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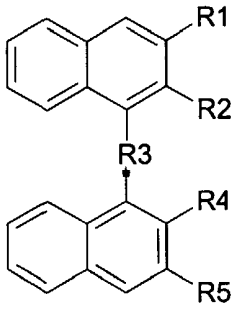
[Continued on next page]

(54) Title: USE OF PAMOIC ACID OR ONE OF ITS DERIVATIVES, OR ONE OF ITS ANALOGUES, FOR THE PREPARATION OF A MEDICAMENT FOR THE TREATMENT OF DISEASES CHARACTERISED BY DEPOSITS OF AMYLOID AGGREGATES



(I)

(57) Abstract: The use of pamoic acid or of one of its derivatives is described with general formula (I), in which groups R1 and R5 are as indicated in the description, or of one of their pharmaceutically acceptable salts, for the preparation of a medicament for the treatment of diseases characterised by deposits of amyloid aggregates.

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Use of pamoic acid or one of its derivatives, or one of its analogues, for the preparation of a medicament for the treatment of diseases characterised by deposits of amyloid aggregates

The invention described herein relates to the use of pamoic acid or one of its derivatives, or one of its analogues, or one of the pharmaceutically acceptable salts of these, for the preparation of a medicament for the treatment of diseases characterised by deposits of amyloid aggregates.

The presence of amyloid deposits and of abnormalities of the neuronal cytoskeleton are among the most marked manifestations of Alzheimer's disease (AD). These two events, which mainly affect the cerebral cortex at an early stage, even though the final pathological picture of the disease involves the entire central nervous system, are a necessary though not in themselves sufficient condition for onset of the disease (Chen M. (1998) Frontiers in Bioscience 3a, 32-37).

In general, regardless of the protein from which it is formed, the substance amyloid has the characteristics of being composed of fibres measuring 7-8 nm in diameter, of having affinity for Congo Red and not being soluble in water. In AD, amyloid fibres accumulate external to the cell, in the cerebral intracellular spaces and in the tunica media of the cortical and meningeal arterioles, leading to the formation of three different macroscopic abnormalities: the senile plaques and the diffuse plaques, which differ according to the presence or otherwise of an abnormality of

the neuronal processes around the central amyloid deposit, and amyloid angiopathy, which is an expression of infiltration of amyloid fibres into the walls of the arteries, between the smooth muscle fibres and the internal elastic lamina.

Apart from the formation of amyloid and helical filaments, a very serious synaptic rarefaction has been detected in the cortex of subjects suffering from AD. Approximately 80%-90% of neuronal contacts are destroyed in the final phase of the disease and this abnormality is the actual pathological correlate of dementia. On analysing the dementia trend, it would appear certain that amyloid is the early, primary abnormality of the disease and that the intraneuronal helical filaments are an intermediate expression of the distress of the neurons, which eventually lose their synaptic contacts, with the resulting clinical effect of a deterioration of mental functions.

The soluble form of a particular type of β amyloid, βA_{1-42}, so far regarded as toxic only in its aggregate form, is involved in the progressive loss of memory and cognitive functions of Alzheimer's patients. βA_{1-42}, which is produced in the initial phase of the disease, suppresses the activity of pyruvate dehydrogenase which fuels the synthesis of ACh providing for the transport of acetyl-CoA, reducing the release of the neurotransmitter, modifying the synaptic connections and causing the cholinergic deficits responsible for the disease (Hoshi M., Takashima A., Murayama M., Yasutake K.,

Yoshida N., Ishiguro K., Hoshino T., Imahori K. (1997) The Journal of Biological Chemistry 272:4, 2038-2041).

It is known that a number of dyes bind to amyloid fibres in a specific manner and the most important of these is Congo Red (CR) (Lorenzo A. and Yankner B.A, 1994 PNAS 91;12243-12247).

This dye causes an increase in birefringence of the amyloid fibres and gives rise to a characteristic circular dichroism indicative of a specific interaction between the dye and the substrate (the fibres) facilitating the diagnostic detection of amyloidosis in the tissue.

The β–amyloid protein (βA) derives from the proteolytic action of a number of specific enzymes on the precursor of the amyloid protein (βAPP) (Vassar R. et al. 1999 Science 286;735-740).

The mechanisms whereby the β-amyloid fragment may induce neurotoxic effects are multiple. In the first place, immunohistochemical studies have revealed the presence, in senile plaques, of inflammatory interleukins (IL-1, IL-6), complement factors, other inflammatory factors and lysosomal hydrolases. It has been demonstrated that the β-amyloid protein is capable of stimulating the synthesis and secretion of IL-1, IL-6 and IL-8 by microglial cells and thus of activating the cytotoxic mechanisms of acute inflammation (Sabbagh M.N., Galasko D., Thal J.L. (1997) Alzheimer's Disease Review 3, 1-19).

The diseases characterised by deposits of amyloid aggregates include, in addition to Alzheimer's disease, Down's syndrome, hereditary cerebral haemorrhage associated with "Dutch-type" amyloidosis, amyloidosis associated with chronic inflammation, amyloidosis associated with multiple myeloma and other dyscrasias of the haematic B lymphoid cells, amyloidosis associated with type II diabetes, amyloidosis associated with prion diseases such as Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, Kuru and the sheep disease scrapie.

In general, however, the damage caused by βA can be summarised as:

1. abnormalities of amyloidogenesis;
2. increase in vulnerability of neurons to exocytoxicity;
3. increase in vulnerability of neurons to hypoglycaemic damage;
4. abnormalities of calcium homeostasis;
5. increase in oxidative damage;
6. activation of inflammatory mechanisms;
7. activation of the microglia;
8. induction of lysosomal proteases;
9. abnormalities of tau protein phosphorylation;
10. induction of apoptosis;
11. damage to membranes.

From a strictly theoretical point of view, the reduction of βA-induced damage can be tackled via different therapeutic approaches:

1. reducing the production of βA using secretase inhibitors to alter APP metabolism (increasing α or reducing β and γ secretases);
2. preventing or blocking βA aggregation;
3. increasing βA clearance;
4. blocking the neurotoxic effects of βA by restoring calcium homeostasis;
5. preventing the toxicity produced by free radicals;
6. preventing exocytoxicity;
7. reducing the damage caused by the inflammatory response;
8. correcting the altered copper-zinc equilibrium;
9. inhibiting neuronal apoptosis;

(Sabbagh M.N., Galasko D., Thal J.L. (1997) Alzheimer's Disease Review 3, 1-19).

To date there is no specific therapy capable of preventing, slowing or arresting the amyloidogenic process underlying Alzheimer's disease.

In fact, the therapies currently used for the treatment of this disease are exclusively symptomatic and, though acting on different aspects, interfere fundamentally only with the neurotransmitter mechanisms regulating learning and memory. Among the molecules most commonly used figure the reversible acetylcholinesterase inhibitors such as tacrine, donezepil and rivastigmine.

At the present time, moreover, the only diagnostic instruments available for the diagnosis of Alzheimer's disease are behavioural

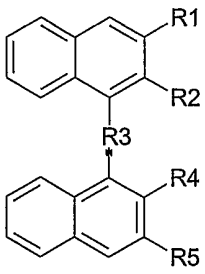
examinations and clinical scores, while radiographic or scintigraphic procedures are still unable to distinguish with precision between Alzheimer-type forms of degeneration and other degenerative phenomena, the precise reason for this being the lack of suitable tracings.

The difficulties encountered in the management of Alzheimer's disease, its severity and the difficulty in diagnosing it make it desirable not only to identify new drugs capable of curing the disease or of slowing down its course but also to discover compounds to be used in radiographic or scintigraphic procedures for its diagnosis.

It is therefore surprising that pamoic acid, or one of its derivatives, or one of its analogues, or one of the pharmaceutically acceptable salts thereof, or derivatives of said acid described and known in the literature have proved to be potentially effective drugs in the treatment and prevention of Alzheimer's disease and of diseases characterised by deposits of amyloid aggregates.

In the context of this discovery, new derivatives of pamoic acid have been found, described here below, which are potentially effective in the treatment of the above-mentioned diseases and which have proved to be useful agents for the preparation of a medicament for the treatment of diseases characterised by deposits of amyloid aggregates.

In fact, those derivatives of pamoic acid with general formula (I)



(I)

in which:

1 R1 = R5 = $-COOCH_2C_6H_5$

R2 = R4 = -OH

R3 = $-CH_2-$

2 R1 = R5 = $-COOCH(CH_3)_2$

R2 = R4 = -OH

R3 = $-CH_2-$

3 R1 = R5 = $-COOC_2H_5$

R2 = R4 = -OH

R3 = $-CH_2-$

4 R1 = R5 = $-COOC_6H_{11}$

R2 = R4 = -OH

R3 = $-CH_2-$

5 R1 = R5 = $-COOCH_3$

R2 = R4 = -OH

R3 = $-CH_2-$

6 R1 = R5 = $-COOC(CH_3)_3$

R2 = R4 = -OH

R3 = $-CH_2-$

are described in patent N° ES 432416, and for these compounds no use is described or claimed;

7 R1 = R5 = $-CONHC_6H_5$

R2 = R4 = -OH

R3 = $-CH_2-$

is described in patent N° JP 7138347, as a useful agent for the preparation of nylon fibres;

8 R1 = R5 = $-CONH-CH(CH(CH_3)_2)-COOH$

R2 = R4 = -OH

R3 = $-CH_2-$

is described in Reetz, Manfred T. et al; Chem. Commun, (Cambridge) (1998), (19), 2075-2076 as an inhibitor of HIV-1 protease;

9 R1 = R5 = -COOH

R2 = R4 = $-OCOCH_3$

R3 = $-CH_2-$

is described in Poupelin, Jean Pierre; Eur. J. Med. Chem. - Chim. Ther. (1978), 13(4), 381-5, as an agent with anti-inflammatory activity;

10 R1 = R5 = -COOH

R2 = R4 = $-OCOCH_2CH_3$

R3 = $-CH_2-$

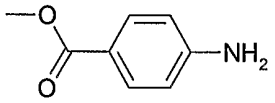
is described in patent N° DE 1945254, which states that the salts of this compound with streptomycin makes its effect longer-lasting as an agent for the treatment of tuberculosis;

11 R1 = R5 = -H

R2 = R4 = $-OCOC_6H_5$

R3 = $-CH_2-$

12 R1 = R5 = -H

R2 = R4 = 

R3 = $-CH_2-$

are described in in Dorogov, M.V.; Khim. Khim. Tekhnol. (1996), 39 (4-5), 170-172; no use is indicated for them;

13 R1 = R5 = -H

R2 = R4 = $-OCOCH=CH_2$

R3 = $-CH_2-$

is described in Kielkiewicz, Jedrzej, et al.; Polimery (Warsaw) (1984), 29 (6), 216-19; no use is indicated for it;

14 R1 = R5 = -H

R2 = R4 = -OH

R3 = $-CH_2-$

this compound is 1,1'-methylen-di(2-naphtol), which is described in US 4,147,806 as anti-inflammatory and analgesic medicament.

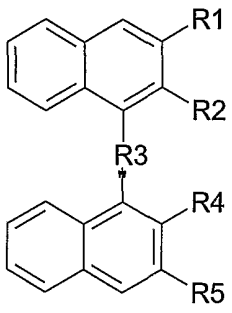
15 R1 = R5 = -COOH

R2 = R4 = -OH

R3 = -CH_2-

this compound is pamoic acid; it is described as an agent useful as a counter-ion in drugs used as antihelminthic agents (Pyrantel pamoate) or in the treatment of cancer (Octreotide pamoate).

The object of the invention described herein is therefore the use of pamoic acid, or one of its derivatives, or one of its analogues, or one of the pharmaceutically acceptable salts of these, with general formula (I)



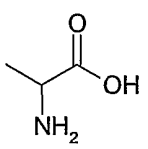
(I)

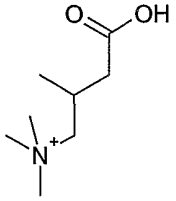
in which:

R1 and R5, which may be the same or different, are COOR6, CONHR6, SO_2R6, SO_2NHR6, SO_3R6, OR6, COR6, NHR6, R6;

in which R6 is H or a straight or branched, saturated or unsaturated alkyl chain, with from 1 to 5 carbon atoms, or phenyl, substituted by R7;

in which: R7 is OH, COOH, SO_3H, NR8R9,

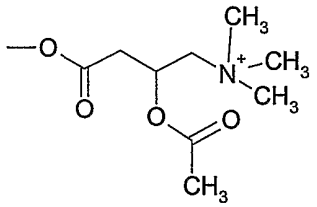


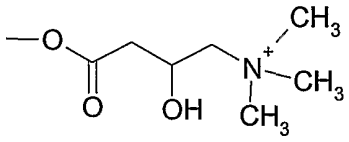


in which:

R8 and R9, which may be the same or different, are H, alkyl with 1 to 5 carbon atoms;

R2 and R4, which may be the same or different, are H, OH, NHR6, OCO-R10-NR8R9,





in which R10 is a straight or branched, saturated or unsaturated alkyl chain with from 1 to 5 carbon atoms;

R3 is -[CH_2]n-, -CH_2-O-, -CH(R11)-,

in which n is an integer from 1 to 4,

R11 is a straight or branched alkyl with from 1 to 5 carbon atoms, substituted by an amino group, alkylamino C_1-C_5, dialkylamino C_1-C_5, OH, alkyloxy C_1-C_5;

for the preparation of a medicament for the treatment of diseases characterised by deposits of amyloid aggregates.

Among the formula (I) compounds the one preferred is pamoic acid, and particularly sodium pamoate.

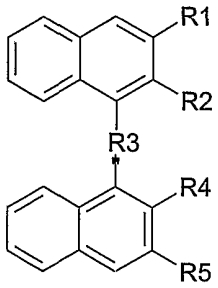
A further object of the invention described herein is the use of the above-mentioned formula (I) compounds for the preparation of a diagnostic kit for the diagnosis of diseases characterised by deposits of amyloid aggregates.

In fact, the compounds according to the invention described herein may contain in their molecular structure atoms of elements commonly used in diagnostic imaging procedures. For example, radioactive isotopes of carbon, hydrogen, nitrogen, oxygen, iodine and indium can be introduced into their molecular structure. More precisely, the formula (I) compound can have at least one of the elements, carbon, hydrogen, nitrogen, oxygen of its own molecular structure substituted by a corresponding radioactive isotope; or it will carry at least one atom of radioactive iodine; or it is in the form of a complex with radioactive indium.

Such isotopes are useful for techniques such as PET (Positron Emission Tomography), SPECT (Single Photon Emission Computerized Tomography), and planar scintigraphy. Alternatively, the compounds according to the invention, whether or not they contain radioactive isotopes or atoms of elements useful as radio-opaque substances (e.g. iodine), can be used as complexing agents for elements commonly used in diagnostic imaging techniques, such as, for example, gadolinium (NMR) and technetium (scintigraphy techniques).

On the basis of this diagnostic application, the compounds according to the invention are also useful for the prevention of the diseases indicated above.

A further object of the invention described herein are new compounds with general formula (I)



(I)

in which:

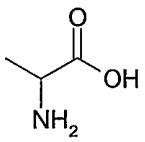
R1 and R5, which may be the same or different, are COOR6, CONHR6, SO_2R6, SO_2NHR6, SO_3R6, OR6, COR6, NHR6, R6;

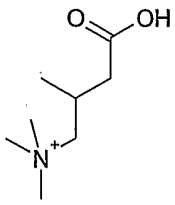
in which:

R6 is H or a straight or branched, saturated or unsaturated alkyl chain with from 1 to 5 carbon atoms, or phenyl, substituted by R7;

in which:

R7 is OH, COOH, SO_3H, NR8R9,

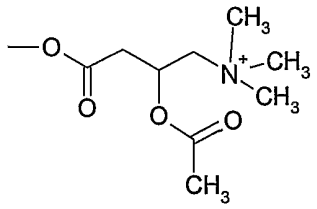


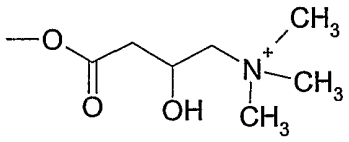


in which:

R8 and R9, which may be the same or different, are H, alkyl with from 1 to 5 carbon atoms;

R2 and R4, which may be the same or different, are H, OH, NHR6, OCO-R10-NR8R9,





in which:

R10 is a straight or branched, saturated or unsaturated alkyl chain with from 1 to 5 carbon atoms;

R3 is $-[CH_2]_{n-}$, $-CH_2-O-$, -CH(R11)-,

in which n is an integer from 1 to 4,

R11 is a straight or branched alkyl with from 1 to 5 carbon atoms, substituted by an amino group, alkylamino C1-C5, dialkylamino C1-C5, OH, alkyloxy C1-C5;

with the proviso that the substituents R1, R2, R3, R4 and R5 are not:

1 R1 = R5 = $-COOCH_2C_6H_5$

R2 = R4 = -OH

R3 = $-CH_2-$

2 R1 = R5 = $-COOCH(CH_3)_2$

R2 = R4 = -OH

R3 = $-CH_2-$

3 R1 = R5 = $-COOC_2H_5$

R2 = R4 = -OH

R3 = -CH_2-

4 R1 = R5 = -$COOC_6H_{11}$

R2 = R4 = -OH

R3 = -CH_2-

5 R1 = R5 = -$COOCH_3$

R2 = R4 = -OH

R3 = -CH_2-

6 R1 = R5 = -$COOC(CH_3)_3$

R2 = R4 = -OH

R3 = -CH_2-

7 R1 = R5 = -$CONHC_6H_5$

R2 = R4 = -OH

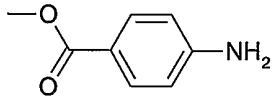
R3 = -CH_2-

11 R1 = R5 = -H

R2 = R4 = -$OCOC_6H_5$

R3 = -CH_2-

12 R1 = R5 = -H

R2 = R4 = 

R3 = -CH_2-

13 R1 = R5 = -H

R2 = R4 = -$OCOCH=CH_2$

R3 = -CH_2- ;

14 R1 = R5 = -H

R2 = R4 = -OH

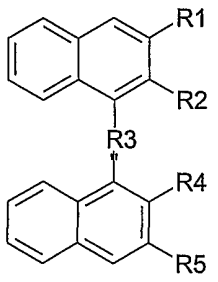
R3 = $-CH_2-$

R1 = R5 = -COOH

R2 = R4 = -OH

R3 = $-CH_2-$

A further object of the invention described herein is a process for the preparation of compounds with general formula (I)



(I)

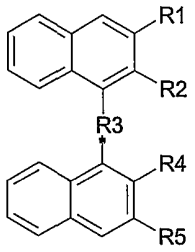
in which:

R1 and R5 are -COOR6,

in which R2, R3, R4 and R5 have the meanings defined above,

characterised in that a general formula (I) compound in which R6 is H, is treated with a halogenating agent, such as $SOCl_2$ or PCl_5, to yield the corresponding acyl chloride, then reacted at a temperature ranging from 25 to 60°C for time periods ranging from 2 to 24 hours, under stirring with an R6-OH alcohol in a molar ratio of 1 to 6, or in an inert anhydrous solvent, such as, for example, dimethylformamide, with the stoichiometric amount of R6-OH.

A further object of the invention described herein is a process for the preparation of formula (I) compounds



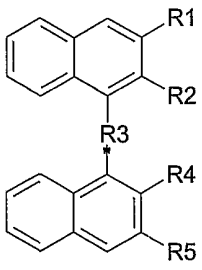
(I)

in which R1 and R5 are CONHR6;

in which R2, R3, R4 and R6 have the meanings defined above,

characterised in that a compound with general formula (I), in which R6 is H, is treated with a halogenating agent such as $SOCl_2$ or PCl_5, to yield the corresponding acyl chloride, or with a coupling agent such as DCC, EEDQ, then reacted at a temperature ranging from 25 to 60°C, for times periods ranging from 2 to 24 hours, under stirring, with an R6-NH_2 amine in a molar ratio of 6 to 1, or in an inert anhydrous solvent with the stoichiometric amount of R6-NH_2.

A further object of the invention described herein is a process for the preparation of formula (I) compounds



(I)

in which R2 and R4 are OH;

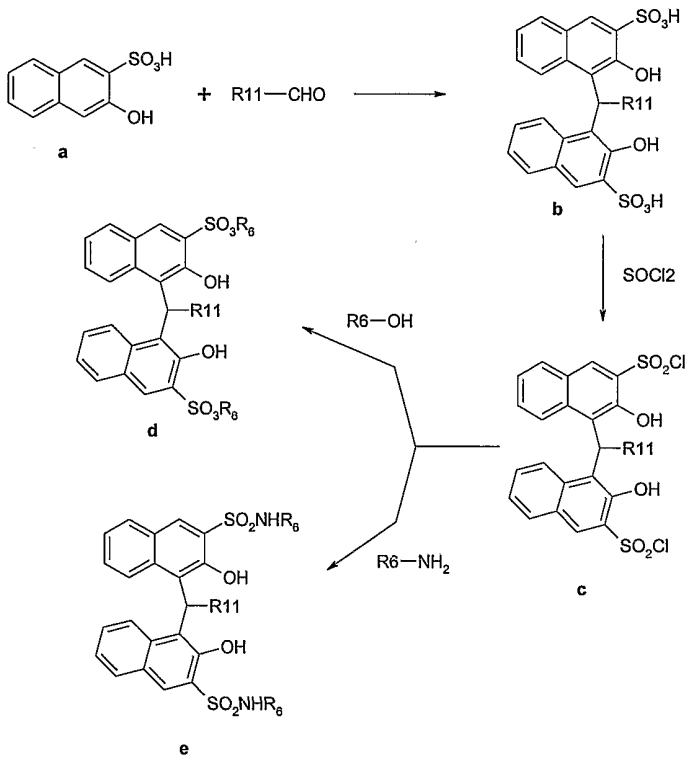
in which R1 and R5 are SO_3R6, SO_2NHR6;

R3 is -CH(R11)-,

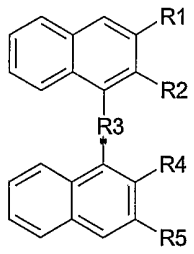
in which R11 has the meaning indicated above;

characterised in that said process is carried out according to reaction scheme 1 below, where a formula “a” compound is reacted with an R11-CHO aldehyde in glacial acetic acid at a temperature ranging from 90°C to 150°C to yield compounds with general formula “b”. Subsequently, a general formula "b" compound is treated with a halogenating agent, such as SOCl2 or PCl5, to yield the corresponding sulphonyl chloride, then reacted with an R6-OH alcohol to yield compounds with general formula “d” or with an R6-NH_2 amine to yield compounds with general formula “e”.

Scheme 1



A further object of the invention described herein is a process for the preparation of formula (I) compounds



(I)

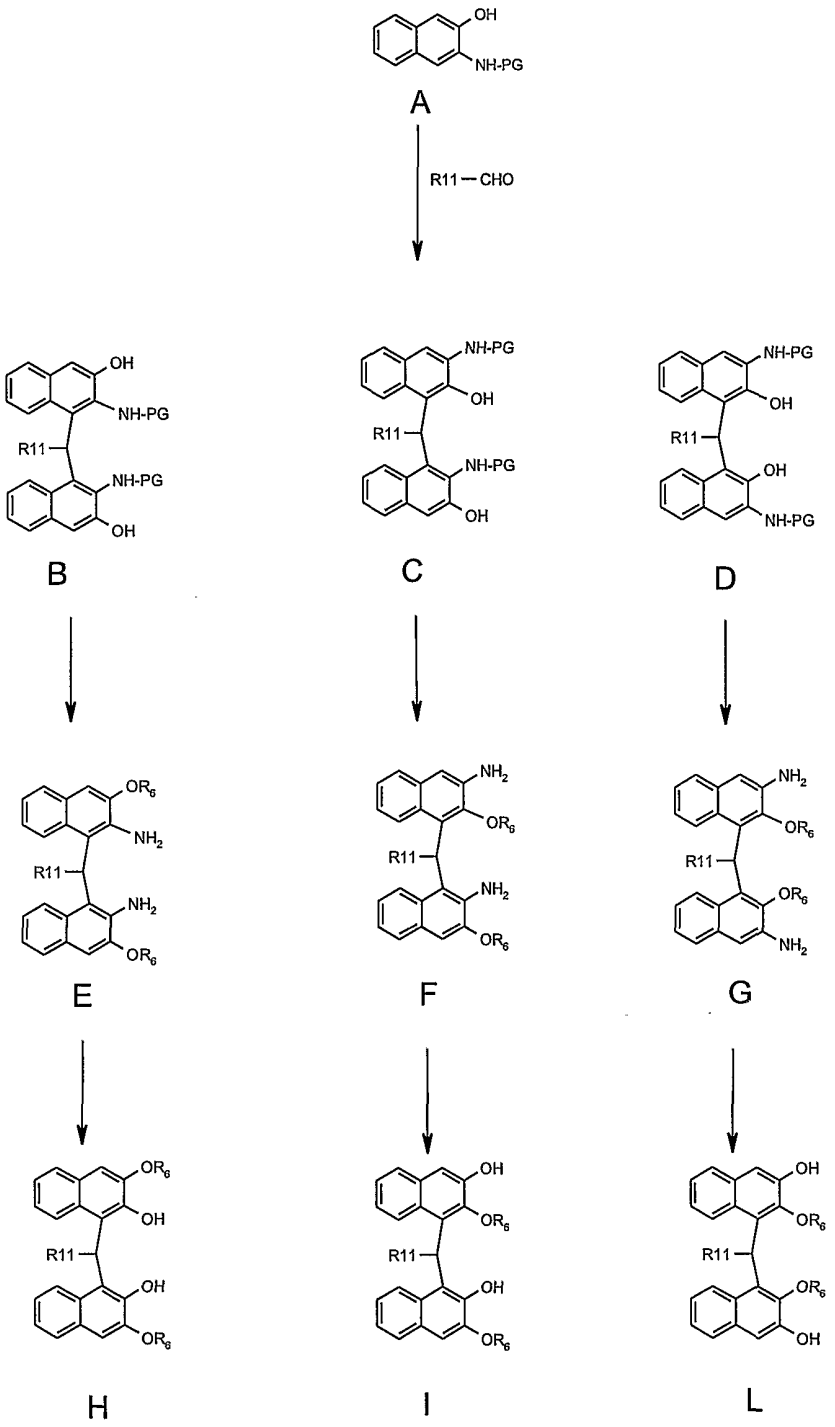
in which:

R1, R2, R4 and R5 are OR6 and/or NHR6; R3 is -CH(R11)-,

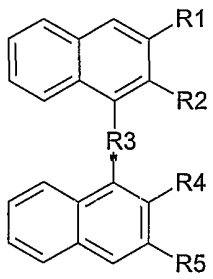
in which R6 and R11 have the meanings indicated above; characterised in that said process is carried out according to reaction scheme 2 below, where a formula A compound is reacted with R11-CHO aldehyde in an acid milieu, for example in acetic acid, to yield a mixture of compounds corresponding to the structures B, C and D which are separated and purified by chromatography. These compounds are reacted with an alkyl halide R6-X in the presence of a base and then deprotected in an acid or basic milieu to yield the corresponding naphthyl ethers E, F and G. After treatment of the latter with $NaNO_2$ in sulphuric acid, compounds H, I and L are obtained.

Scheme 2

PG = protective group (for example: acetyl, tosyl)



A further object of the invention described herein is a pharmaceutical composition containing as active ingredient a compound with general formula (I)



(I)

in which R1, R2, R3, R4 and R5 have the meanings indicated above,

with the proviso that R1, R2, R3, R4 and R5 are not:

1 R1 = R5 = $-COOCH_2C_6H_5$

R2 = R4 = -OH

R3 = $-CH_2-$

2 R1 = R5 = $-COOCH(CH_3)_2$

R2 = R4 = -OH

R3 = $-CH_2-$

3 R1 = R5 = $-COOC_2H_5$

R2 = R4 = -OH

R3 = $-CH_2-$

4 R1 = R5 = $-COOC_6H_{11}$

R2 = R4 = -OH

R3 = $-CH_2-$

5 R1 = R5 = $-COOCH_3$

R2 = R4 = -OH

R3 = $-CH_2-$

6 R1 = R5 = $-COOC(CH_3)_3$

R2 = R4 = -OH

R3 = $-CH_2-$

7 R1 = R5 = $-CONHC_6H_5$

R2 = R4 = -OH

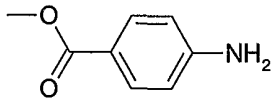
R3 = $-CH_2-$

11 R1 = R5 = -H

R2 = R4 = $-OCOC_6H_5$

R3 = $-CH_2-$

12 R1 = R5 = -H

R2 = R4 = 

R3 = $-CH_2-$

13 R1 = R5 = -H

R2 = R4 = $-OCOCH=CH_2$

R3 = $-CH_2-$;

14 R1 = R5 = -H

R2 = R4 = -OH

R3 = $-CH_2-$

15 R1 = R5 = -COOH

R2 = R4 = -OH

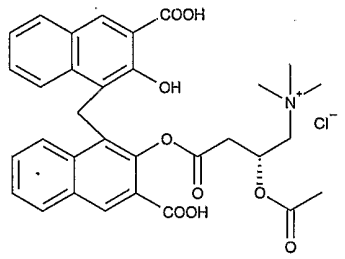
R3 = $-CH_2-$

and a pharmaceutically acceptable excipient and/or diluent.

Given here below are a number of examples which further illustrate the invention.

EXAMPLE 1

Preparation of (2R)-2-(acetyloxy)-4-({3-carboxy-1-[(3-carboxy-2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-N,N,N-trimethyl-4-oxo-1-butanaminium chloride (ST1722)



A solution of 2.39 g (0.01 mol) of acetyl L-carnitine chloride, 2 ml of anhydrous CH_2Cl_2, and 1.1 ml (0.015 mol) of thionyl chloride was stirred at ambient temperature for 4 hours. The solvent was removed and the residual solid washed three times with anhydrous CH_2Cl_2. An oil was obtained, namely the acyl chloride of acetyl L-carnitine chloride, which was used as such for the next step.

A suspension of 2.58 g (0.01 mol) of acyl chloride of acetyl L-carnitine chloride, 3.88 g (0.01 mol) of pamoic acid and 10 ml of N-methyl-2-pyrrholidinone was left to stir for one night. After precipitaion with ethyl ether, a yellow solid was obtained (7 g). The crude product thus obtained was purified by chromatography on a silica gel column, eluting first with CH_2Cl_2 – MeOH 90:10 to collect

the unreacted pamoic acid and then with CH_2Cl_2 – MeOH 85:15 to collect the product. After removal of the solvent, 1.2 grams of (2R)-2-(acetyloxy)-4-({3-carboxy-1-[(3-carboxy-2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-N,N,N-trimethyl-4-oxo-1-butanaminium chloride were obtained.

Yield = 19.7%, M.P. = decomposes at 185°C, $[\alpha]_D^{20}$ = -17.5°,

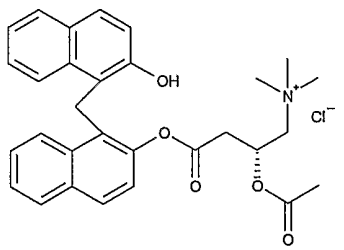
^{1}H NMR (DMSO, 300 MHz), δ 7.1-8.5 (m, 10H, H-Ar), 5.50 (m, 1H, -C-CH-C-N), 4.76 (s, 2H, Ar-CH_2-Ar), 3.70 (m, 2H, -CH_2-N), 3.11 (s, 9H, -N-CH_3), 2.85 (m, 2H, -CH_2-COO-), 2.01 (s, 3H, CH_3-COO-).

K.F. = 1.4%

C, H, N values calculated for $C_{32}H_{32}NO_9Cl$ and corrected for the amount of water present: C, 63.00; H, 5.29; N, 2.30; found C, 60.45; H, 5.83; N, 2.87.

EXAMPLE 2

Preparation of (2R)-2-(acetyloxy)-4-({1-[(2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-N,N,N-trimethyl-4-oxo-1-butanaminium chloride (ST1745)



A solution of 2.39 g (0.01 mol) of acetyl L-carnitine chloride, 2 ml of anhydrous CH_2Cl_2, and 1.1 ml (0.015 mol) of thionyl chloride

was stirred at ambient temperature for 4 hours. The solvent was removed and the residual solid washed three times with anhydrous CH_2Cl_2. An oil was obtained, namely the acyl chloride of acetyl L-carnitine chloride, which was used as such for the next step.

To a solution of 2.58g (0.01 mol) of acyl chloride of acetyl L-carnitine chloride in CH_3CN (5ml) was added 3g (0.01 mol) of 1,1'-methylene-di(2-naphthol) (ST1859). The mixture was stirred at room temperature overnight. After precipitation with ethyl ether a crude product was obtained. This product was washed with diethyl ether, dried under vacuum, and purified by silica-gel chromatography (9:1 CH_2Cl_2 /MeOH mixture). The fractions contained the product, controlled by TLC, were combined. The solvent was removed to give 2 g (0.0038 mol) of (2R)-2-(acetyloxy)-4-({1-[(2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-N,N,N-trimethyl-4-oxo-1-butanaminium chloride (ST1745). Yield = 38%

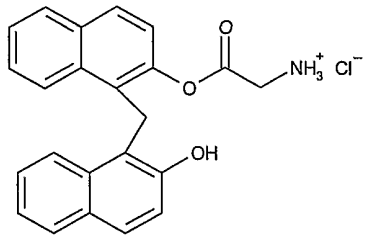
^{1}H NMR (DMSO, 300 MHz), δ 10.05 (s, 1H, -O<u>H</u>), 7.15-8.3 (m, 12H, <u>H</u>-Ar), 5.55 (m, 1H, -C-C<u>H</u>-C-N), 4.65 (s, 2H, Ar-C<u>H$_2$</u>-Ar), 3.6-3.9 (m, 2H, -C<u>H$_2$</u>-N), 3.10 (s, 9H, -N-C<u>H$_3$</u>), 2.95(m, 2H, -C<u>H$_2$</u>-COO-), 2.00 (s, 3H, C<u>H$_3$</u>-COO-)

K.F. =4.4 %

C, H, N values calculated for $C_{30}H_{32}NO_5Cl$ and corrected for the amount of water present: C, 69.02; H, 6.18; N, 2.68; found C, 68.6; H, 6.3; N, 2.61.

EXAMPLE 3

Preparation of 2-({1-[(2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-2-oxoethanaminium chloride (ST1913)



To a solution of 2g (0.011 mol) of N-(tert-butoxycarbonyl)-glycine (BOC-GLY-OH) in 2 ml of toluene was added 0.62 g (0.011 mol) of KOH and 2 ml of H_2O.

The mixture was undergone to azeotropic distillation (150°C) in order to eliminate the water. The obtained solution was cooled at 0°C and 0.85ml of isobutanol, 11 µl (d=0.92, 0.1mmol) of N-methyl-morfolin, and 1.68 ml of isobutyl chloroformiate (d=1.044, 0.0128 mol) was added. The reaction mixture was stirred at 0°C for 2 h.

Subsequently, a solution of 1.65g of 1,1'-methylen-di(2-naphtol) (ST1859) (0.0055 mol) and 0.62 g of KOH in 15ml of H_2O was prepared. Such solution was added to reaction mixture and was stirred at room temperature. After 1h the pH was adjusted to a 3 with HCl 3N and the phases were separated. The organic phase, toluene, was extracted with 20 ml of H_2O adjusted to a pH of 9 with NaOH 3N and washed with H_2O until neutrality. The separated organic phase was dried over Na_2SO_4 and the solvent was removed

to give a crude product. After recrystallization from n-exane/ethyl acetate 8:2 0.2g of product was obtained that were dissolved in 1 ml of trifluoroacetic acid for tert-butoxy-carconyl hydrolisys. After 20 min was obtained the precipitation of a solid which was filtered, and washed with a mixture of n-exane/diethyl ether 8:2. The obtained product was dissolved in methanol and got through a A21/Cl- resin eluating with 100 ml of MeOH to give 60 mg of 2-({ 1- [(2-hydroxy – 1 - naphthyl) methyl]- 2-naphthyl } oxy) – 2 -oxoethanaminium chloride (ST1913).

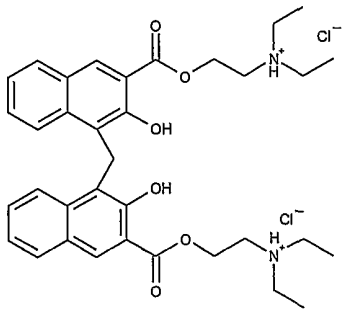
^{1}H NMR (DMSO, 300 MHz), δ 9.6 (s, 1H, -O<u>H</u>), 8.7 (s, 3H, -N<u>H</u>$_3$), 7.2-8.4 (m, 12H, <u>H</u>-Ar), 4.7 (s, 2H, Ar-C<u>H</u>$_2$-Ar), 3.72 (s, 2H, C-C<u>H</u>$_2$-N).

K.F. =1.2 %

C, H, N values calculated for $C_{23}H_{20}NO_3Cl$ and corrected for the amount of water present: C, 70.14; H, 5.12; N, 3.56; found C, 69.1; H, 5.4; N, 3.3.

EXAMPLE 4

Preparation of 2-({4-[(3-{[2-(diethylammonio)ethoxy]carbonyl}-2-hydroxy-1-naphthyl)methyl]-3-hydroxy-2-naphthoyl}oxy)-N,N-diethylethanaminium dichloride (ST1800)



3.88 g (0.01 mol) of pamoic acid (ST1641) was suspended in 4.36 ml of thyonil chloride (0.06 mol) and refluxed at 80°C for 5h. At the end, the solvent was removed under vacuum and the residue was washed with diethyl ether. The acylic chloride obtained was suspended in 30 ml of CH_2Cl_2 and 0.7 ml of N,N-diethyl ethanol was added dropwise. The mixture was stirred at room temperature overnight. At the end a white solid was obtained which was filtered and washed with a mixture of n-exane/ethyl acetate 8:2 to give 0.5 g 2-({4-[(3-{[2-(diethylammonio)ethoxy]carbonyl}-2-hydroxy-1-naphthyl)methyl]-3-hydroxy-2-naphthoyl}oxy)-N,N-diethylethanaminium dichloride (ST1800).

^{1}H NMR ($CDCl_3$, 300 MHz), δ 10.05 (s, 2H, -O<u>H</u>), 7.1-8.4 (m, 10H, <u>H</u>-Ar), 4.85 (s, 2H, Ar-C<u>H$_2$</u>-Ar), 4.55 (t, 4H, -O-C<u>H$_2$</u>-CH$_2$-N), 3.0 (t, 4H, -O-CH$_2$-C<u>H$_2$</u>-N), 2.75 (m, 8H, -N-C<u>H$_2$</u>-CH$_3$), 1.0 (t, 12H, -N-CH$_2$-C<u>H$_3$</u>).

K.F. =0.8 % C, H, N values calculated for $C_{35}H_{44}N_2O_6Cl_2$ and corrected for the amount of water present: C, 63.72; H, 6.72; N, 4.24; found C, 63.5; H, 5.87; N, 4.6.

<u>EXAMPLE 5</u>

<u>Evaluation of antiaggregant effects of sodium pamoate (ST1641) on β-amyloid $_{25-35}$ peptide</u>

To 250 µl of a solution consisting of sodium pamoate 2 mM and phosphate buffer 200 mM pH 5 were added 250 µl of an aqueous solution of βA_{25-35} 2mM (cat. Bachem n° H-1192.0001). 500

µl of a solution of sodium pamoate 1 mM, βA_{25-35} 1 mM and phosphate buffer 100 mM pH 5 were thus obtained.

The same process was carried out for the control sample where sodium pamoate was not present.

After 24 hours at ambient temperature, the sample and control were centrifuged at 12000 rpm for 20 minutes, separating the settled solids from the supernatants. To the settled solids were added 250 µL of water. After 3 hours at ambient temperature the samples were centrifuged again at a 12000 rpm for 20 minutes. After centrifuging, no presence of any solid was observed in the sample, unlike the control. This result demonstrated the complete inhibition of aggregation of βA_{25-35} peptide in fibrils by sodium pamoate.

EXAMPLE 6

Evaluation of antiaggregant effects of sodium pamoate (ST1641) on β–amyloid $_{1-42}$ peptide

The antiaggregant effects of sodium pamoate on βA_{1-42} peptide were evaluated by measuring thioflavin T binding according to the following procedure.

βA_{1-42} peptide (cat. Bachem n°H-1368.0500) at a concentration of 0.22 mM was incubated at 37°C in Tris buffer 100 mM pH 7.4, alone or in the presence of sodium pamoate, for 5 days. The molar ratios of the peptide to sodium pamoate were generally 1:8, 1:4 and 1:2.

The solution was centrifuged at 13000 rpm for 5 minutes and the supernatant was eliminated. The precipitate was washed with 500 µl of H_2O and centrifuged at 13000 rpm for 5 minutes. In the precipitate, the aggregate in fibril form was detected with 600 µl of thioflavin T (ThT) 2 µM dissolved in glycine-NaOH buffer 50 mM, pH 9.4. After 5 minutes' incubation 500 µl of samples were transferred to a quartz cuvette and the fluorimetric signal was determined at 420 nm excitation and 480 nm emission in a spectrophotofluorimeter. In these conditions the fluorimetric signal is proportional to the amount of amyloid aggregate (Le Vine, Methods in Enzymology, vol.309 pp 274-284).

Sodium pamoate, in this experiment, proved capable of producing a consistent and dose-dependent reduction in the formation of βA_{1-42} aggregates in the form of fibrils. The effect is significant and the reduction reaches as much as 70% as compared to controls.

The inhibition of fibril formation was also measured as a function of incubation time. On going from 1 to 5 days' incubation, sodium pamoate showed a progressive increase in efficacy in reducing thioflavin T binding.

EXAMPLE 7

Evaluation of antiaggregant effects of ST compounds on β–amyloid $_{1-42}$ peptide

The ST1641, ST1722, ST1859, ST1745, ST1800, ST1913 capability to counteract βA_{1-42} polimerization was evaluated using the Thioflavina "T" binding assay with the following procedure (M.A. Findeis, S.M. Molineaux; Mehods in Enzymology 309, 487-488 (1999)): βA_{1-42} peptide (1mg/ml) was dissolved in H_2O/CH_3CN (1:1), lyophilized, solubilized in DMSO + PBS and incubated at 37°C for 8 days. The peptide was then sonicated and dissolved in PBS (1:5). 96 well plates were prepared with a solution of βA_{1-42} (40µl/well) and ST testing compounds (50µl/well, at concentrations between 0.8 and 100µM). 50µl of not aggregated βA_{1-42} was added after 15 minutes to each well and the plates were incubated overnight at 37°C with agitation. 200µl of a reaction mixture containing Thioflavina "T" (10µM) and Na_2HPO_4 x $2H_2O$ (50µM) solution (pH 6.5) was then added to each well. The fluorescence was measured at 450nm of excitation and 482nm of emission with a 96 well fluorimetric plate reader within 60 seconds. At this experimental conditions fluorimetric measures were related to the amount of βA_{1-42} polimerized peptide.

Table 1 shows the DE_{50} values of ST tested compounds.

TABLE 1

Compound	DE_{50} (µM)
ST1641	38.2
ST1745	90.3
ST1859	5.4
ST1745	8.0
ST1800	>50
ST1913	7.8

EXAMPLE 8

Dissolution of aggregates of preformed β-amyloid $_{1-42}$ in fibril form by sodium pamoate (ST1641)

This experiment was conducted in order to assess the antiaggregant capacity of sodium pamoate on previously aggregated βA_{1-42} peptide, according to the following procedure.

βA_{1-42} peptide was left to agggregate for 48 hours at 37°C in the conditions described in Example 6. Sodium pamoate was added (peptide:pamoate ratio 1:8).

In these conditions, sodium pamoate proved extremely active in reducing thioflavin T binding.

Incubation with sodium pamoate led to a 70% reduction in fluorescence as compared to controls not incubated with sodium pamoate.

This result demonstrates that sodium pamoate was capable of exerting an antiaggregant effect a posteriori on the fibrillar structure of βA_{1-42}.

EXAMPLE 9

Reduction of resistance of β-amyloid$_{1-42}$ peptide to trypsin digestion induced by sodium pamoate (ST1641)

βA_{1-42} peptide was dissolved with 15 µl of NaOH 0.1 M. The solution was brought to pH 7.4 with 15 µl of TRIS buffer 100 mM to which were added 30 µl of buffer alone or 30 µl of buffer solution containing sodium pamoate. The final concentration of βA_{1-42} peptide

was 0.22 mM, and that of sodium pamoate ranged from 0.055 to 1.76 mM, thus with a βA_{1-42} peptide:sodium pamoate ratio ranging from 4:1 to 1:8.

The samples thus prepared were incubated at 37°C for 5 days; in these conditions βA_{1-42} peptide formed aggregates in the form of fibrils modifying its structure from random-coil to β-sheet (Zagorski M.G. et al. 1999 "Methodological and Chemical Factors Affecting Amyloid β Peptide Amyloidogenicity" Methods in Enzymology 309:189-204). After 5 days' incubation, 24 μg of trypsin (Merck) were added to each sample, stirred and centrifuged for 1 minute at 13000 rpm; the samples were then left to incubate at 37°C for 1 hour.

When this period had elapsed, the mixture was centrifuged for 5 minutes at 13000 rpm, eliminating 50 μl of supernatant, and the precipitate was dissolved with 40 μl of HCOOH and 10 μl of H_2O containing 0.1% of trifluoroacetic acid (TFA).

At this point the sample was ready for quantitative HPLC analysis. The HPLC profile of the sample incubated with sodium pamoate was compared with that obtained with peptide alone, thereby quantifying the βA_{1-42} peptide.

Trypsin, in the conditions described above, was capable of hydrolysing from 30 to 50% of the βA_{1-42} peptide. The trypsin hydrolysis of βA_{1-42} was increased by sodium pamoate by more than 50% at the highest dose (peptide:pamoate ratio 1:8) amd by more than 40% at the lowest dose (1:4).

EXAMPLE 10

Sodium pamoate (ST1641) inhibition of neurotoxicity induced by β-amyloid$_{25-35}$

To verify the potential neuroprotective activity of sodium pamoate, primary cortical neuronal cultures obtained by microdissection of rat foetal brain at day 16-18 of gestation were used. The cerebral tissue was cultivated in the presence of foetal calf serum and the glial proliferation was inhibited by adding to the incubation medium the antimitotic agent cytosine arabinoside on days 3 and 5 (Andreoni et al. 1997 Exp. Neurology 148:281-287). The cell cultures were exposed to βA_{25-35} peptide for 5-7 days in the presence or absence of sodium pamoate. The neuroprotective action was evaluated in conditions of neurotoxicity induced by kainic acid to verify the specificity of action of sodium pamoate and its effective antiaggregant activity against the neurotoxic agent. The ability of sodium pamoate to protect the cells against degeneration was also evaluated in neuronal cells cultured in the absence of foetal calf serum in the culture medium. In this case, 24 hours after seeding, the medium was replaced with one without serum containing glutamine, insulin, transferrin, putrescin, progesterone, sodium selenite and Hepes.

Experimental procedure

Primary cultures of neurons of the cerebellar cortex were taken from the rat foetal brain on days 16-18 of gestation and cultured in

foetal calf serum. On incubation days 3 and 5, glial proliferation was inhibited using cyctosine arabinoside as an antimitotic agent.

The cultures were exposed to βA_{25-35} peptide at concentrations of 25 and 50 μM from the day following seeding for 5 to 7 days.

βA_{25-35} peptide was added to the cultures together with sodium pamoate which had equimolar concentrations or concentrations lower than those of the peptide itself.

The protection against neurotoxicity was evaluated using the colorimetric method and densitometric analysis with an image analyser.

The results obtained show that sodium pamoate was capable of affording complete protection against the toxicity induced by βA_{25-35}. The results obtained are given in the Table 2.

TABLE 2

Control	βA_{25-35} 50 μM	Sodium pamoate 25 μM	Sodium pamoate 25 μM + βA_{25-35} 50 μM
% S	% S	% S	% S
100	16	88	100

% S: percentage survival

EXAMPLE 11

Sodium pamoate (ST1641) reduction of apoptosis of cerebellar granules induced by K^+ deprivation

Granules isolated from cerebellum of 8-day-old rats are differentiated biochemically and morphologically in approximately one week, becoming morphologically mature and with a glutamatergic interneuron phenotype (Gallo et al. 1982 PNAS 79:7919-7923). On depriving the culture medium of serum and reducing the extracellular concentration of potassium ions (25 mM) to the extent of bringing it down to a non-depolarising condition (5 mM), cell death by apoptosis is obtained in approximately 24 hours.

Programmed neuronal death is a phenomenon observed not only in numerous physiological processes but also in many neurodegenerative diseases such as AD, Parkinson's disease, Huntington's chorea and amyotrophic lateral sclerosis. In the case of AD, the existence of a close relationship is detected between apoptosis and the presence of βA mutation of the presenile 2 (PS2) gene which regulates the production of amyloid itself. In fact, in cases of AD in which a PS2 mutation is present, a classic increase in cerebral and plasma βA_{1-42} is also detectable (Scheuner D., Eckman C., Jensen M., Song X., Citron M., Suzuki N., Bird T.D., Hardy J., Hutton M., Kukull W., Laeson E., Levy-Lahad E., Viitanen M., Peskind E., Selkoe D., Yunkin S. (1996) Nat. Med. 2, 864-870.); moreover, the mutated form of the PS2 gene, expressed in PC12, causes apoptosis (Wolozin B., Iwasaki K., D'Adamio L. (1996) Science 274, 1710-1713).

This experimental model made it possible to obtain a "self-fuelling" βA production system where neuronal apoptosis of the cerebellar granules brought about changes in the processing of the amyloid precursor APP, of such a nature as to favour the course of amyloidogenic metabolism. The increase in βA levels, in turn, favours programmed cell death. In this experimental setting, the potential efficacy of the study substances was measured in terms of cell survival at given times (24, 48 and 72 hours) after the reduction of KCl in the medium.

Experimental procedure

In primary cultures of cerebellar granules of 8-day-old rats, maintained in a culture medium containing KCl 25 mM, the cells were labelled with ^{35}S-methionine after 6 days in culture.

Apoptosis was induced by deprivation of the serum and reduction of the KCl concentration from 25 mM to 5 mM.

This situation represented the neuronal deafferentation condition *in vitro* or resection of the dendritic and axonal branches entering and exiting the nerve tissue cells.

As a result of the apoptosis there was an overproduction of βA.

The cultures were incubated with sodium pamoate at concentrations ranging from 1 μM to 100 μM.

The protection against toxicity was assessed in terms of cell viability at 24, 48 and 72 hours.

Results

The results obtained in this experiment showed that sodium pamoate, at a concentration of 10 μM, has a protective effect (89% protection) against the damage induced by amyloid forming during the apoptotoic process.

EXAMPLE 12

ST1859 capability to cross "in vivo" the blood brain barrier

Post-mortem examination of AD brain sections reveals the presence of abundant extracellular senile plaques composed of fibrillar amyloid aggregates. The relationship between the presence of beta amyloid peptide and the severity of the illness suggests that the inibition of peptide fibril formation may be a potential tool for the therapy of this illness. ST1859 inhibited "in vitro" the beta amyloid aggregation and to test its permeability through the intact blood-brain barrier, ST1859, labelled with ^{14}C (S.A. 50μCi/mM), was injected i.v. into normal rats at the dose of 18μCi/rat. The brain and blood were up-taken 30' after the injection, the blood was then centrifuged (3000RPM x 15 min) and serum obtained was diluted 1:20 with water while brain tissue was homogenized 1:20 w/v in water. To each sample was then added 4 ml of scintillation liquid for aqueous samples The amount of radioactivity was counted with an automatic β-counter (Packard 4600). Data reported in DPM (table 1) were normalized vs. weight or volume of each sample. Results

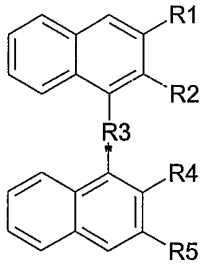
obtained in this experiment showed that ST1859 is able to cross the blood brain barrier with a rate serum/brain <1 (table 3).

TABLE 3

	Serum (DPM/ml)	**Brain (DPM/g)**	**Serum/Brain**
Mean	29.776	35.643	0.833
S.E.	±1253	±1349	±0.042

CLAIMS

1. Compound with general formula (I)



(I)

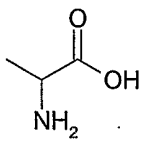
in which:

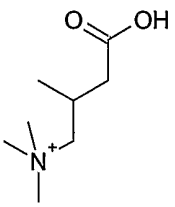
R1 and R5, which may be the same or different, are COOR6, CONHR6, SO_2R6, SO_2NHR6, SO_3R6, OR6, COR6, NHR6, R6;

in which R6 is H or a straight or branched, saturated or unsaturated alkyl chain, with from 1 to 5 carbon atoms, or phenyl, substituted by R7;

in which:

R7 is OH, COOH, SO_3H, NR8R9,

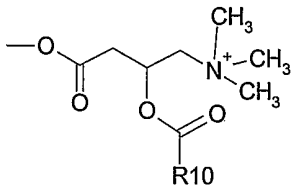


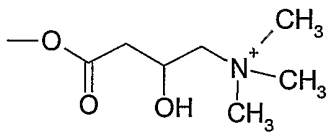


in which:

R8 and R9, which may be the same or different, are H, alkyl with 1 to 5 carbon atoms;

R2 and R4, which may be the same or different, are H, OH, NHR6, OCO-R10-NR8R9,





in which R10 is a straight or branched, saturated or unsaturated alkyl chain with from 1 to 5 carbon atoms;

R3 is -[CH_2]n-, -CH_2-O-, -CH(R11)-,

in which n is an integer from 1 to 4, R11 is a straight or branched alkyl with from 1 to 5 carbon atoms, substituted by an amino group, alkylamino C_1-C_5, dialkylamino C_1-C_5, OH, alkyloxy C_1-C_5; and its pharmaceutically acceptable salts;

with the proviso that the substituents R1, R2, R3, R4 and R5 are not:

1 R1 = R5 = -$COOCH_2C_6H_5$

R2 = R4 = -OH

R3 = -CH_2-

2 R1 = R5 = -$COOCH(CH_3)_2$

R2 = R4 = -OH

R3 = -CH_2-

3 R1 = R5 = -$COOC_2H_5$

R2 = R4 = -OH

R3 = -CH_2-

4 R1 = R5 = -$COOC_6H_{11}$

R2 = R4 = -OH

R3 = -CH_2-

5 R1 = R5 = -$COOCH_3$

R2 = R4 = -OH

R3 = -CH_2-

6 R1 = R5 = -$COOC(CH_3)_3$

R2 = R4 = -OH

R3 = -CH_2-

7 R1 = R5 = -$CONHC_6H_5$

R2 = R4 = -OH

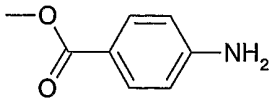
R3 = -CH_2-

11 R1 = R5 = -H

R2 = R4 = -$OCOC_6H_5$

R3 = -CH_2-

12 R1 = R5 = -H

R2 = R4 = 

R3 = -CH_2-

13 R1 = R5 = -H

R2 = R4 = -OCOCH=CH_2

R3 = -CH_2-;

14 R1 = R5 = -H

R2 = R4 = -OH

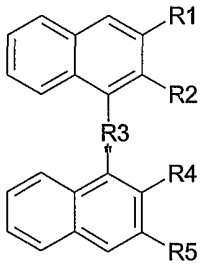
R3 = $-CH_2-$

15 R1 = R5 = -COOH

R2 = R4 = -OH

R3 = $-CH_2-$.

2. (2R)-2-(acetyloxy)-4-({3-carboxy-1-[(3-carboxy-2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-N,N,N-trimethyl-4-oxo-1-butanaminium chloride.
3. (2R)-2-(acetyloxy)-4-({1-[(2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-N,N,N-trimethyl-4-oxo-1-butanaminium chloride.
4. 2-({1-[(2-hydroxy-1-naphthyl)methyl]-2-naphthyl}oxy)-2-oxoethanaminium chloride.
5. 2-({4-[(3-{[2-(diethylammonio)ethoxy]carbonyl}-2-hydroxy-1-naphthyl)methyl]-3-hydroxy-2-naphthoyl}oxy)-N,N-diethylethanaminium dichloride.
6. Compound according to claim 1-5, for use as a medicament.
7. Process for the preparation of compounds with general formula (I)



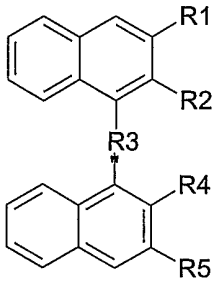
(I)

R1 and R5 are -COOR6,

in which R2, R3, R4 and R5 have the meanings defined in claim 1,

characterised in that a general formula (I) compound in which R6 is H, is treated with a halogenating agent to yield the corresponding acyl chloride, which is then reacted under stirring with an R6-OH alcohol in a molar ratio of 1 to 6, or in an inert anhydrous solvent with the stoichiometric amount of R6-OH.

8. Process for the prepartion of formula (I) compounds



(I)

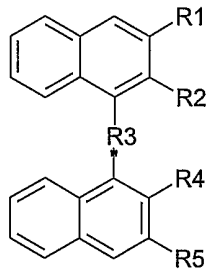
in which R1 and R5 are CONHR6;

in which R2, R3, R4 and R6 have the meanings defined in claim 1,

characterised in that a compound with general formula (I), in which R6 is H, is treated with a halogenating agent to yield the corresponding acyl chloride, or with a coupling agent, and reacted under stirring with an R6-NH_2 amine in a molar ratio of

6 to 1, or in an inert anhydrous solvent with the stoichiometric amount of R6-NH_2.

9 Process for the preparation of formula (I) compounds



(I)

in which R2 and R4 are OH;

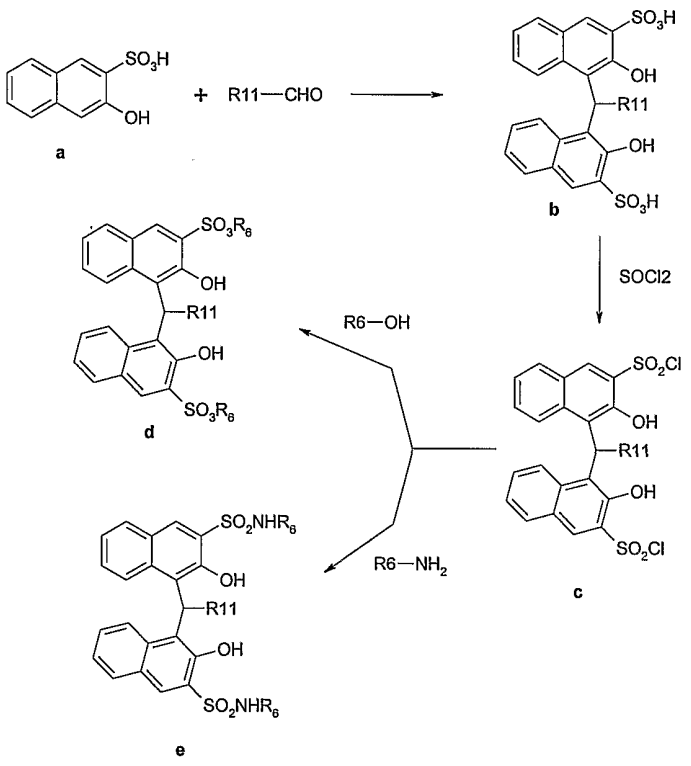
in which R1 and R5 are SO_3R6, SO_2NHR6;

R3 is -CH(R11)-,

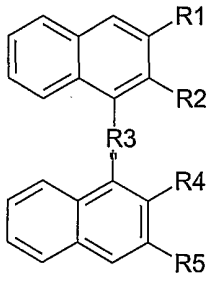
in which R6 and R11 have the meanings indicated in claim 1;

characterised in that said process is carried out according to reaction scheme 1 below, where a formula "a" compound is reacted with an R11-CHO aldehyde in glacial acetic acid at a temperature ranging from 90°C to 150°C to yield compounds with general formula "b", subsequently, a general formula "b" compound is treated with a halogenating agent to yield the corresponding sulphonyl chloride, and reacted with R6-OH alcohol to yield compounds with general formula "d" or with an R6-NH_2 amine to yield compounds with general formula "e";

SCHEME 1



8. Process for the preparation of formula (I) compounds



(I)

in which R1, R2, R4 and R5 are OR6 and/or NHR6 ;

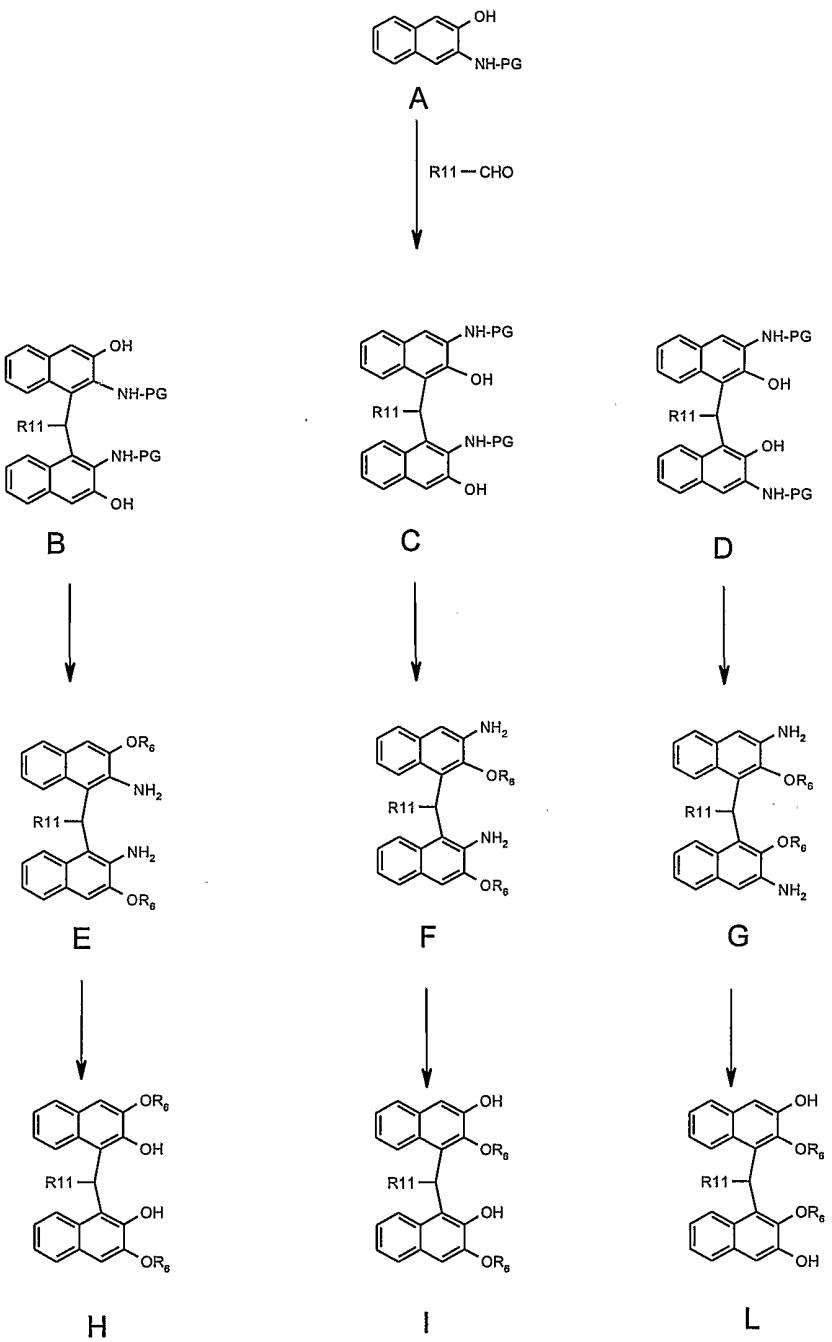
R3 is -CH(R11)-,

in which R6 and R11 have the meanings defined in claim 1; characterised in that said process is carried out according to

reaction scheme 2 below, where a formula A compound is reacted with R11-CHO aldehyde in an acid milieu to yield a mixture of compounds corresponding to the structures B, C and D which are separated, and purified; these compounds are reacted with an R6-X alkyl halide in the presence of a base and then deprotected in an acid milieu to yield the corresponding naphthyl ethers E, F, G; after treatment of the latter with $NaNO_2$ in sulphuric acid, compounds H, I and L are obtained;

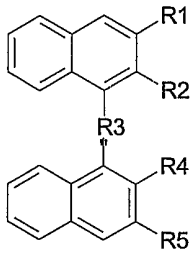
SCHEME 2

PG = protective group



9. Pharmaceutical composition containing as its active ingredient a compound according to claim 1-5 and at least one pharmaceutically acceptable excipient and/or diluent.

10. Use of pamoic acid or one of its derivatives or one of the pharmaceutically acceptable salts of these with general formula (I)



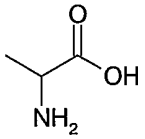
(I)

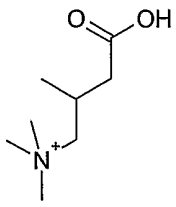
in which:

R1 and R5, which may be the same or different, are COOR6, CONHR6, SO_2R6, SO_2NHR6, SO_3R6, OR6, COR6, NHR6, R6;

in which R6 is H or a straight or branched, saturated or unsaturated alkyl chain with from 1 to 5 carbon atoms, or phenyl, substituted by R7;

in which: R7 is OH, COOH, SO_3H, NR8R9,

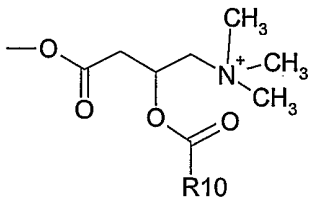


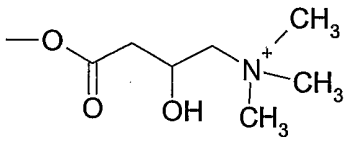


in which:

R8 and R9, which may be the same or different, are H, alkyl with from 1 to 5 carbon atoms;

R2 and R4, which may be the same or different, are H, OH, NHR6, OCO-R10-NR8R9,





in which R10 is a straight or branched, saturated or unsaturated alkyl chain with from 1 to 5 carbon atoms;

R3 is -[CH_2]n-, -CH_2-O-, -CH(R11)-,

in which n is an integer from 1 to 4,

R11 is a straight or branched alkyl with from 1 to 5 carbon atoms, substituted by an amino group, alkylamino C_1-C_5, dialkylamino C_1-C_5, OH, alkyloxy C_1-C_5;

for the preparation of a medicament for the treatment of diseases characterised by deposits of amyloid aggregates.

11. Use according to claim 12, in which the disease characterised by deposits of amyloid aggregates is selected from the group consisting of Alzheimer's disease, Down's syndrome, hereditary cerebral haemorrhage associated with Dutch-type amyloidosis, amyloidosis associated with chronic inflammation, amyloidosis associated with multiple myeloma and other dyscrasias of the

haematic B lymphoid cells, amyloidosis associated with type-II diabetes, and amyloidosis associated with prion disease, kuru or ovine scrapie.

12. Use according to claim 13, in which the amyloidosis associated with prion disease is selected from the group consisting of Creutzfeldt-Jakob disease and Gerstmann-Straussler syndrome.

13. Use according to claims 12-14, in which the compound is pamoic acid sodium salt.

14. Diagnostic kit, containing at least one compound as described in claim 12, for the diagnosis of diseases characterised by deposits of amyloid aggregates.

15. Kit according to claim 16 in which at least one of the elements, carbon, hydrogen, nitrogen, or oxygen, of said compound is substituted by a corresponding radioactive isotope.

16. Kit according to claim 16, in which said compound carries at least one atom of radioactive iodine.

17. Kit according to claim 16, in which said compound, whether or not it carries an isotope as per claims 17-18, is in the form of a complex with one radioactive isotope of a metal.

18. Kit according to claim 19 in which said metal is selected from the group consisting of indium, gadolinium, and technetium.

19. Use of the kit according to claims 16-20 for diagnosis by means of a diagnostic imaging technique.

20. Use according to claim 21, in which said diagnostic imaging technique is selected from the group consisting of PET, SPECT, NMR, and scintigraphy techniques.

21. Use according to claim 22, in which the scintigraphy technique is planar scintigraphy.

22. Compound as described in claim 12, in which at least one of the elements carbon, hydrogen, nitrogen, or oxygen is substituted by a corresponding radioactive isotope.

23. Compound as described in claim 12, carrying at least one atom of radioactive iodine.

24. Compound as described in claim 12, whether or not it carries a radioactive isotope as per claims 24-25, complexed with elements used in diagnostic imaging.

25. Compound according to claim 26, in which the complexed element is selected from the group consisting of indium, gadolinium and technetium.

INTERNATIONAL SEARCH REPORT

I onal Application No
PCT/IT 01/00313

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C229/22 C07C229/08 C07C219/14 C07C65/11 A61P25/28
A61K51/04 A61K49/00 A61K31/19 A61K31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 998 946 A (LEUVEN K U RES & DEV) 10 May 2000 (2000-05-10) page 2, line 52 -page 3, line 4 page 27, left-hand column, line 20 - line 45; claims 20,23	24-27
A	the whole document	16-23

A	WO 00 01662 A (SCAFETTA NAZARENO ;TINTI MARIA ORNELLA (IT); SANTANIELLO MOSE (IT)) 13 January 2000 (2000-01-13) claim 1	2-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2001	06/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bedel, C

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INTERNATIONAL SEARCH REPORT

onal Application No
PCT/IT 01/00313

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	FINDEIS M A: "BETA-AMYLOID AGGREGATION INHIBITORS" CURRENT OPINION IN CPNS INVESTIGATIONAL DRUGS, PHARMA PRESS, LONDON,, GB, vol. 1, no. 3, 1999, pages 333-339, XP000933869 ISSN: 1464-844X page 334; figure 1 ---	2-6, 11-15
A,P	WO 01 28546 A (FELICE FERNANDA GUARINO DE ;FERREIRA LOUZADA PAULO ROBERTO (BR); T) 26 April 2001 (2001-04-26) page 14; table 1 claims ---	2-6, 11-15
A	WO 94 01116 A (US HEALTH) 20 January 1994 (1994-01-20) page 2, line 17 - line 22; claims -----	2-6, 11-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

	ional Application No
	PCT/IT 01/00313

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WO 0128546 A	26-04-2001	BR 9904931 A	12-06-2001
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		WO 9401116 A1	20-01-1994