sprague-Dawley rats (Charles River, Wilmington, MA), age 25 weeks and weighing 350-400 g, were separately housed in stainless steel cages with continuous access to food and water, a 12-hour light-dark cycle, and constant room temperature of 22° to 24°C. All testing took place approximately 6 hours into the dark component of the light-dark cycle and was conducted in a dimly lighted soundproof room using a standard shuttle box device (Lehigh Valley Electronics #146-04), a plexiglass chamber (50 x 20 x 20 cm) divided by a center barrier 7 cm in height. The conditioned stimulus consisted of a 10-second tone provided by a Sonlert mounted in the midpoint of the ceiling of the chamber. Floor current of 0.8 mA was delivered by a constant current shocker-scrambler (Lehigh Valley Electronics #133-33).

The day before the initiation of training each animal was allowed to explore the experimental chamber for 10 minutes without any tone or shock. Training was conducted for 15 days following the day of experimental chamber exploration. Each animal received 20 trials per day on a 30-second variable interval schedule. No drug treatment was administered during the training period. Shock could be avoided by shuttling from one side of the center barrier to the other during the

10-second tone period. If an animal did not cross the center barrier during this period, the tone remained on and the floor shock was delivered until the animal escaped to the other half of the chamber. Animals which consistently remained on the center barrier were removed from the study. Automatic counters recorded the number of avoidance responses, escapes, and intertrial crossings, while a running time meter recorded the total shock duration for each animal.

Animals not meeting the admittance criterion of correct avoidance responding on at least 85% of the trials for 4 out of the last 5 days of training were removed from the study. A total of 36 rats reaching the admittance criterion were tested for extinction of conditioned avoidance response (CAE) during 14 days. They were randomly assigned to SQ 29,852 (1 mg/kg, 10 mg/kg and 30 mg/kg) and saline control, with each test group at each dosage comprising 9 rats. All solutions were prepared fresh and administered i.p. (1 mg/ml volume) on the 2 days prior to testing and then 1 hour before it. Testing consisted of 20 trials per day identical to those previously described, except that no shock was administered if an animal failed to shuttle during the 10-second tone period. The tone was simply discontinued and the testing proceeded.

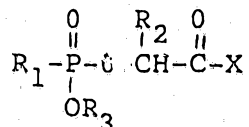
Two-way analysis of variance of the CAE data yielded an overall significant difference in the rate of shuttle extinction between treatment groups.

The present findings as seen from the accompanying Figure indicate that the ACE inhibitor, SQ 29,852, possesses protective effects on memory of previously learned tasks while the saline control which does not have ACE inhibiting activity does not have protective effects against loss of memory of previously learned tasks.

It will also be appreciated that all of the above compounds and formulations may be employed in treating or delaying progression of Alzheimer's disease.

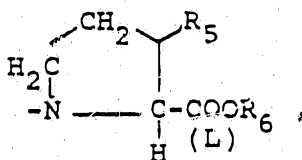
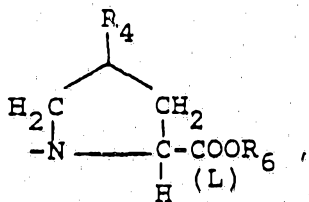
The claims defining the invention are as follows:-

1. A method for inhibiting loss of cognitive function in a mammalian specie over a prolonged period of time, which comprises administering to a mammalian specie in need of such treatment an effective amount of an angiotensin converting enzyme inhibitor having the formula

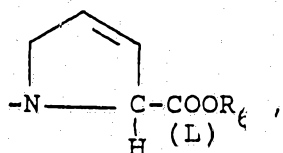
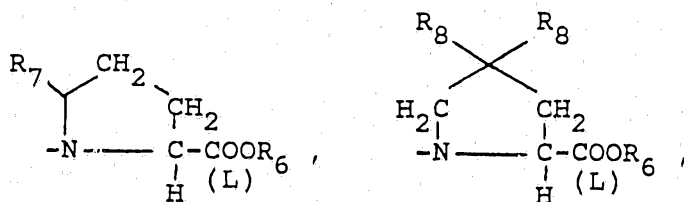


wherein:

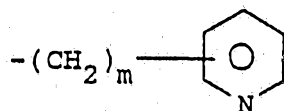
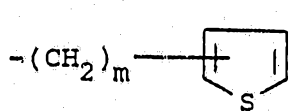
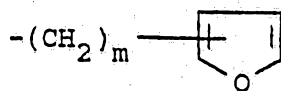
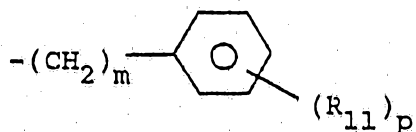
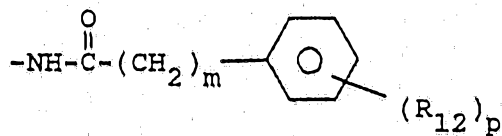
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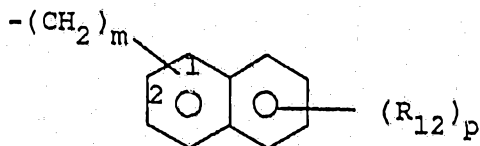
JM

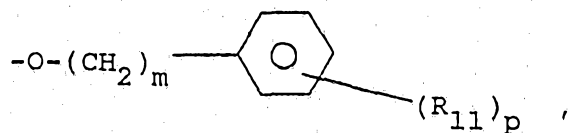
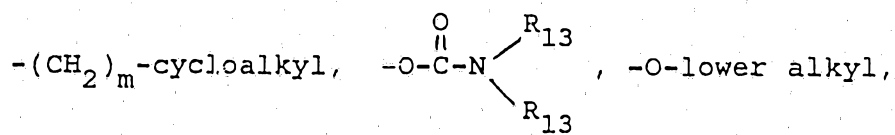


$R_4$  is hydrogen, lower alkyl, halogen, keto, hydroxy,  $-NH-C(=O)$ -lower alkyl, azido, amino,  $-N \begin{matrix} R_{17} \\ R_{18} \end{matrix}$ ,

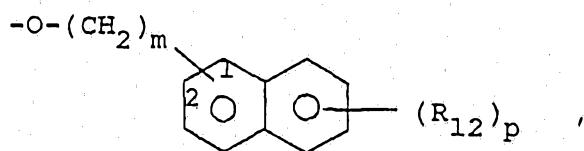


a 1- or 2-naphthyl of the formula

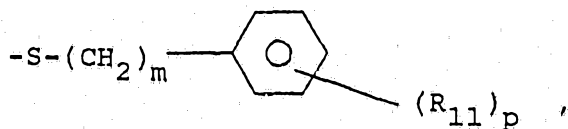




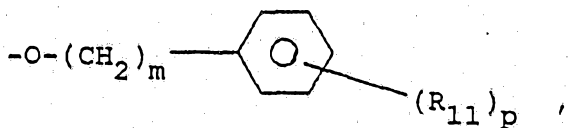
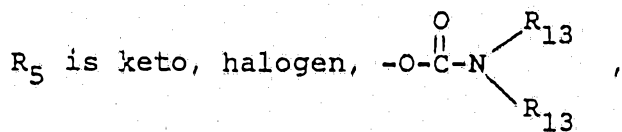
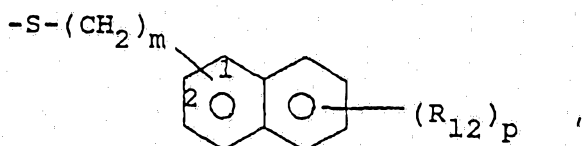
a 1- or 2-naphthyloxy of the formula



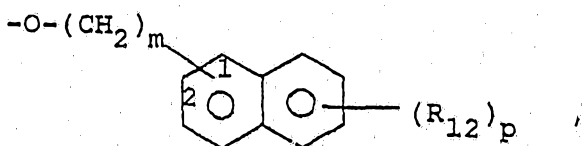
-S-lower alkyl,



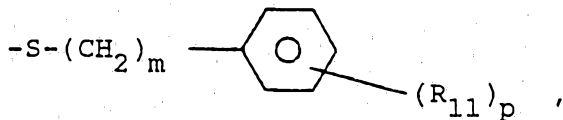
or a 1- or 2-naphthylthio of the formula



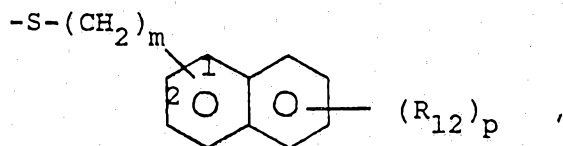
-O-lower alkyl, a 1- or 2-naphthyloxy of the formula



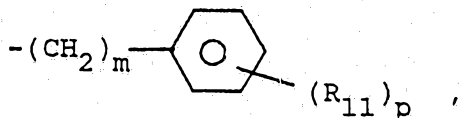
-S-lower alkyl,



or a 1- or 2-naphthylthio of the formula



$R_7$  is keto or



each  $R_8$  is the same or different and is halogen or  $-Y-R_{14}$ ;

$R_{11}$  is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl, hydroxy, phenyl, phenoxy, phenylthio, or phenylmethyl;

$R_{12}$  is hydrogen, lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, chloro, bromo, fluoro, trifluoromethyl or hydroxy;

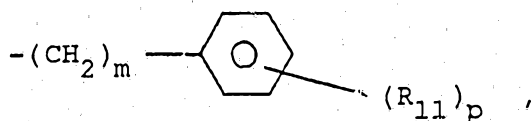
$m$  is zero, one, two or three;

$p$  is one, two or three provided that  $p$  is more than one only if  $R_{11}$  or  $R_{12}$  is hydrogen, methyl, methoxy, chloro or fluoro;

$R_{13}$  is hydrogen or lower alkyl of 1 to 4 carbons;

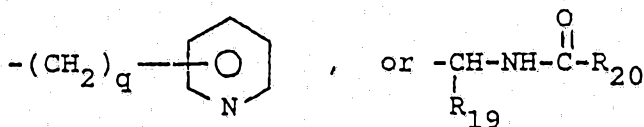
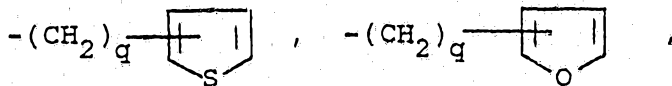
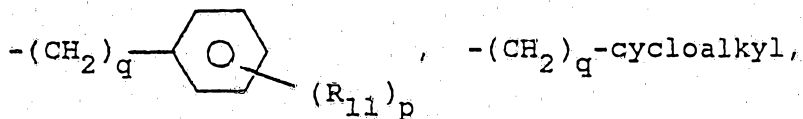
$Y$  is oxygen or sulfur.

$R_{14}$  is lower alkyl of 1 to 4 carbons,



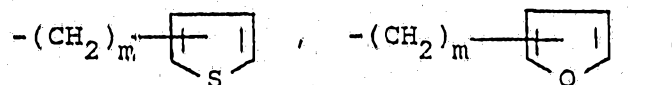
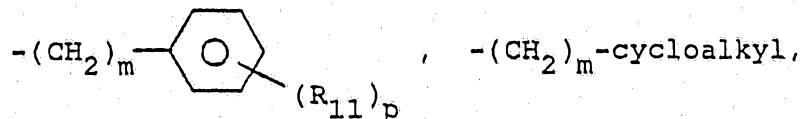
or the  $\text{R}_{14}$  groups join to complete an unsubstituted 5- or 6-membered ring or said ring in which one or more of the carbons has a lower alkyl of 1 to 4 carbons or a di(lower alkyl of 1 to 4 carbons) substituent;

$\text{R}_1$  is alkyl of 1 to 10 carbons, aminoalkyl, haloalkyl,

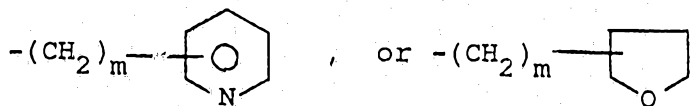


wherein  $q$  is zero or an integer from 1 to 7 and  $\text{R}_{11}$  and  $p$  are as defined above;

$\text{R}_{19}$  and  $\text{R}_{20}$  are independently selected from hydrogen, lower alkyl, halo substituted lower alkyl,

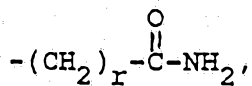
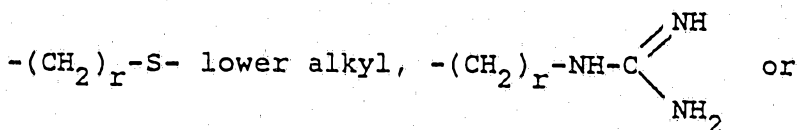
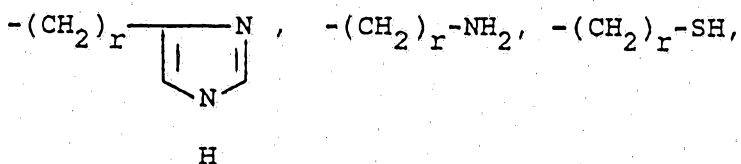
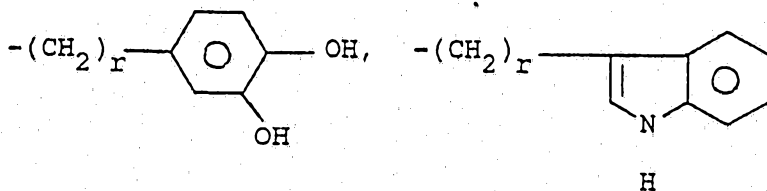
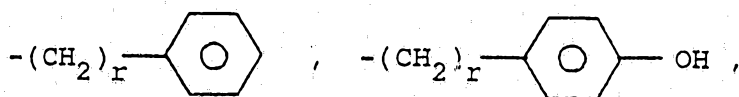






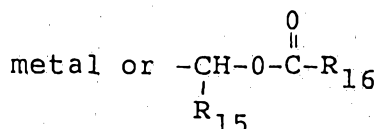
wherein  $m$ ,  $R_{11}$ , and  $p$  are as defined above;

$R_2$  is hydrogen, lower alkyl, halo substituted lower alkyl,

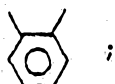


wherein  $r$  is an integer from 1 to 4;

$R_3$  and  $R_6$  are independently selected from hydrogen, lower alkyl, benzyl, benzhydryl, alkali



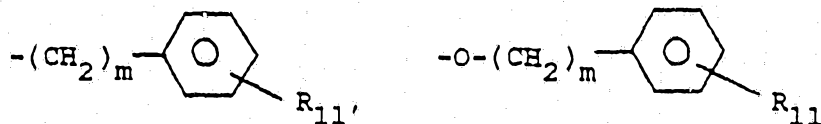
wherein  $\text{R}_{15}$  is hydrogen, lower alkyl, cycloalkyl or phenyl, and  $\text{R}_{16}$  is hydrogen, lower alkyl, lower alkoxy, phenyl, or  $\text{R}_{15}$  and  $\text{R}_{16}$  taken together are  $-(\text{CH}_2)_2-$ ,  $-(\text{CH}_2)_3-$ ,  $-\text{CH}=\text{CH}-$ , or



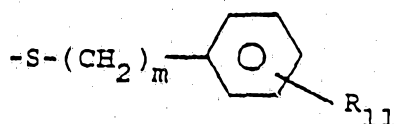
$\text{R}_{17}$  is lower alkyl, benzyl, or phenethyl; and

$\text{R}_{18}$  is hydrogen, lower alkyl, benzyl or phenethyl or a pharmaceutically acceptable salt thereof to inhibit loss of cognitive function during such period of treatment.

2. The method as defined in Claim 1 wherein in the compound employed  $\text{R}_4$  is hydrogen, hydroxy, chloro, fluoro, lower alkyl of 1 to 4 carbons, cyclohexyl, amino, -O-lower alkyl wherein lower alkyl is of 1 to 4 carbons,

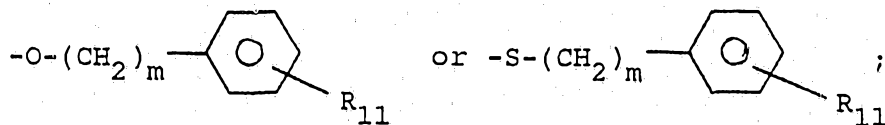


1- or 2-naphthyloxy, -S-lower alkyl wherein lower alkyl is of 1 to 4 carbons,



or 1- or 2- naphthylthio;

$R_5$  is -O-lower alkyl wherein lower alkyl is of 1 to 4 carbons, -S-lower alkyl wherein lower alkyl is of 1 to 4 carbons,



$R_7$  is phenyl, 2-hydroxyphenyl, or 4-hydroxyphenyl; each  $R_8$  is fluoro, chloro or -Y- $R_{14}$ ;

Y is oxygen or sulfur;

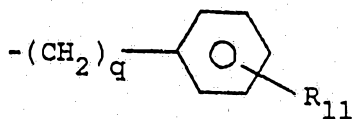
$R_{14}$  is lower alkyl of 1 to 4 carbons or the  $R_{14}$  groups join to complete an unsubstituted 5- or 6-membered ring or said ring in which one or more of the carbons has a methyl or dimethyl substituent;

m is zero, one or two;

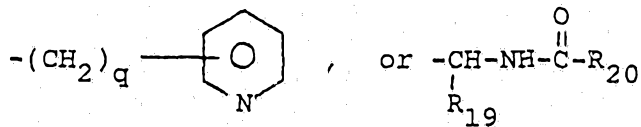
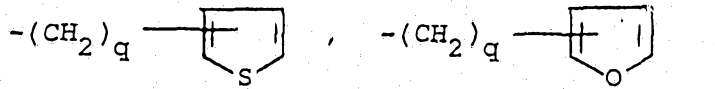
$R_{11}$  is hydrogen, methyl, methoxy, methylthio, chloro, bromo, fluoro or hydroxy;

$R_2$  is hydrogen, lower alkyl of 1 to 4 carbons,  $\text{CF}_3$ , or amino substituted lower alkyl of 1 to 4 carbons;

$R_1$  is alkyl of 1 to 10 carbons,

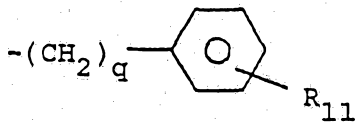


$-(\text{CH}_2)_q$ -cycloalkyl wherein cycloalkyl is of 5 or 6 carbons,



wherein  $q$  is zero or an integer from 1 to 4 and  $\text{R}_{11}$  is as defined above;

$\text{R}_{19}$  and  $\text{R}_{20}$  are independently selected from lower alkyl of 1 to 4 carbons or



wherein  $q$  and  $\text{R}_{11}$  are as defined above;

$\text{R}_3$  and  $\text{R}_6$  are independently selected from hydrogen, alkali metal salt, lower alkyl of 1 to 4

carbons, or  $-\underset{\text{R}_{15}}{\text{CH}} - \overset{\text{O}}{\parallel} \text{C} - \text{R}_{16}$  ;

$\text{R}_{15}$  is hydrogen, methyl or isopropyl; and

$\text{R}_{16}$  is lower alkyl of 1 to 4 carbons or phenyl.

~~6. The method as defined in claim 5 where in the compound employed X is~~





imino acid or salt thereof.

11. The method as defined in Claim 7 wherein said angiotensin converting enzyme inhibitor is administered over a prolonged period of treatment to inhibit loss of cognitive function during such period of treatment.

12. The method as defined in Claim 17 wherein the angiotensin converting enzyme inhibitor is (S)-1-[6-amino-2-[[hydroxy-(4-phenylbutyl)phosphinyloxy]-1-oxohexyl-L-proline.

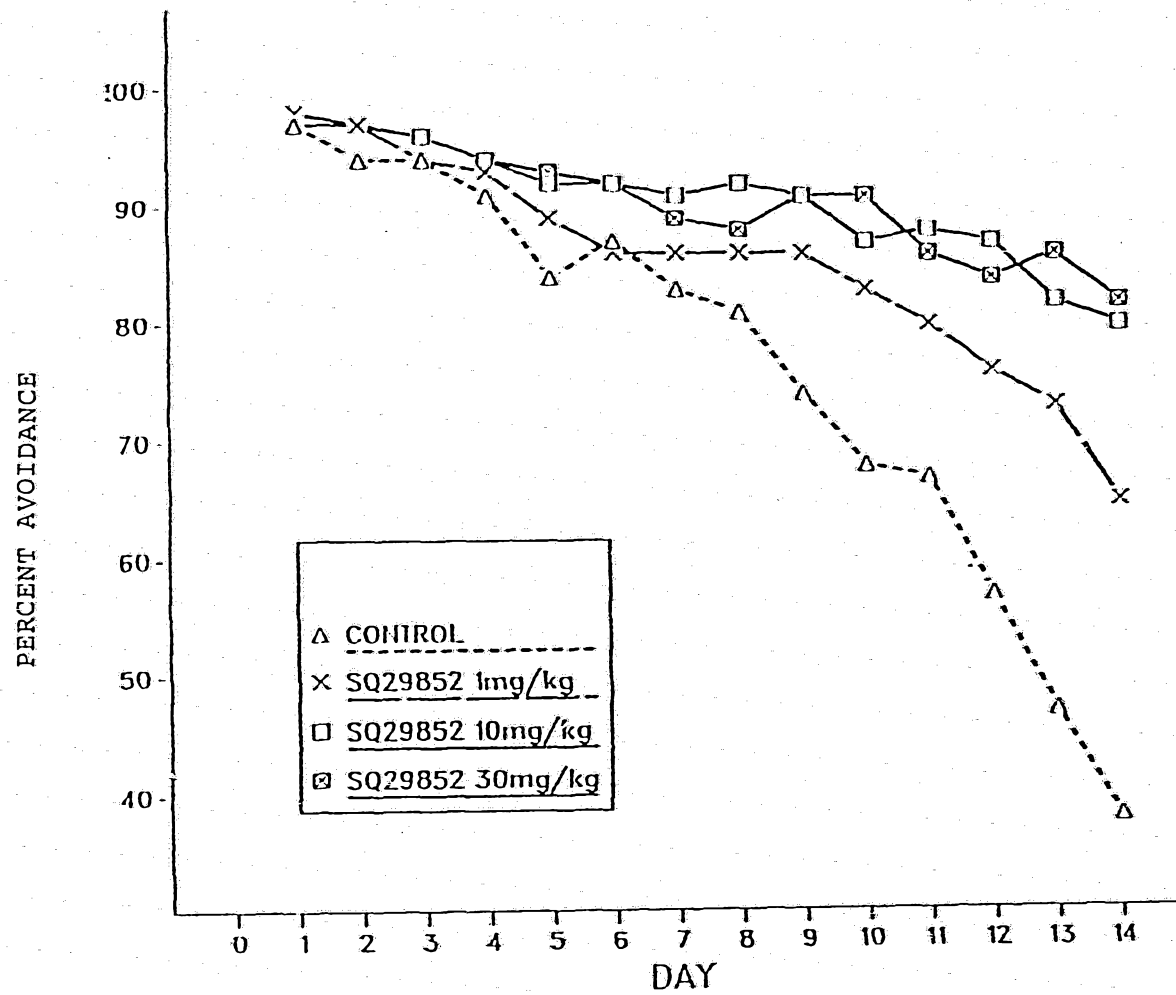
10 13. A method according to Claim 1 substantially as hereinbefore described with reference to any one of the examples.

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FIGURE

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