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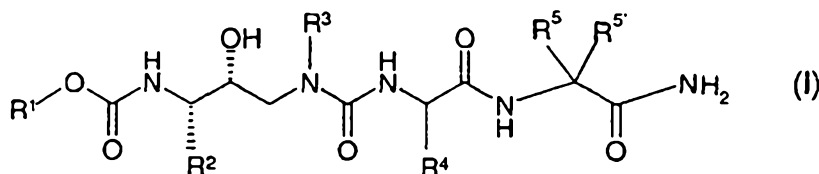
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(54) Title: GAMMA-SECRETASE INHIBITORS



(57) Abstract: Novel urea derivatives of formula (I) are disclosed: The compounds are inhibitors of γ -secretase, and hence useful in the treatment or prevention of Alzheimer's disease.

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GAMMA-SECRETASE INHIBITORS

The present invention relates to compounds, their salts,
pharmaceutical compositions comprising them, processes for making them
5 and their use in treating Alzheimer's Disease.

Alzheimer's Disease (AD) is characterised by the abnormal
deposition of amyloid in the brain in the form of extra-cellular plaques and
intra-cellular neurofibrillary tangles. The rate of amyloid accumulation is
a combination of the rates of formation, aggregation and egress from the
10 brain. It is generally accepted that the main constituent of amyloid
plaques is the 4kD amyloid protein (β A4, also referred to as A β , β -protein
and β AP) which is a proteolytic product of a precursor protein of much
larger size. The ragged NH₂- and COOH-termini of the native A β amyloid
indicates that a complex mechanism of proteolysis is involved in its
15 biogenesis.

The amyloid precursor protein (APP or A β PP) has a receptor-like
structure with a large ectodomain, a membrane spanning region and a
short cytoplasmic tail. Different isoforms of APP result from the
alternative splicing of three exons in a single gene and have 695, 751 and
20 770 amino acids respectively.

The A β domain encompasses parts of both extra-cellular and
transmembrane domains of APP, thus its release implies the existence of
two distinct proteolytic events to generate its NH₂- and COOH-termini. At
least two secretory mechanisms exist which release APP from the
25 membrane and generate the soluble, COOH-truncated forms of APP
(APP_s). Proteases which release APP and its fragments from the
membrane are termed "secretases". Most APP_s is released by a putative α -
secretase which cleaves within the A β domain (between residues Lys¹⁶ and
Leu¹⁷) to release α -APP_s and precludes the release of intact A β . A minor
30 portion of APP_s is released by a β -secretase, which cleaves near the NH₂-

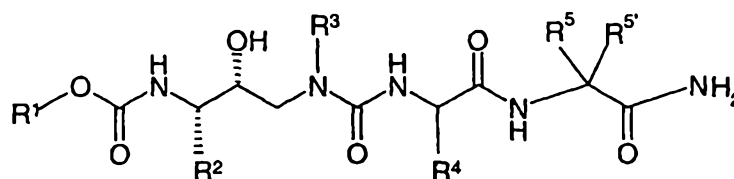
terminus of A β and produces COOH-terminal fragments (CTFs) which contain the whole A β domain. Finding these fragments in the extracellular compartment suggests that another proteolytic activity (γ -secretase) exists under normal conditions which can generate the COOH-terminus of A β .

It is believed that γ -secretase itself depends for its activity on the presence of presenilin-1. In a manner that is not fully understood presenilin-1 appears to undergo autocleavage.

The compounds of the present invention are useful for treating AD by inhibiting the activity of the putative γ -secretase thus preventing the formation of insoluble A β and arresting the production of A β . Further, some of the present compounds also stabilise full-length presenilin-1.

In a further aspect some of the compounds of the present application are useful as inhibitors of presenilin-1 cleavage.

The present invention accordingly provides a compound of formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R¹ is (1) C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₁₀alkynyl optionally substituted with one to three substituents independently chosen from:

- (i) hydroxy;
- (ii) carboxy;
- (iii) halogen;
- (iv) C₁₋₄alkoxy;
- (v) C₁₋₄alkoxycarbonyl;

- (vi) $-NR^6R^7$ wherein R^6 and R^7 are independently chosen from hydrogen, C_{1-5} alkyl and C_{1-5} alkoxy C_{1-5} alkyl;
- (vii) $-CONR^6R^7$ or $OCOR^6R^7$ wherein R^6 and R^7 are independently as defined above;
- 5 (viii) $-N(R^8)QR^9$ wherein:
Q is C(O), C(S), SO_2 or C(NH);
 R^8 is hydrogen or C_{1-4} alkyl; and
 R^9 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino
di(C_{1-4} alkyl)amino wherein each alkyl group is independently
10 chosen;
- (ix) C_{3-7} cycloalkyl;
- (x) phenyl or naphthyl; a five-membered heterocyclic ring
containing 1, 2, 3 or 4 heteroatoms independently chosen
from O, N and S, at most one of the heteroatoms being O or S;
15 a six-membered heterocyclic ring containing 1, 2 or 3 nitrogen
atoms; each of which is optionally substituted by one to three
groups independently chosen from:
- (a) halogen, cyano and nitro,
- (b) hydroxy,
- 20 (c) C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl,
- (d) C_{1-4} alkoxy,
- (e) NR^6R^7 wherein R^6 and R^7 are independently as defined
above,
- (f) CO_2R^8 wherein R^8 is independently as defined above,
- 25 (g) $-CONR^6R^7$ or $OCOR^6R^7$ wherein R^6 and R^7 are
independently as defined above,
- (h) $SO_2NR^6R^7$ wherein R^6 and R^7 are independently as
defined above,
- (i) $CH_2NR^6R^7$ wherein R^6 and R^7 are independently as
30 defined above,

- (j) $N(R^8)COR^{8'}$ wherein R^8 is independently as defined above and $R^{8'}$ is independently as defined for R^8 , and
- (k) $NR^8SO_2R^{8'}$ wherein R^8 and $R^{8'}$ are independently as defined above; or
- 5 (2) phenyl or naphthyl; a five-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N and S, at most one of the heteroatoms being O or S; a six-membered heterocyclic ring containing 1, 2 or 3 nitrogen atoms; each of which is optionally substituted by one to three groups independently
- 10 chosen from:
- (a) halogen, cyano and nitro,
- (b) hydroxy,
- (c) C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl,
- (d) C_{1-4} alkoxy,
- 15 (e) NR^6R^7 wherein R^6 and R^7 are independently as defined above,
- (f) CO_2R^8 wherein R^8 is independently as defined above,
- (g) $CONR^6R^7$ or ONR^6R^7 wherein R^6 and R^7 are independently as defined above,
- 20 (h) $SO_2NR^6R^7$ wherein R^6 and R^7 are independently as defined above,
- (i) $CH_2NR^6R^7$ wherein R^6 and R^7 are independently as defined above,
- (j) $N(R^8)COR^{8'}$ wherein R^8 and $R^{8'}$ are independently as
- 25 defined above, and
- (k) $NR^8SO_2R^{8'}$ wherein R^8 and $R^{8'}$ are independently as defined above;

R^2 and R^3 are independently chosen from C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} alkenyl, C_{2-10} alkenyloxy, C_{2-10} alkynyl or C_{2-10} alkynyloxy; phenyl;

30 naphthyl; a five-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N and S, at most one of the

heteroatoms being O or S; a six-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; and a group $(CH_2)_pQ^1$ wherein Q^1 is phenyl, naphthyl, a five-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N and S, at most one of the
 5 heteroatoms being O or S, and a six-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; and wherein each of R^2 and R^3 is independently optionally substituted by one to three groups independently chosen from:

- (a) halogen, cyano and nitro,
- 10 (b) hydroxy,
- (c) C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl,
- (d) C_{1-6} alkoxy and phenoxy each of which is optionally substituted by one to three halogen atoms,
- (e) NR^6R^7 wherein R^6 and R^7 are independently as defined
 15 above,
- (f) CO_2R^8 wherein R^8 is independently as defined above,
- (g) $CONR^6R^7$ or ONR^6R^7 wherein R^6 and R^7 are independently as defined above,
- (h) $SO_2NR^6R^7$ wherein R^6 and R^7 are independently as
 20 defined above,
- (i) $CH_2NR^6R^7$ wherein R^6 and R^7 are independently as defined above,
- (j) $N(R^8)COR^8$ wherein R^8 and R^8 are independently as defined above,
- 25 (k) $NR^8SO_2R^8$ where R^8 and R^8 are independently as defined above;

alternatively R^3 may be hydrogen;

R^4 and R^5 are independently chosen from hydrogen, C_{1-6} alkyl optionally substituted by halogen, hydroxy, thiol, amino, C_{1-4} alkoxy, C_{1-4} alkylthio, carboxy, C_{1-4} alkoxycarbonyl and $(CH_2)_qQ^2$ wherein Q^2 is a five-
 30 membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatom

optionally chosen from O, N, and S providing that not more than one heteroatom is O or S, a six-membered unsaturated heterocycle containing 1, 2 or 3 N atoms, phenyl, naphthyl or a fused ring which is indolyl, each of the foregoing rings being optionally substituted with one to three groups
 5 independently chosen from hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, thiol, C₁₋₄alkylthio, halogen, amino, carboxy, amido, CO₂H and -NHC(NH₂)₂; and

R^{5'} is a hydrogen atom;

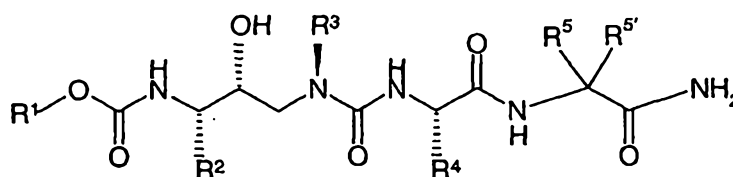
alternatively R⁵ and R^{5'} together represent an oxo group;

10 p is zero, one, two or three; and

q is zero, one, two or three;

with the proviso that no carbon atom is substituted by more than one hydroxy group.

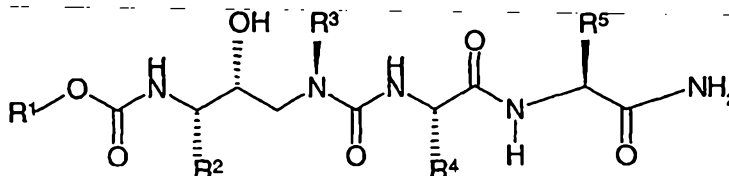
In one embodiment the compounds of the present invention are of
 15 formula I':



(I')

20 where R¹, R², R³, R⁴ and R⁵ are as defined above.

In another embodiment there are provided compounds of formula I'':



(I'')

25

where R^1 , R^2 , R^3 , R^4 and R^5 are as defined above.

The following preferred definitions of substituents apply to each of the formulae I, I' and I'' which refer to those substituents.

Preferably R^1 is

5 (1) C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl optionally substituted with one to three substituents independently chosen from:

- (i) hydroxy;
- (ii) halogen;
- (iii) amino;
- 10 (iv) C_{1-4} alkoxy; and
- (v) phenyl which is optionally substituted by one or two groups independently chosen from:

- (a) halogen, cyano and nitro,
- (b) hydroxy,
- 15 (c) C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl,
- (d) C_{1-4} alkoxy and
- (e) amino; or

(2) phenyl which is optionally substituted by one or two groups independently chosen from:

- 20 (a) halogen, cyano and nitro,
- (b) hydroxy,
- (c) C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl,
- (d) C_{1-4} alkoxy and
- (e) amino.

25 Most preferably R^1 is C_{1-6} alkyl or benzyl optionally substituted by one or two groups chosen from halogen, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy and amino.

R^1 may be unsubstituted benzyl or unsubstituted C_{1-6} alkyl such as t-butyl.

When R^1 is a heterocyclic ring it may be saturated, partially saturated or unsaturated. Preferably the heterocyclic ring is a heteroaromatic ring.

R^2 and R^3 may be independently chosen from phenyl; naphthyl; a
5 five-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N and S, at most one of the heteroatoms being O or S; a six-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; and a group $(CH_2)_pQ^1$ wherein Q^1 is phenyl; naphthyl; a
10 five-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N and S, at most one of the heteroatoms being O or S; and a six-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; and wherein each of R^2 and R^3 is independently optionally substituted by one to three groups independently chosen from:

- (a) halogen, cyano and nitro,
- 15 (b) hydroxy,
- (c) C_{1-4} alkyl, C_{2-4} alkenyl and C_{2-4} alkynyl,
- (d) C_{1-6} alkoxy and phenoxy each of which is optionally substituted by one to three halogen atoms,
- (e) NR^6R^7 wherein R^6 and R^7 are independently as defined
20 above,
- (f) CO_2R^8 wherein R^8 is independently as defined above,
- (g) $CONR^6R^7$ wherein R^6 and R^7 are independently as defined above,
- (h) $SO_2NR^6R^7$ wherein R^6 and R^7 are independently as
25 defined above,
- (i) $CH_2NR^6R^7$ wherein R^6 and R^7 are independently as defined above,
- (j) $N(R^8)COR^8$ wherein R^8 and R^8 are independently as defined above,
- 30 (k) $NR^8SO_2R^8$ where R^8 and R^8 are independently as defined above.

More preferably R^2 and R^3 are $(CH_2)_pQ^1$.

Preferably Q^1 is phenyl, pyridyl or furyl optionally substituted by one or two groups independently chosen from:

- (a) halogen, cyano and nitro,
- 5 (b) hydroxy,
- (c) C_{1-3} alkyl, C_{2-3} alkenyl and C_{2-3} alkynyl,
- (d) C_{1-3} alkoxy and phenoxy each of which is optionally substituted by up to three halogen atoms,
- (e) amino.

10 Particularly Q^1 is phenyl, pyridyl or furyl optionally substituted by chlorine, trifluoromethoxy or phenoxy.

R^3 is particularly benzyl, phenethyl, 4-phenoxyphenethyl, 4-chlorobenzyl, 3-chlorobenzyl, 2-chlorobenzyl, 2-pyridylmethyl, 2-furyl or 4-trifluoromethoxybenzyl.

15 In one embodiment R^2 is benzyl.

Preferably R^4 and R^5 are independently chosen from optionally substituted C_{1-6} alkyl and $(CH_2)_qQ^2$. More preferably R^4 and R^5 are independently chosen from C_{1-6} alkyl and $(CH_2)_qQ^2$.

20 Preferably Q^2 is optionally substituted phenyl. More preferably Q^2 is phenyl.

In particular R^4 and R^5 are independently chosen from isobutyl, benzyl, n-butyl, n-propyl, methyl, s-butyl, isopropyl and phenyl.

In one embodiment R^5 and $R^{5'}$ are an oxo group.

p is preferably one, two or three, especially one or two.

25 q is preferably zero or one.

Thus a subclass of compounds of formula I and I' is provided wherein:

R^1 is C_{1-6} alkyl or benzyl optionally substituted by one or two groups chosen from halogen, cyano, nitro, hydroxy, C_{1-4} alkyl, C_{2-4} alkenyl,

30 C_{2-4} alkynyl, C_{1-4} alkoxy and amino;

R² and R³ are both (CH₂)_pQ¹ wherein Q¹ is phenyl, pyridyl or furyl optionally substituted by one or two groups independently chosen from:

- (a) halogen,
- (b) hydroxy,
- 5 (c) C₁₋₃alkyl, C₂₋₃alkenyl and C₂₋₃alkynyl,
- (d) C₁₋₃alkoxy and phenoxy each of which is optionally substituted by up to three halogen atoms,
- (e) amino;

R⁴ and R⁵ are independently chosen from C₁₋₆alkyl optionally substituted by halogen, hydroxy, amino or C₁₋₄alkoxy and (CH₂)_qQ² wherein Q² is phenyl optionally substituted by hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, thiol, C₁₋₄alkylthio, halogen, amino, carboxy, amido, CO₂H and –NHC(NH₂)₂;

p is one or two; and
15 q is zero or one.

For the avoidance of doubt each time the moieties R⁶, R⁷, R⁸ and R^{8'} occur more than once in the definition of the compounds of formula (I) they are chosen independently.

As used herein, the expression "C₁₋₁₀alkyl" includes methyl and ethyl groups, and straight-chained and branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C₁₋₆alkyl", "C₁₋₄alkyl", "C₂₋₁₀alkenyl", "C₂₋₄alkenyl", "C₂₋₁₀alkynyl and "C₂₋₄alkynyl" are to be construed in an analogous manner.

25 The expression "C₃₋₇cycloalkyl" as used herein includes cyclic propyl, butyl, pentyl, hexyl and heptyl groups such as cyclopropyl and cyclohexyl.

The term "heterocyclic" includes rings which are saturated, partially saturated or unsaturated. Unsaturated heterocyclic rings are also known as heteroaromatic rings.

30 Suitable 5- and 6-membered heteroaromatic rings include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, oxazolyl,

isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl and thiadiazolyl groups. A suitable 5-membered heteroaromatic ring containing four nitrogen atoms is tetrazolyl. Suitable 6-membered heteroaromatic rings containing three nitrogen atoms include 1,2,4-triazine and 1,3,5-triazine.

- 5 Suitable saturated heterocyclic rings include piperazine, morpholine, piperidine, tetrahydrofuran and tetrahydrothiophene. Tetrahydrofuran is preferred.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine and particularly
10 chlorine is/are preferred.

As used herein the term "C₁₋₄alkoxy" includes methoxy and ethoxy groups, and straight-chained, branched and cyclic propoxy and butoxy groups, including cyclopropylmethoxy.

Specific Examples according to the present invention include:

- 15 L-phenylalaninamide, N-[[[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- 20 L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-phenoxyphenyl)ethyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- 25 L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(3-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-
- 30 (R*,S*)]-;

- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- 5 L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-pyridyl)ethyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-furyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-trifluoromethoxyphenyl)methyl]amino]carbonyl]-L-leucyl-,
 10 [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-phenylalanyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-norleucyl-, [R-(R*,S*)]-;
- 15 L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-norvalyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-phenylglycyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-alanyl-, [R-(R*,S*)]-;
- 20 L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-isoleucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-valyl-, [R-(R*,S*)]-;
- 25 L-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-norleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-norvalinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- 30

L-phenylglycinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;

D-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;

5 L-alaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;

L-isoleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;

10 L-valinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;

L-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-;

L-phenylglycinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-;

15 L-isoleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-

and the pharmaceutically acceptable salts thereof.

Other examples include a compound selected from the group consisting of:

20 L-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-;

L-phenylglycinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-; and

L-isoleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-

25 and the pharmaceutically acceptable salts thereof.

Examples of pharmaceutically acceptable salts are hydrochlorides, sulfates, citrates, tartrates, acetates, methanesulfonates, phosphates, oxalates and benzoates.

The compounds of the present invention have an activity as inhibitors of γ secretase. In a preferred embodiment the compounds of the invention inhibit proteolysis of PS-1.

30 The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, 35 sublingual or rectal administration, or for administration by inhalation or insufflation. For

preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or
5 surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is
10 meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of
15 the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can
20 comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used
25 for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The present invention also provides a compound of the invention or a pharmaceutically acceptable salt thereof for use in a method of
30 treatment of the human body. Preferably the treatment is for a condition associated with the deposition of β -amyloid. Preferably the condition is a

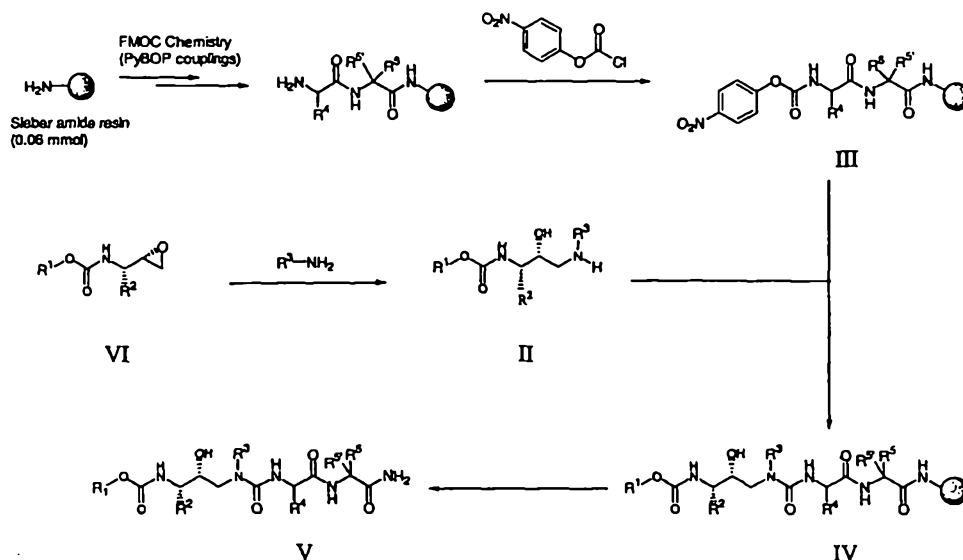
neurological disease having associated β -amyloid deposition such as Alzheimer's disease.

The present invention further provides the use of a compound of the present invention or a pharmaceutically acceptable salt thereof in the
5 manufacture of a medicament for treating or preventing Alzheimer's disease.

Also disclosed is a method of treatment of a subject suffering from or prone to Alzheimer's disease which comprises administering to that subject an effective amount of a compound according to the present
10 invention or a pharmaceutically acceptable salt thereof.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed
15 oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

20 For treating or preventing Alzheimer's Disease, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, and especially about 0.01 to 5 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.



General Procedures

- 5 Parallel synthesis techniques were used for the synthesis of all compounds. Solid phase chemistry was carried out using a Quest 210 synthesizer [Argonaut Technologies, Inc]. Where stated, purification by mass-directed preparative HPLC refers to preparative reversed phase HPLC using a Platform LCZ mass spectrometer running under MassLynx 3.3 / FractionLynx control [Micromass, UK] to trigger fraction collection when a compound of the molecular weight corresponding to the desired compound was detected. A generic acetonitrile / water gradient of 20% → 100% with a constant 0.1% trifluoroacetic acid was used for the preparative HPLC, and the mass spectrometer was operated with an APcI probe in positive ionization mode. Solvent was removed from the resulting purified samples by lyophilization.

All products V were analyzed by analytical LC-MS utilizing diode array detection (210 – 250 nm) and APcI detection (150 – 850 amu) using a full 5% → 95% MeCN gradient with 0.1% aqueous TFA. A strong M+Na⁺ peak was observed in the mass spectrum in each case.

Conversion of VI → II

0.20 mmol of the amine R^3-NH_2 was weighed into a test tube, treated with 0.067 mmol of the epoxide VI [$R^1 = \text{tert-butyl}$, $R^2 = \text{benzyl}$,
5 CAS RN 98737-29-2; $R^2 = \text{benzyl}$, CAS RN 128018-44-0] in 0.5 ml of isopropyl alcohol, and heated at 65 °C for 16 h in a test tube heating block. The sample was allowed to cool, concentrated (SpeedVac), dissolved in DMSO (0.5 ml) and purified by mass-directed preparative HPLC to give the desired compound II as its trifluoroacetate salt. This was used directly
10 in the reaction with III to give IV as indicated below.

Synthesis of compounds V

50 mg (0.030 mmol) of Fmoc-Sieber amide resin was placed in a
15 Quest 210 solid phase reactor and treated with piperidine / DMF (0.5 ml; 1 : 1 mixture) with mixing for 30 min. The reactor was drained and washed with DMA (10 x 1 ml).

Step 1

20 1 ml of a 0.1 M solution of Fmoc-NH-CH(R^5)-COOH in DMA was added to the reactor followed by 0.2 ml of a DMA mixed solution of HOBT and Hunig's base (0.5 M in both) and 0.5 ml of a 0.2 M solution of PyBOP in DMA. The reactor was mixed for 60 minutes, drained, and washed with DMA (10 x 1 ml). The reactor was treated with piperidine / DMF (0.5 ml;
25 1 : 1 mixture) and mixed for 30 minutes. The reactor was drained and washed with DMA (10 x 1 ml).

Step 2

30 1 ml of a 0.1 M solution of Fmoc-NH-CH(R^4)-COOH in DMA was added to the reactor followed by 0.2 ml of a DMA mixed solution of HOBT and Hunig's base (0.5 M in both) and 0.5 ml of a 0.2 M solution of PyBOP in DMA. The reactor was mixed for 60 minutes, drained, and washed with

DMA (10 x 1 ml). The reactor was treated with piperidine / DMF (0.5 ml; 1 : 1 mixture) and mixed for 30 minutes. The reactor was drained and washed with DMA (10 x 1 ml).

5 Step 3

The reactor was washed with 1,2-dichloroethane (DCE) (10 x 1 ml) and treated with 1.0 ml of a mixed solution of p-nitrophenylchloroformate and Hünigs base (0.1 M in each) in THF / DCE (1 : 1). The reactor was mixed for 60 min, drained, and washed with DCE (10 x 1 ml) to give III.

10

Step 4

The reactor was washed with DMA (10 x 1.0 ml) and treated with the appropriate amine II in 1.0 ml of DMA containing Hünigs base (0.2 M). The reactor was mixed for 16 h, drained, and washed with DMA (5 x 1.0 ml), MeOH (2 x 1.0 ml) and DCE (10 x 1.0 ml) to give IV.

15

Step 5

The reactor was treated with 0.5 ml of a 1% solution of TFA in DCM and allowed to stand for 30 min. The reactor was drained into a test tube.

20

Five further identical treatments with TFA were carried out. The resulting filtrate was concentrated and the crude product purified by mass-directed preparative HPLC to give the claimed compound V.

Compounds of formulae $R^3 - NH_2$ and VI are commercially available or known in the prior art or can be made from commercially available or known compounds by standard methods.

25

It will be understood that any compound of formula I initially obtained from the above process may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example compounds in which $R^{5'}$ is hydrogen can be converted into compounds where R^5 and $R^{5'}$ together form an oxo group by standard oxidation reactions.

30

It will also be appreciated that where more than one isomer can be obtained from a reaction then the resulting mixture of isomers can be separated by conventional means.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

A typical assay which can be used to determine the level of activity of compounds of the present invention is as follows:

- (1) Mouse neuroblastoma neuro 2a cells expressing human app695 are cultured at 50-70% confluency in the presence of sterile 10mM sodium butyrate.
- (2) Cells are placed in 96-well plates at 30,000/well/100 μ L in minimal essential medium (MEM) (phenol red-free) + 10% foetal bovine serum (FBS), 50mM HEPES buffer (pH7.3), 1% glutamine, 0.2mg/ml G418 antibiotic, 10mM sodium butyrate.
- (3) Make dilutions of the compound plate. Dilute stock solution to 5.5% DMSO/110 μ M compound. Mix compounds vigorously and store at 4°C until use.
- (4) Add 10 μ L compound/well. Mix plate briefly, and leave for 18h in 37°C incubator.

- (5) Remove 90 μ L of culture supernatant and dilute 1:1 with ice-cold 25mM HEPES (pH.3), 0.1% BSA, 1.0mM EDTA (+ broad spectrum protease inhibitor cocktail; pre-aliquotted into a 96-well plate). Mix and keep on ice or freeze at -80°C.
- 5 (6) Add back 100 μ L of warm MEM + 10% FBS, 50mM HEPES (pH7.3), 1% glutamine, 0.2mg/ml G418, 10mM sodium butyrate to each well, and return plate to 37°C incubator.
- (7) Prepare reagents necessary to determine amyloid peptide levels, for example by ELISA assay
- 10 (8) To determine if compounds are cytotoxic cell viability following compound administration is assessed by the use of redox dye reduction. A typical example is a combination of redox dye MTS (Promega) and the electron coupling reagent PES. This mixture is made up according to the manufacturer's instructions and left at room temperature.
- 15 (9) Quantitate amyloid beta 40 and 42 peptides using an appropriate volume of diluted culture medium by standard ELISA techniques.
- (10) Add 15 μ L/well MTS/PES solution to the cells; mix and leave at 37°C.
- (11) Read plate when the absorbance values are approximately 1.0 (mix
20 briefly before reading to disperse the reduced formazan product).

The Examples of the present invention all had an ED₅₀ of less than 500nM, preferably less than 200nM and most preferably less than 100nM in the above assay.

- 25 The following examples, made by the above method, illustrate the present invention.

Example 1. L-phenylalaninamide, N-[[[3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
30 *m/z* 696.4 (M+Na)⁺

Example 2. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 730.4 (M+Na)⁺

5

Example 3. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 744.4 (M+Na)⁺

10

Example 4. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-phenoxyphenyl)ethyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 836.4 (M+Na)⁺

15

Example 5. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 764.3 (M+Na)⁺

20

Example 6. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl][(3-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 764.3 (M+Na)⁺

25

Example 7. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 764.3 (M+Na)⁺

30

Example 8. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-pyridyl)ethyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 745.4 (M+Na)⁺

5

Example 9. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-furyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 720.4 (M+Na)⁺

10

Example 10. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-trifluoromethoxyphenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-

m/z 814.4 (M+Na)⁺

15

Example 11. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-phenylalanyl-, [R-(R*,S*)]-

m/z 778.4 (M+Na)⁺

20

Example 12. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-norleucyl-, [R-(R*,S*)]-

m/z 744.4 (M+Na)⁺

25

Example 13. L-phenylalaninamide, N-[[[3-[[[benzyloxy]carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-norvalyl-, [R-(R*,S*)]-

m/z 730.4 (M+Na)⁺

30

Example 14. L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-phenylglycyl-, [R-(R*,S*)]-
 m/z 764.4 (M+Na)⁺

5

Example 15. L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-alanyl-, [R-(R*,S*)]-
 m/z 702.3 (M+Na)⁺

10

Example 16. L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-isoleucyl-, [R-(R*,S*)]-
 m/z 744.4 (M+Na)⁺

15

Example 17. L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-valyl-, [R-(R*,S*)]-
 m/z 730.4 (M+Na)⁺

20

Example 18. L-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 710.4 (M+Na)⁺

25

Example 19. L-norleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 710.4 (M+Na)⁺

30

Example 20. L-norvalinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 696.4 (M+Na)⁺

5

Example 21. L-phenylglycinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 730.4 (M+Na)⁺

10

Example 22. D-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 710.4 (M+Na)⁺

15

Example 23. L-alaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 668.4 (M+Na)⁺

20

Example 24. L-isoleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 710.4 (M+Na)⁺

25

Example 25. L-valinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-
 m/z 696.4 (M+Na)⁺

30

Example 26. L-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-
m/z 597.3 (M+Na)⁺

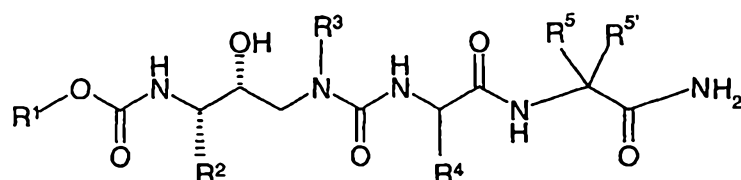
5 **Example 27.** L-phenylglycinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-
m/z 617.3 (M+Na)⁺

Example 28. L-isoleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-
10 hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-
m/z 597.3 (M+Na)⁺

CLAIMS

1. A compound of formula I or a pharmaceutically acceptable salt thereof:

5



(I)

wherein:

R¹ is (1) C₁₋₁₀alkyl, C₂₋₁₀alkenyl or C₂₋₁₀alkynyl optionally substituted with one to three substituents independently chosen from:

- 10 (i) hydroxy;
 (ii) carboxy;
 (iii) halogen;
 (iv) C₁₋₄alkoxy;
 (v) C₁₋₄alkoxycarbonyl;
 15 (vi) -NR⁶R⁷ wherein R⁶ and R⁷ are independently chosen from hydrogen, C₁₋₅alkyl and C₁₋₅alkoxyC₁₋₅alkyl;
 (vii) -CONR⁶R⁷ or OCONR⁶R⁷ wherein R⁶ and R⁷ are independently as defined above;
 (viii) -N(R⁸)QR⁹ wherein:
 20 Q is C(O), C(S), SO₂ or C(NH);
 R⁸ is hydrogen or C₁₋₄alkyl; and
 R⁹ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, amino, C₁₋₄alkylamino di(C₁₋₄alkyl)amino wherein each alkyl group is independently chosen;
 25 (ix) C₃₋₇cycloalkyl;
 (x) phenyl or naphthyl; a five-membered heterocyclic ring containing 1, 2, 3 or 4 heteroatoms independently chosen

from O, N and S, at most one of the heteroatoms being O or S; a six-membered heterocyclic ring containing 1, 2 or 3 nitrogen atoms; each of which is optionally substituted by one to three groups independently chosen from:

- 5 (a) halogen, cyano and nitro,
(b) hydroxy,
(c) C₁₋₄alkyl, C₂₋₄alkenyl and C₂₋₄alkynyl,
(d) C₁₋₄alkoxy,
(e) NR⁶R⁷ wherein R⁶ and R⁷ are independently as defined
10 above,
(f) CO₂R⁸ wherein R⁸ is independently as defined above,
(g) CONR⁶R⁷ or OCONR⁶R⁷ wherein R⁶ and R⁷ are
independently as defined above,
(h) SO₂NR⁶R⁷ wherein R⁶ and R⁷ are independently as
15 defined above,
(i) CH₂NR⁶R⁷ wherein R⁶ and R⁷ are independently as
defined above,
(j) N(R⁸)COR^{8'} wherein R⁸ is independently as defined
above and R^{8'} is independently as defined for R⁸, and
20 (k) NR⁸SO₂R^{8'} wherein R⁸ and R^{8'} are independently as
defined above; or
(2) phenyl or naphthyl; a five-membered heterocyclic ring
containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N
and S, at most one of the heteroatoms being O or S; a six-membered
25 heterocyclic ring containing 1, 2 or 3 nitrogen atoms; each of which
is optionally substituted by one to three groups independently
chosen from:
(a) halogen, cyano and nitro,
(b) hydroxy,
30 (c) C₁₋₄alkyl, C₂₋₄alkenyl and C₂₋₄alkynyl,
(d) C₁₋₄alkoxy,

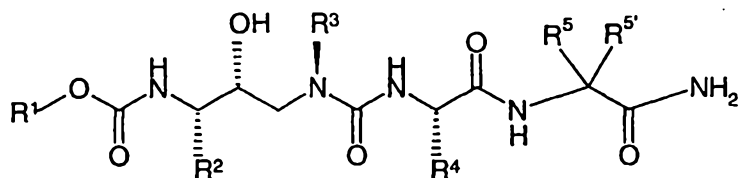
- (e) NR^6R^7 wherein R^6 and R^7 are independently as defined above,
- (f) CO_2R^8 wherein R^8 is independently as defined above,
- (g) CONR^6R^7 or OCONR^6R^7 wherein R^6 and R^7 are independently as defined above,
- (h) $\text{SO}_2\text{NR}^6\text{R}^7$ wherein R^6 and R^7 are independently as defined above,
- (i) $\text{CH}_2\text{NR}^6\text{R}^7$ wherein R^6 and R^7 are independently as defined above,
- (j) $\text{N}(\text{R}^8)\text{COR}^{8'}$ wherein R^8 and $\text{R}^{8'}$ are independently as defined above, and
- (k) $\text{NR}^8\text{SO}_2\text{R}^{8'}$ wherein R^8 and $\text{R}^{8'}$ are independently as defined above;

R^2 and R^3 are independently chosen from $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkoxy}$, $\text{C}_{2-10}\text{alkenyl}$, $\text{C}_{2-10}\text{alkenyloxy}$, $\text{C}_{2-10}\text{alkynyl}$ or $\text{C}_{2-10}\text{alkynyloxy}$; phenyl; naphthyl; a five-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N and S, at most one of the heteroatoms being O or S; a six-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; and a group $(\text{CH}_2)_p\text{Q}^1$ wherein Q^1 is phenyl, naphthyl, a five-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from O, N and S, at most one of the heteroatoms being O or S, and a six-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms; and wherein each of R^2 and R^3 is independently optionally substituted by one to three groups independently chosen from:

- (a) halogen, cyano and nitro,
- (b) hydroxy,
- (c) $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$ and $\text{C}_{2-6}\text{alkynyl}$,
- (d) $\text{C}_{1-6}\text{alkoxy}$ and phenoxy each of which is optionally substituted by one to three halogen atoms,

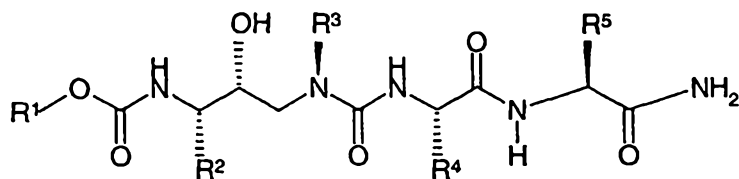
- (e) NR^6R^7 wherein R^6 and R^7 are independently as defined above,
- (f) CO_2R^8 wherein R^8 is independently as defined above,
- (g) CONR^6R^7 or OCONR^6R^7 wherein R^6 and R^7 are independently as defined above,
- (h) $\text{SO}_2\text{NR}^6\text{R}^7$ wherein R^6 and R^7 are independently as defined above,
- (i) $\text{CH}_2\text{NR}^6\text{R}^7$ wherein R^6 and R^7 are independently as defined above,
- (j) $\text{N}(\text{R}^8)\text{COR}^8$ wherein R^8 and R^8 are independently as defined above,
- (k) $\text{NR}^8\text{SO}_2\text{R}^8$ where R^8 and R^8 are independently as defined above;
- alternatively R^3 may be hydrogen;
- R^4 and R^5 are independently chosen from hydrogen, C_{1-6} alkyl optionally substituted by halogen, hydroxy, thiol, amino, C_{1-4} alkoxy, C_{1-4} alkylthio, carboxy, C_{1-4} alkoxycarbonyl and $(\text{CH}_2)_q\text{Q}^2$ wherein Q^2 is a five-membered unsaturated heterocycle containing 1, 2, 3 or 4 heteroatom optionally chosen from O, N, and S providing that not more than one heteroatom is O or S, a six-membered unsaturated heterocycle containing 1, 2 or 3 N atoms, phenyl, naphthyl or a fused ring which is indolyl, each of the foregoing rings being optionally substituted with one to three groups independently chosen from hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, thiol, C_{1-4} alkylthio, halogen, amino, carboxy, amido, CO_2H and $-\text{NHC}(\text{NH}_2)_2$;
- and
- $\text{R}^{5'}$ is a hydrogen atom;
- alternatively R^5 and $\text{R}^{5'}$ together represent an oxo group;
- p is zero, one, two or three; and
- q is zero, one, two or three;
- with the proviso that no carbon atom is substituted by more than one hydroxy group.

2. A compound according to claim 1 of formula I' or formula I'':



5

(I')



10

(I'')

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 wherein:

15 R¹ is C₁₋₆alkyl or benzyl optionally substituted by one or two groups chosen from halogen, cyano, nitro, hydroxy, C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy and amino;

R² and R³ are both (CH₂)_pQ¹ wherein Q¹ is phenyl, pyridyl or furyl optionally substituted by one or two groups independently chosen from:

- 20 (a) halogen,
 (b) hydroxy,
 (c) C₁₋₃alkyl, C₂₋₃alkenyl and C₂₋₃alkynyl,
 (d) C₁₋₃alkoxy and phenoxy each of which is optionally substituted by up to three halogen atoms,
 25 (e) amino;

- R^4 and R^5 are independently chosen from C_{1-6} alkyl optionally substituted by halogen, hydroxy, amino or C_{1-4} alkoxy and $(CH_2)_qQ^2$ wherein Q^2 is phenyl optionally substituted by hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, thiol, C_{1-4} alkylthio, halogen, amino, carboxy, amido, CO_2H and –
- 5 $NHC(NH_2)_2$;
- p is one or two; and
- q is zero or one.

4. A compound according to claim 1 selected from:
- 10 L-phenylalaninamide, N-[[[3-[[[1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]carbonyl]-L-leucyl-, [R-(R^* , S^*)]-;
- L-phenylalaninamide, N-[[[3-[[[benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylmethyl)amino]carbonyl]-L-leucyl-, [R-(R^* , S^*)]-;
- 15 L-phenylalaninamide, N-[[[3-[[[benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R^* , S^*)]-;
- L-phenylalaninamide, N-[[[3-[[[benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-phenoxyphenyl)ethyl]amino]carbonyl]-L-leucyl-, [R-(R^* , S^*)]-;
- 20 L-phenylalaninamide, N-[[[3-[[[benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R^* , S^*)]-;
- L-phenylalaninamide, N-[[[3-[[[benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(3-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-
- 25 (R^* , S^*)]-;
- L-phenylalaninamide, N-[[[3-[[[benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-chlorophenyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R^* , S^*)]-;
- L-phenylalaninamide, N-[[[3-[[[benzyloxy)carbonyl]amino]-2-hydroxy-4-
- 30 phenylbutyl][(2-pyridyl)ethyl]amino]carbonyl]-L-leucyl-, [R-(R^* , S^*)]-;

- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(2-furyl)methyl]amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl][(4-trifluoromethoxyphenyl)methyl]amino]carbonyl]-L-leucyl-,
5 [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-phenylalanyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-norleucyl-, [R-(R*,S*)]-;
- 10 L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-norvalyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-phenylglycyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-alanyl-, [R-(R*,S*)]-;
- 15 L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-isoleucyl-, [R-(R*,S*)]-;
- L-phenylalaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-valyl-, [R-(R*,S*)]-;
- 20 L-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-norleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- L-norvalinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- 25 L-phenylglycinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- D-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;
- 30 L-alaninamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;

L-isoleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-;

L-valinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-L-leucyl-, [R-(R*,S*)]-; and pharmaceutically acceptable salts thereof.

5. A compound selected from the group consisting of:

L-leucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-;

L-phenylglycinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-; and

L-isoleucinamide, N-[[[3-[[[(benzyloxy)carbonyl]amino]-2-hydroxy-4-phenylbutyl](phenylethyl)amino]carbonyl]-, [R-(R*,S*)]-

and the pharmaceutically acceptable salts thereof.

6. A pharmaceutical composition comprising one or more compounds according to any one of the previous claims and a pharmaceutically acceptable carrier.

7. A compound according to any one of claims 1-5 for use in a method of treatment of the human body.

8. A compound of claim 7 wherein said treatment is for a condition associated with the deposition of β -amyloid.

9. The use of a compound according to any one of claims 1-5 in the manufacture of a medicament for treating or preventing Alzheimer's disease.

10. A process of making a compound of claim 1 which process is substantially as herein described with reference to the process described under the heading General Procedures.

11. A compound of formula (I) as defined in claim 1 and substantially as herein described with reference to any one of Examples 1 to 28.

12. A pharmaceutical composition comprising a compound of claim 11 together with a pharmaceutically acceptable carrier.

13. A method of treating or preventing Alzheimer's disease in a subject requiring such treatment said method comprising administering to said subject an effective amount of a compound of any one of claims 1 to 5 or 11 or a composition of claim 6 or 12.

14. A compound of any one of claims 1 to 5 or 11 or a composition of claim 6 or 12 when used in an effective amount to treat or prevent Alzheimer's disease in a subject in need thereof.

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