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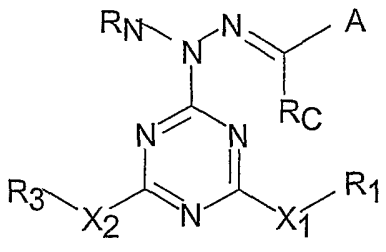
(54) Title: TRIAZINE BETA-SECRETASE INHIBITORS



(I)

(57) Abstract: It has been found that compounds of formula (I) wherein, in preferred embodiments, X_1 and X_2 are N-H or N- R_3 or N-R_4, R_N and R_C are both H, R_1 and R_3 are independently from each other optionally substituted phenyl, or R_1 and R_2 and/or R_3 and R_4 form together with the N to which R_2 and/or R_4 , respectively, are bound a 5 or 6 membered heterocycle comprising 1 or 2 heteroatoms, and A is preferably halogen substituted phenyl or a preferably phenyl substituted furanyl are good β-secretase inhibitors and are useful for the treatment of Alzheimer's disease.

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Triazine β-secretase inhibitors

Field of the Invention

This invention relates to compounds acting as beta-secretase inhibitors.

Background Art

Alzheimer's disease (AD) is the most common form of dementia among older people, and affects parts of the brain that control thought, memory and language. Susceptibility to Alzheimer's disease increases with age, but Alzheimer's disease is not a normal part of the ageing process.

A characteristic of this disease is the presence of extracellular senile plaque, the major component of which is the β-amyloid peptide (Aβ). The hydrophobic, 39-43-amino-acid-long Aβ peptide is excised from the amyloid precursor protein (APP) by sequential cleavage by the so-called β- and γ-secretases.

Known genetic predispositions for AD mostly affect genes involved in Aβ generation or Aβ deposition. Since the Aβ peptide seems to play an important role in the pathogenesis of AD, current therapeutic strategies often focus on inhibition of Aβ deposition and generation. Inhibition of β-secretase activity represents an attractive option to achieve this goal.

Despite major efforts to identify novel β-secretase inhibitors by applying in vitro high-throughput screening (HTS) assays with purified soluble BACE-1 fragments and fluorogenic peptide substrates, the best progress towards efficient BACE-1 inhibition has been achieved so far by the use of peptidic transition-state mimetic compounds. However, for efficient inhibition of β-secretase in cells, their molecular weight must be reduced and their structure modified so as to allow for permeation

of cellular membranes, the blood-brain barrier and for activity in the natural cellular environment.

There also exist some assays for identifying low molecular weight inhibitors of secretases that can block these membrane-bound enzymes at the natural location within intracellular compartments. Cell-based HTS assays, however, are generally faced with the problem that selection signals are often caused by compounds that interfere with cellular processes or pathways that are redundant with that of the target. For example, some compounds found by mammalian cell based assays impair the production of Aβ through the increase of the pH in intracellular compartments, or they function through protein phosphorylation, or they simply catalyze polymerization of Aβ, thus reducing the percentage of soluble peptide.

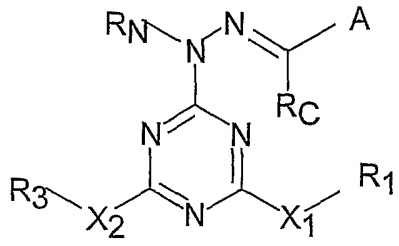
Some candidate compounds for inhibiting the production of Aβ peptide in a biological system have been proposed in US 5,814,646 and US 5,624,937, and triazine compounds have already been suggested for the treatment of Alzheimer's disease (see GB 2 397 301, WO 2004/063196).

Nevertheless, there is still a need for potent β-secretase inhibitors that directly inhibit β-secretase.

Disclosure of the Invention

Hence, it is a general object of the invention to provide compounds that directly act as β-secretase inhibitors.

Now, in order to implement these and still further objects of the invention, which will become more readily apparent as the description proceeds, the β-secretase inhibitors of the present invention are manifested by the following formula I



(I)

wherein

X_1 and X_2 independently from each other are selected from O or S or N-R_2 or N-R_4, and in particular X_1 is N-R_2 and X_2 is N-R_4,

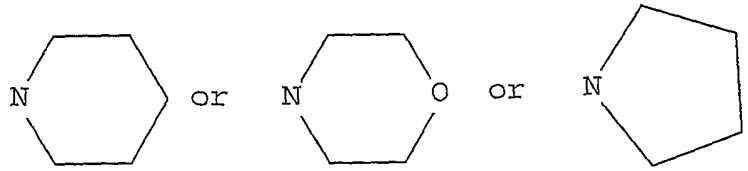
R_N and R_C are independently from each other chosen from small substituents such as -H, -OH, -CH=O, NH_2, preferably -H,

R_1 and R_3 are independently from each other selected from the group comprising C1-C3 alkoxy, in particular C1-C3 alkoxy, 3- to 8-membered aliphatic or heteroaliphatic cycles, optionally substituted 5- or 6-membered heteroaryl or aryl, in particular optionally substituted phenyl, with the substituents being independently from each other selected from 1 to 5, in particular 1 or 2, of C1-C6 alkyl, halogen, C1-C6 alkoxy, hydroxy and C2-C6 alkene, wherein preferred alkyls are C1-C3 alkyl, in particular methyl, the halogens are selected from fluorine, chlorine, bromine and iodine, in particular from fluorine and chlorine, preferred alkoxy are C1-C3 alkyloxy, in particular methoxy, and preferred alkene are vinyl or allyl,

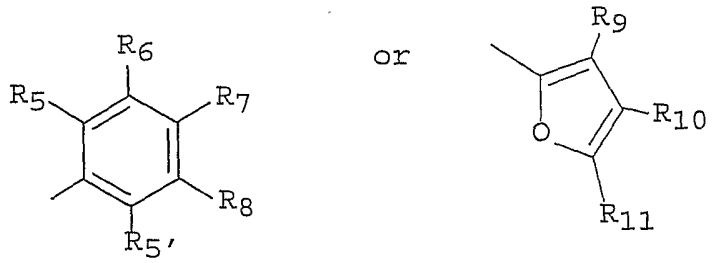
R_2 and R_4 are independently from each other selected from the group comprising hydrogen, C1-C3 alkyl, C1-C3 alkoxy, phenoxy, C1-C3 thioalkyl, wherein preferred C1-C3 alkyl is methyl, preferred C1-C3 alkoxy is methoxy, and preferred C1-C3 thioalkyl is -S-CH_3,

or R_1 and R_2 and/or R_3 and R_4 form together with the N to which R2 and/or R_4, respectively, are bound a 5 or 6 membered heterocycle comprising 1 or 2

heteroatoms, the second heteroatom being N or O, in particular



A is



wherein

R_5 is selected from the group comprising -H, -OH, $-CH_3$, $-CH_2OH$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-NH-CH_2CH_3$,

$R_{5'}$ is selected from the group comprising -H, -OH, $-CH_3$, $-CH_2OH$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-NH-CH_2CH_3$, $-O-CH_2CH_3$, -O-phenyl, $-CH_2$-phenyl, -NH-phenyl, -F, -Cl, -Br, -I, and much preferred is -H,

R_6 is selected from the group comprising -H, -F, -Cl, -Br, -I,

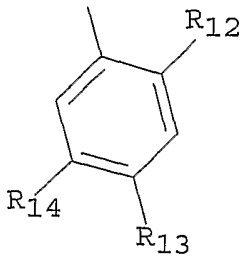
R_7 is selected from the group comprising -H, -OH, $-CH_3$, $-CH_2OH$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-NH-CH_2CH_3$, $-O-CH_2CH_3$, -O-phenyl, $-CH_2$-phenyl, -NH-phenyl,

R_8 is selected from the group comprising -H, -F, -Cl, -Br, -I, and wherein

R_9 is selected from the group comprising -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, phenyl, $-CH_2$-phenyl, -O-phenyl, -NH-phenyl, Br,

R_{10} is selected from the group comprising -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, phenyl, $-CH_2$-phenyl, -O-phenyl, -NH-phenyl, Br,

R_{11} is selected from the group comprising -$CH_2CH_2CH_2COOH$, -CH_2CH_2COOH, -NH-CH_2CH_2COOH, -NH-CH_2COOH, -O-CH_2CH_2COOH, -O-CH_2COOH, -S-CH_2CH_2COOH, -S-CH_2COOH, -Br, 5- or 6-membered heteroaromatic or aromatic rings which are optionally substituted, in particular



wherein R_{12} is selected from the group comprising -H, halogen selected from -Cl, -Br, -I, in particular -Cl, C1-C3 alkyl, in particular -CH_3, -OH, C1-C3 alkoxy, in particular methoxy,

R_{13} is selected from the group comprising -H, -OH, -NO_2, -Cl, -Br, -I, in particular -Cl, C1-C3 alkyl, in particular -CH_3, C1-C3 alkoxy, in particular methoxy,

R_{14} is selected from the group comprising -H, -COOH, -COOR with R being selected from C1-C6 alkyl or C2-C6 alkenyl, -NO_2, -Cl, -(C=O)CH_3, SO_2,

or pharmaceutically acceptable salts thereof.

In preferred embodiments, at least one of the below mentioned preferences is present, preferably two or more of them, most preferred all of them.

(i) X_1 is N-R_2 and X_2 is N-R_4;

(ii) at least one of R_1 and R_3 are optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of C1-C3 alkyl, in particular methyl; halogen selected from chlorine, bromine and iodine, in particular fluorine and chlorine; C1-C3 alkyloxy, in particular methoxy, and

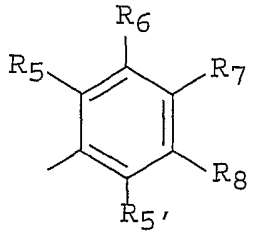
R_2 and R_4 are hydrogen;

(iii) R_1 and R_2 and/or R_3 and R_4 form together with the N to which R2 and/or R_4, respectively, are bound

a 5 or 6 membered heterocycle comprising 1 or 2 heteroatoms, the second heteroatom being N or O, in particular piperidinyl, morpholinyl, pyrrolinyl;

(iv) at most one of R_1 or R_3 is C1-C3-alkoxy, in particular methoxy

(v) A is



wherein

R_5 is -H or -OH,

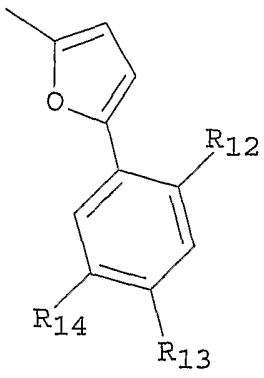
R_5' is -H,

R_6 is selected from the group comprising -H, -Cl, -Br, -I, $-OCH_3$,

R_7 is -H or -OH,

R_8 is selected from the group comprising H, Cl, Br, or I,

(vi) A is



wherein

R_{12} is selected from the group comprising -H, -Cl, $-CH_3$,

R_{13} is selected from the group comprising -H, -OH, -Cl, $-NO_2$,

R_{14} is selected from the group comprising -H, -COOH, $-NO_2$, -Cl;

(vii) R_N and R_C are both -H.

Much preferred are compounds wherein X_1 is N-R_2, X_2 is N-R_4, and R_N and R_C are both -H, and which additionally have at least one of the preferences below, namely

(i) R_1 and R_3 are optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of methyl, fluorine, chlorine, and methoxy, and

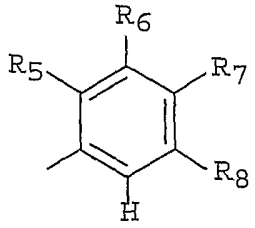
R_2 and R_4 are hydrogen;

(ii) R_1 and R_2, and R_3 and R_4 form together with the N to which R2 and R_4 are bound a heterocycle selected from the group consisting of piperidinyl, morpholinyl, pyrrolinyl;

(iii) R_1 is optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of methyl, fluorine, chlorine, and methoxy, and R_2 is hydrogen, and R_3 and R_4 form together with the N to which R_4 is bound a heterocycle selected from the group consisting of piperidinyl, morpholinyl, pyrrolinyl;

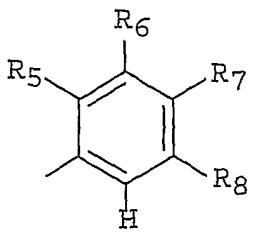
(iv) R_1 is as defined in (i) or (ii) and R_3 is methoxy;

(v) A is



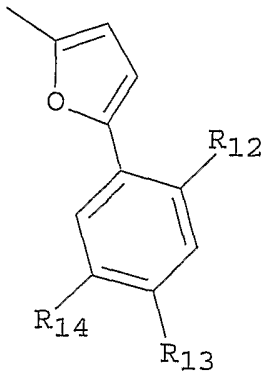
wherein at least one of R_6 and R_8 is Cl, Br, I, preferably both, and much preferred both are the same;

(vi) A is



wherein at least 3 of R_5 to R_8 are not hydrogen, preferably at least R_8 and much preferred R_8 and R_6 are Cl, Br or I , in particular R_8 and R_6 are the same;

(vii) A is

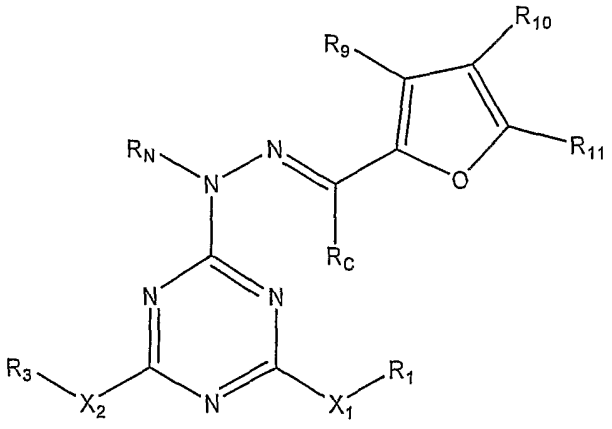


wherein R_{14} is -COOH;

(vii) R_{14} is -COOH and R_{13} is -OH or -Cl;

(viii) R_{13} is -OH or -Cl or $-NO_2$.

In a further aspect, the invention relates to a compound of formula (I-B)



(I-B)

wherein

X_1 represents O, S or N-R_2;

X_2 represents O, S or N-R_4;

R_N represents hydrogen, hydroxy, formyl or amino;

R_C represents hydrogen, hydroxy, formyl or amino;

R_1 represents C1-C6 alkyl, 3- to 8-membered aliphatic cycles or 3- to 8-membered heteroaliphatic cycles, optionally substituted 5- or 6-membered heteroaryl or optionally substituted aryl, in particular optionally substituted phenyl, with the substituents of the phenyl being independent from each other selected from 1 to 5, preferably from 1 or 2, of C1-C6 alkyl, halogen selected from fluorine, chlorine, bromine, iodine, C1-C6 alkyloxy, hydroxy, C1-C6 alkene;

R_2 represents hydrogen, C1-C3 alkyl, C1-C3 alkoxy, phenoxy, C1-C3 thioalkyl;

R_3 represents C1-C6 alkoxy, 3- to 8-membered aliphatic cycles or 3- to 8-membered heteroaliphatic cycles, optionally substituted 5- or 6-membered heteroaryl or optionally substituted aryl, in particular optionally substituted phenyl, with the substituents of the phenyl being independent from each other selected from 1 to 5, preferably from 1 or 2, of C1-C6 alkyl, fluorine, chlorine, bromine, iodine, C1-C6 alkyloxy, hydroxy, C1-C6 alkene; and

R_4 represents hydrogen, C1-C3 alkyl, C1-C3 alkoxy, phenoxy, C1-C3 thioalkyl; or

R_1 and R_2 and/or R_3 and R_4 form together with the N to which R2 and/or R_4, respectively, are bound a 5 or 6 membered heterocycle comprising 1 or 2 heteroatoms, the second heteroatom being N or O;

R_9 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, phenyl, benzyl, phenoxy, -NH-phenyl, Br;

R_{10} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, phenyl, benzyl, phenoxy, -NH-phenyl, Br;

R_{11} represents $-(C_1-C_3$-alkyle)COOH, -NH-(C_1-C_3-alkyl)COOH, -O-(C_1-C_3-alkyle)COOH, -S-(C_1-C_3-alkyl)COOH, halogen, or a 5-membered or 6-membered heteroaromatic or aromatic ring, which ring is optionally substituted by 1 to 3

substituents, the substituents are selected from the group comprising halogene, $-NO_2$, hydroxy, $-SO_2$, -COOH, C1-C6 alkyl, C1-C6 alkoxy, -(C=O)-(C1-C6 alkyl), -COOR, wherein R is selected from C1-C6 alkyl or C2-C6 alkenyl;

or pharmaceutically acceptable salts thereof.

Advantageous embodiments of compounds of formula (I-B) are described as follows:

(i) A compound of formula (I-B) wherein X_1 represents N-R_2 and X_2 represents N-R_4.

(ii) A compound of formula (I-B) wherein R_N represents hydrogen.

(iii) A compound of formula (I-B)wherein

R_1 represents methyl, optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of methyl, fluorine, chlorine, methoxy;

R_2 represents hydrogen, methoxy;

R_3 represents methoxy, optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of methyl, fluorine, chlorine, methoxy;

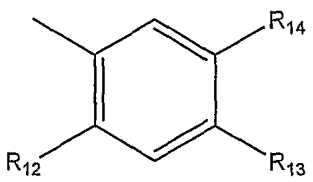
R_4 represents hydrogen, methoxy;

and / or

R_1 and R_2 and/or R_3 and R_4 form together with the N to which R_2 and/or R_4, respectively, are bound a 5 or 6 membered heterocycle selected from pyrrolidinyl, piperidinyl, morpholinyl.

(iv) A compound of formula (I-B), wherein

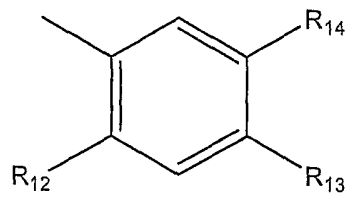
R_{11} represents



and R_{12}, R_{13}, and R_{14} are as defined in claim 1.

(v) A compound of formula (I-B)wherein

R_{11} represents $-CH_2CH_2CH_2COOH$, $-CH_2CH_2COOH$, $-NH-CH_2CH_2COOH$, $-NH-CH_2COOH$, $-O-CH_2CH_2COOH$, $-O-CH_2COOH$, $-S-CH_2CH_2COOH$, $-S-CH_2COOH$, -Br, or



wherein

R_{12} represents -H, -Cl, -Br, -I, $-CH_3$, -OH, $-OCH_3$;

R_{13} represents -H, -OH, $-NO_2$, -Cl, -Br, -I, $-CH_3$, OCH_3 and

R_{14} represents -H, $-NO_2$, Cl, $-(C=O)-CH_3$, SO_2,-COOH, $-COOCH_3$;

(vi) A compound of formula (I-B)wherein

R_1 represents optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of C1-C3 alkyl (in particular methyl), halogen (in particular fluorine and chlorine). C1-C3 alkyloxy (in particular methoxy)

R_3 represents optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of C1-C3 alkyl (in particular methyl), halogen (in particular fluorine and chlorine). C1-C3 alkyloxy (in particular methoxy).

(vii) A compound of formula (I-B), wherein R_2 and R_4 represent hydrogen.

(iix) A compound of formula (I-B), wherein R_1 and R_2 and/or R_3 and R_4 form together with the N to which R_2 and/or R_4, respectively, are bound a 5 or 6 membered heterocycle comprising 1 or 2 heteroatoms, the second heteroatom being N or O.

(ix) A compound of formula (I-B), wherein R_1 and R_2, and/or R_3 and R_4 form together with the N to which R2 and/or R_4, respectively, are bound a heterocycle

selected from the group of piperidinyl, morpholinyl, pyrrolinyl.

(x) A compound of formula (I-B), wherein

R_{12} represents -H, -Cl, $-CH_3$,

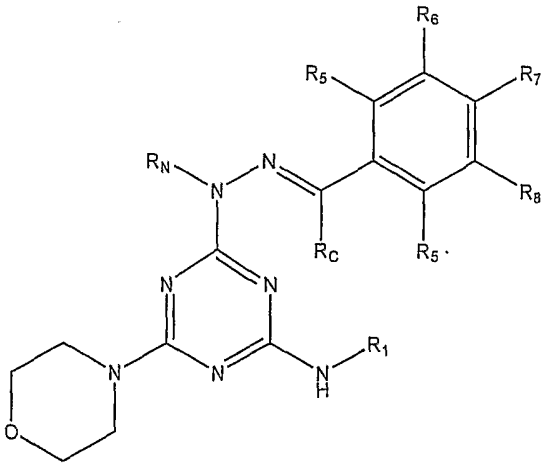
R_{13} represents -H, -OH, -Cl, $-NO_2$,

R_{14} represents -H, -COOH, $-NO_2$, Cl.

(xi) A compound of formula (I-B), wherein R_{14} represents -COOH.

(xii) A compound of formula (I-B), wherein R_{13} represents -OH or Cl.

In a further aspect, the invention relates to a compound of formula (I-C)



(I-C)

wherein

R_1 represents optionally substituted phenyl, with the substituents being independently from each other selected from 1 to 5, in particular 1 or 2, of C1-C6 alkyl, halogen, C1-C6 alkoxy, hydroxy and C2-C6 alkene, wherein preferred alkyls are C1-C3 alkyl, in particular methyl, the halogens are selected from fluorine, chlorine, bromine and iodine, in particular from fluorine and chlorine, preferred alkoxy are C1-C3 alkyloxy, in particular methoxy, and preferred alkene are vinyl or allyl and

R_N, R_C, R_5, R_5`, R_6, R_7, R_8 are as defined above.

Advantageous embodiments of compounds of formula (I-C) are described as follows:

(i) A compound of formula (I-C) wherein R_C represents hydrogen.

(ii) A compound of formula (I-C) wherein R_N represents hydrogen.

(iii) A compound of formula (I-C) wherein R_5 represents hydrogen.

(iv) A compound of formula (I-C) wherein $R_{5'}$ represents hydroxy.

It is to be understood that the various embodiments and preference as disclosed herein may be combined at will. Further, selected definitions may not apply.

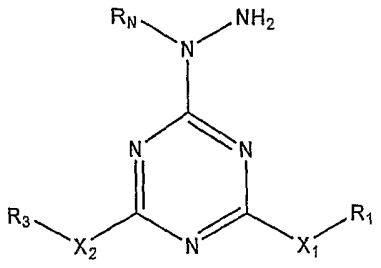
The invention further relates to compounds of formula (I) as pharmaceutical.

The invention further relates to compounds of formula (I-B) as pharmaceutical.

The invention further relates to compounds of formula (I-C) as pharmaceutical.

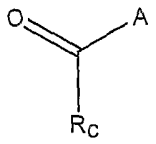
The invention further relates to a pharmaceutical composition comprising one or more compounds or pharmaceutically acceptable salts thereof as described herein, together with a pharmaceutically acceptable carrier and optionally one or more adjuvants.

The invention further relates to the manufacture of a compound of formula (I) comprising the step of reacting a compound of formula (II)



(II)

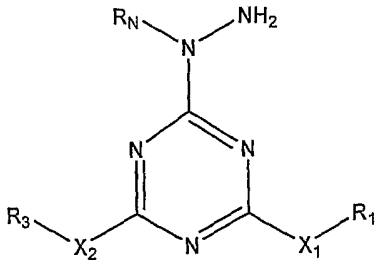
wherein the substituents are as defined above with a compound of formula (III)



(III)

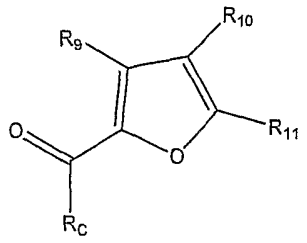
wherein the substituents are as defined above, optionally in the presence of a solvent, such as an alcohol (e.g. methanol) and optionally in the presence of an reaction auxiliary, such as a water-removing agent (e.g. molecular sieve).

The invention further relates to the manufacture of a compound of formula (I-B) comprising the step of reacting a compound of formula (II-B)



(II-B)

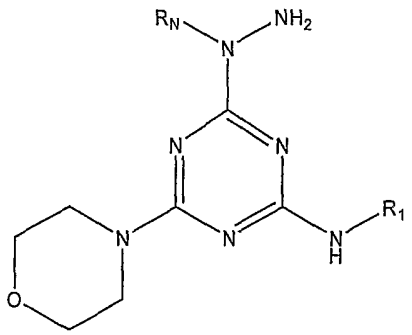
wherein the substituents are as defined above with a compound of formula (III-B)



(III-B)

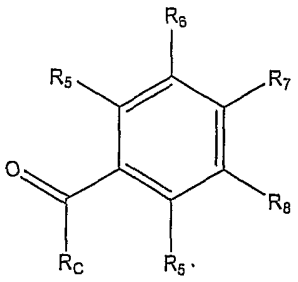
wherein the substituents are as defined above, optionally in the presence of a solvent, such as an alcohol (e.g. methanol) and optionally in the presence of an reaction auxiliary, such as a water-removing agent (e.g. molecular sieve).

The invention further relates to the manufacture of a compound of formula (I-C) comprising the step of reacting a compound of formula (II-C)



(II-C)

wherein the substituents are as defined above with a compound of formula (III)



(III-C)

wherein the substituents are as defined above, optionally in the presence of a solvent, such as an alcohol (e.g. methanol) and optionally in the presence of an reaction auxiliary, such as a water-removing agent (e.g. molecular sieve).

The starting materials used in these reactions are known or available by using known manufacturing steps. The compounds of formula (II). (II-B) and (II-C) are available from the reaction of hydrazine with the corresponding chlorine-derivatives.

It has been found that compounds of the above formulas are efficient in inhibiting β-secretase activity. Thus, such compounds are suitable in the prophylaxis, treatment and/or delay of progression of diseases related to β-secretase activity or diseases related to the deposition of amyloid beta-protein, respectively. Such diseases include Alzheimer's disease (AD), Down's syndrome and advanced aging of brain of which AD is of particular importance.

Further, the invention relates to the use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the β-secretase activity or diseases related to the deposition of amyloid beta-protein (such as the production and/or the accumulation of amyloid beta-protein) mammals, in particular human beings. In particular, the invention relates to the use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of Alzheimer's disease and / or Down's syndrome and / or aging of brain.

Accordingly, the invention also relates to a method of prevention, treatment or delay of progression of a disease involving an abnormal β-secretase activity or a disease related to the deposition of amyloid beta-protein (such as the production and/or the accumulation of amyloid beta-protein), in a subject in need thereof comprising the step of administering an effective amount of a compound as described herein. In particular, the invention relates to method of prevention, treatment or delay of progression of a disease selected from the group consisting of Alzheimer's disease (AD) , Down's syndrome , aging of brain, in a subject in need thereof comprising the step of administering an effective amount of a compound as described herein.

AD, as used in this specification includes all stages of this disease, its mild, moderate and severe form.

In therapeutic applications, the compounds are administered to a host already suffering from the disease. The compounds will be administered in an amount sufficient to inhibit further deposition of senile plaques. The specific dose of compound(s) administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances, such as the specific compound administered, the condition being treated, etc. A daily dose will contain a dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound, preferably from about 0.05 mg/kg to about 20 mg/kg, for example from about 0.1 mg/kg to about 120 mg/kg.

The compound can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular and intranasal either as such, but preferable in a formulation comprising

carriers adjuvants etc. Suitable pharmaceutically acceptable solid and liquid carriers and/or pharmaceutically acceptable adjuvants, such as stabilizing agents, emulsifyers, etc. are known in the art.

For example, a typical pharmaceutical composition for intramuscular injection would contain about one μg to one mg of the compound in from one to four milliliters of sterile buffered water. The typical pharmaceutical composition for intravenous infusion would contain about one to one hundred milligrams of the compound in from one hundred to five hundred milliliters of sterile Ringer's solution.

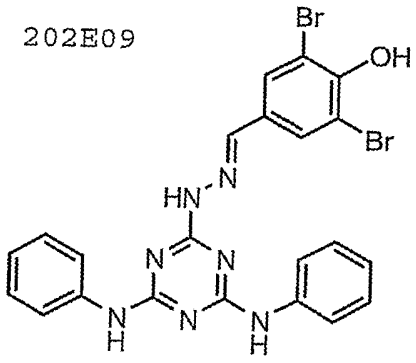
The pharmaceutical formulations are prepared by known procedures using known and readily available ingredients.

Modes for Carrying Out the Invention

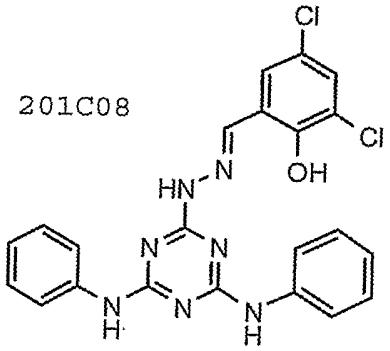
Specific compounds and their β-secretase inhibiting effects are further described below.

The compounds investigated were the compounds with the following formulas:

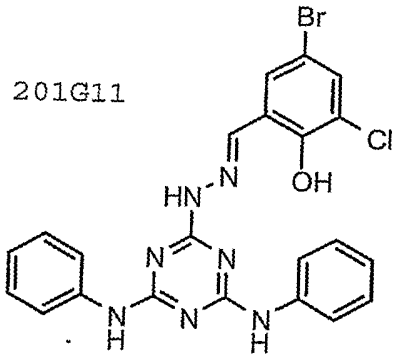
202E09



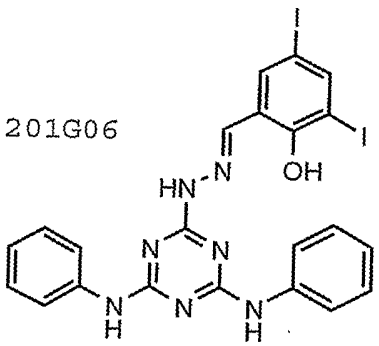
201C08



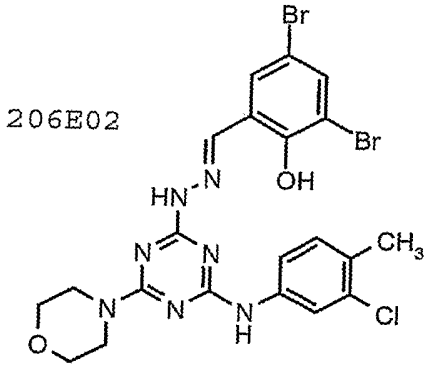
201G11



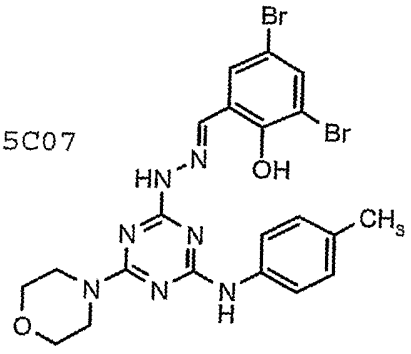
201G06



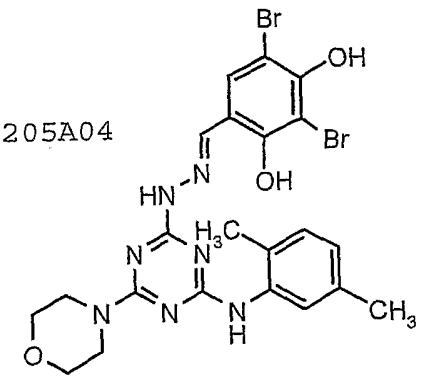
206E02



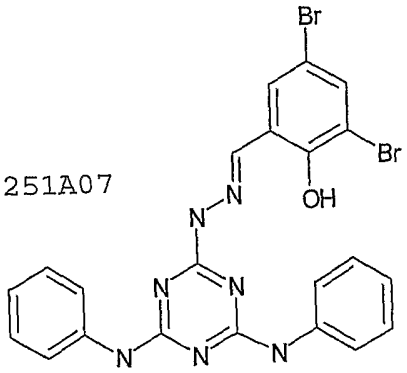
205C07



205A04



251A07



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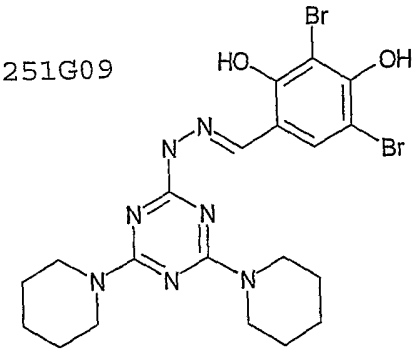
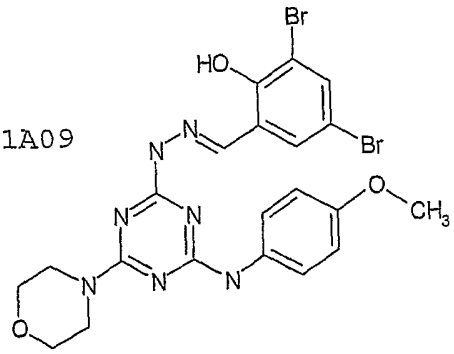
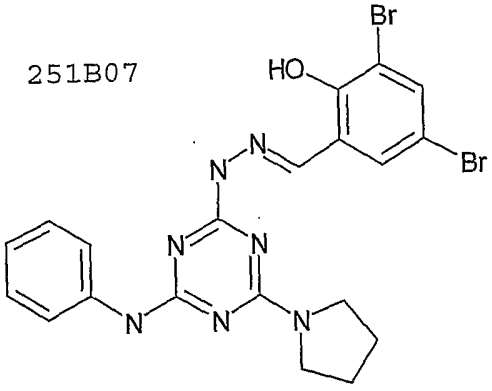
251G09



251A09



251B07



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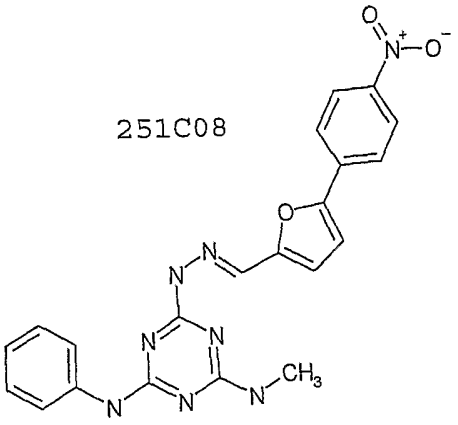
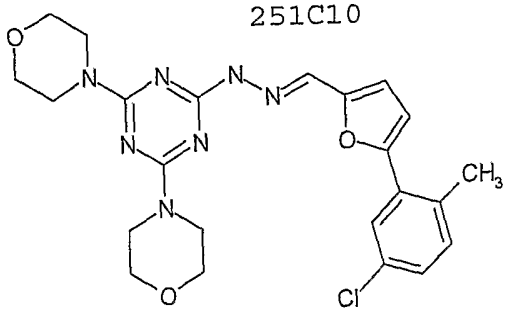
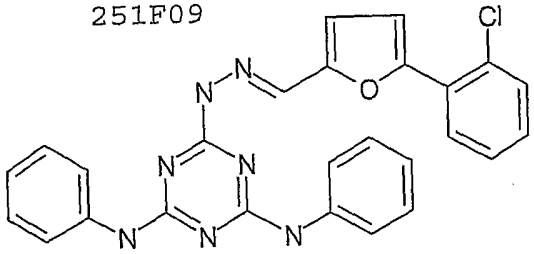
251C08



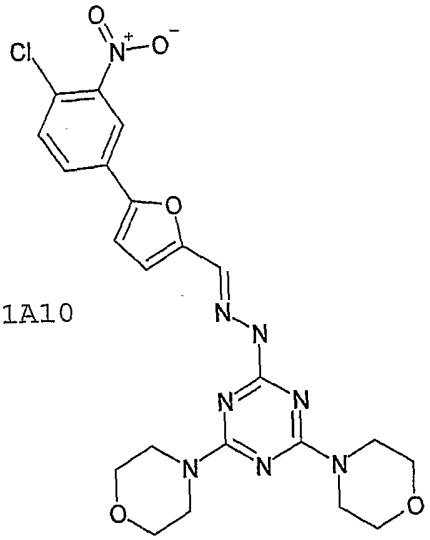
251C10



251F09



251A10



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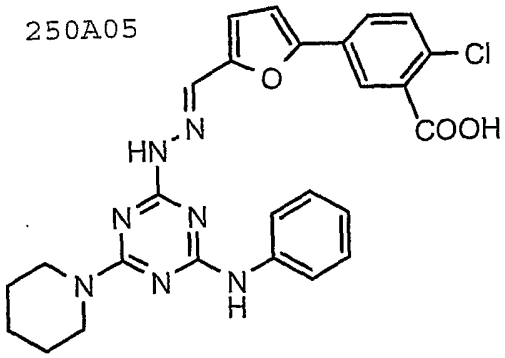
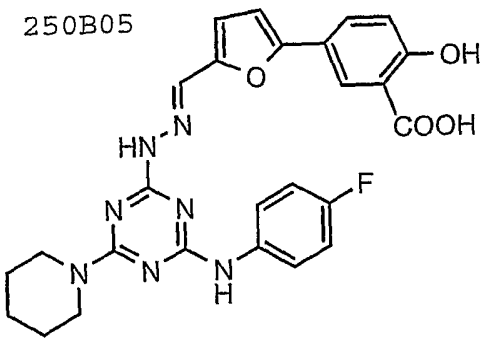
250A05



250B05



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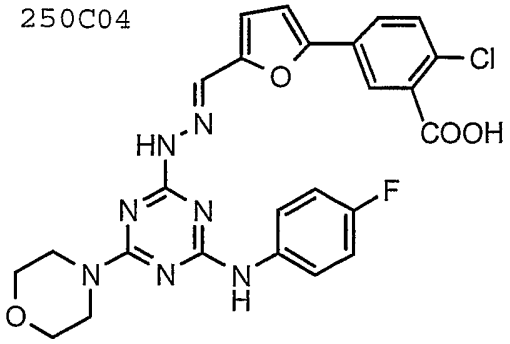
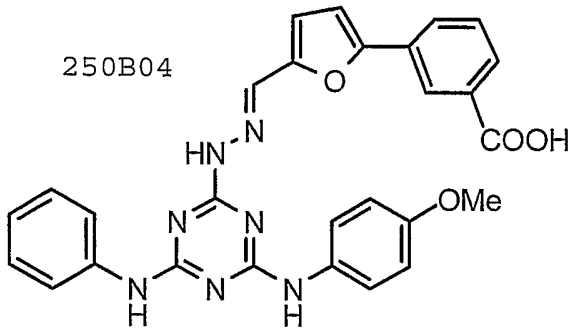
250C04



250B04



The tests performed were

a) Aβ1-40 (Sw) bioassay, which measures the amount of the amyoid peptide Aβ1-40 in the supernatant of Swedish APP695 transgenic HEK293 cells in the presence of the various BACE inhibitors via ELISA (enzyme-linked immunosorbent assay). In the table, the inhibitory concentration that reduces Aβ1-40 secretion to 50 % is indicated (IC50), or the % reduction of Aβ1-40 secretion at the indicated concentration.

b) FRET assay, which measures the activity of recombinant BACE enzyme in the presence of the various BACE inhibitors via a FRET (fluorescence resonance energy transfer)-based readout. In the table, the inhibitory concentration that reduces the activity of BACE to 50 % is indicated (IC50), or the % reduction of the activity of BACE at the indicated concentration.

c) An additional in silico test was performed for the compounds listed in Tables 1 to 3. The compounds were docked with the FFLD approach (Budin et al., Biol. Chem. 382, 1365-1372, 2001) and their binding energy was evaluated with the LIECE method (Huang and Caflisch, J. Med. Chem. 47, 5791-5797, 2004). The affinity evaluated with LIECE is in the low micromolar range for most of these compounds.

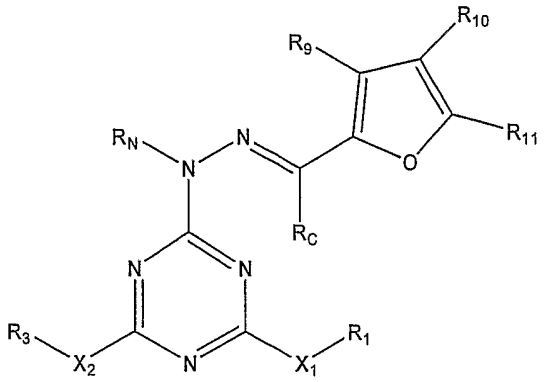
Table 1:

Com-pound	LIECE Ki [μM]	Aß1-40(sw) bioassay (cell-based)	BACE FRET assay (in vitro)
202E09	41.41	25% (5 μM)	IC_{50} 53.9 μM
201C08	20.20	25% (5 μM)	IC_{50} 11.2 μM
201G11	74.22	26% (5 μM)	IC_{50} 11.9 μM
201G06	38.77	No (5 μM)	IC_{50} 25.5 μM
206E02	49.35	27% (50 μM)	IC_{50} 20.6 μM
205C07	30.89	No (50 μM)	IC_{50} 48.1 μM
205A04	56.49	No (5 μM)	IC_{50} 81.8 μM
251A07	13.00	not done	IC_{50} 10.6 μM
251C08	20.00	not done	IC_{50} 24.4 μM
251A09	14.00	not done	IC_{50} 34.4 μM
251G09	24.00	not done	IC_{50} 169.7 μM
251B07	12.00	not done	IC_{50} 45.4 μM
251C10	--	not done	IC_{50} >100 μM
251F09	15.00	not done	IC_{50} 188.5 μM
251A10	18.00	not done	IC_{50} 123.7 μM
250A05	6.64	IC_{50} ~10-20 μM	IC_{50} 141.5 μM
250B05	2.68	IC_{50} ~10-20 μM	IC_{50} 30.9 μM
250C04	12.82	0 (25 μM)	IC_{50} 7.1 μM
250B04	12.61	IC_{50} ~10-20 μM	IC_{50} 66.6 μM

While there are shown and described presently preferred embodiments of the invention, it is to be distinctly understood that the invention is not limited thereto but may be otherwise variously embodied and practiced within the scope of the following claims.

Claims

1. A compound of formula (I-B)



(I-B)

wherein

X_1 represents O, S or N-R_2;

X_2 represents O, S or N-R_4;

R_N represents hydrogen, hydroxy, formyl or amino;

R_C represents hydrogen, hydroxy, formyl or amino;

R_1 represents C1-C6 alkyl, 3- to 8-membered aliphatic cycles or 3- to 8-membered heteroaliphatic cycles, optionally substituted 5- or 6-membered heteroaryl or optionally substituted aryl, in particular optionally substituted phenyl, with the substituents of the phenyl being independent from each other selected from 1 to 5, preferably from 1 or 2, of C1-C6 alkyl, halogen selected from fluorine, chlorine, bromine, iodine, C1-C6 alkyloxy, hydroxy, C1-C6 alkene;

R_2 represents hydrogen, C1-C3 alkyl, C1-C3 alkoxy, phenoxy, C1-C3 thioalkyl;

R_3 represents C1-C6 alkoxy, 3- to 8-membered aliphatic cycles or 3- to 8-membered heteroaliphatic cycles, optionally substituted 5- or 6-membered heteroaryl or optionally substituted aryl, in particular optionally substituted phenyl, with the substituents of the phenyl being independent from each other selected from 1 to 5, preferably from 1 or 2, of C1-C6 alkyl, fluorine,

chlorine, bromine, iodine, C1-C6 alkyloxy, hydroxy, C1-C6 alkene; and

R_4 represents hydrogen, C1-C3 alkyl, C1-C3 alkoxy, phenoxy, C1-C3 thioalkyl; or

R_1 and R_2 and/or R_3 and R_4 form together with the N to which R2 and/or R_4, respectively, are bound a 5 or 6 membered heterocycle comprising 1 or 2 heteroatoms, the second heteroatom being N or O;

R_9 represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, phenyl, benzyl, phenoxy, -NH-phenyl, Br;

R_{10} represents -H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, phenyl, benzyl, phenoxy, -NH-phenyl, Br;

R_{11} represents $-(C_1-C_3$-alkyle)COOH, -NH-(C_1-C_3-alkyl)COOH, -O-(C_1-C_3-alkyle)COOH, -S-(C_1-C_3-alkyl)COOH, halogen, or a 5-membered or 6-membered heteroaromatic or aromatic ring, which ring is optionally substituted by 1 to 3 substituents, the substituents are selected from the group comprising halogene, $-NO_2$, hydroxy, $-SO_2$, -COOH, C1-C6 alkyl, C1-C6 alkoxy, -(C=O)-(C1-C6 alkyl), -COOR, wherein R is selected from C1-C6 alkyl or C2-C6 alkenyl;

or pharmaceutically acceptable salts thereof.

2. The compound of formula (I-B) claim 1 wherein

X_1 represents N-R_2 and

X_2 represents N-R_4.

3. The compound of formula (I-B) claim 1 or 2, wherein R_N represents hydrogen.

4. The compound of formula (I-B) claim 1 or 2, wherein R_C represents hydrogen.

5. The compound of formula (I-B) of anyone of the preceeding claims wherein

R_1 represents methyl, optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of methyl, fluorine, chlorine, methoxy;

R_2 represents hydrogen, methoxy;

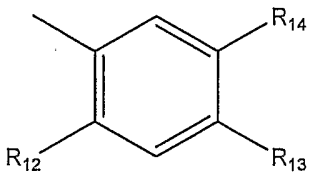
R_3 represents methoxy, optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of methyl, fluorine, chlorine, methoxy;

R_4 represents hydrogen, methoxy; and / or

R_1 and R_2 and/or R_3 and R_4 form together with the N to which R_2 and/or R_4, respectively, are bound a 5 or 6 membered heterocycle selected from pyrrolidinyl, piperidinyl, morpholinyl.

6. The compound of formula (I-B) of anyone of the preceding claims, wherein

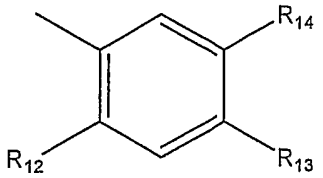
R_{11} represents



and R_{12}, R_{13}, and R_{14} are as defined in claim 1.

7. The compound of formula (I-B) of anyone of the preceding claims, wherein

R_{11} represents $-CH_2CH_2CH_2COOH$, $-CH_2CH_2COOH$, $-NH-CH_2CH_2COOH$, $-NH-CH_2COOH$, $-O-CH_2CH_2COOH$, $-O-CH_2COOH$, $-S-CH_2CH_2COOH$, $-S-CH_2COOH$, -Br, or



wherein

R_{12} represents -H, -Cl, -Br, -I, $-CH_3$, -OH, $-OCH_3$;

R_{13} represents -H, -OH, $-NO_2$, -Cl, -Br, -I, $-CH_3$, OCH_3 and

R_{14} represents -H, $-NO_2$, Cl, $-(C=O)-CH_3$, SO_2,-COOH, $-COOCH_3$

8. The compound of formula (I-B) according to anyone of the preceding claims, wherein

R_1 represents optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of C1-C3 alkyl (in particular methyl), halogen (in particular fluorine and chlorine). C1-C3 alkyloxy (in particular methoxy)

R_3 represents optionally substituted phenyl with the substituents being independent from each other selected from 1 or 2 of C1-C3 alkyl (in particular methyl), halogen (in particular fluorine and chlorine). C1-C3 alkyloxy (in particular methoxy).

9. The compound of formula (I-B) according to anyone of the preceding claims, wherein R_2 and R_4 represent hydrogen.

10. The compound of anyone of the preceding claims, wherein R_1 and R_2 and/or R_3 and R_4 form together with the N to which R_2 and/or R_4, respectively, are bound a 5 or 6 membered heterocycle comprising 1 or 2 heteroatoms, the second heteroatom being N or O.

11. The compound of anyone of the preceding claims, wherein R_1 and R_2, and/or R_3 and R_4 form together with the N to which R_2 and/or R_4, respectively, are bound a heterocycle selected from the group consisting of piperidinyl, morpholinyl, pyrrolinyl.

12. The compound of anyone of the preceding claims, wherein

R_{12} represents -H, -Cl, $-CH_3$,

R_{13} represents -H, -OH, -Cl, $-NO_2$,
R_{14} represents -H, -COOH, $-NO_2$, Cl.

13. The compound of anyone of the preceding claims as pharmaceutical.

14. Use of a compound of anyone of claims 1 - 12, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the production and/or the accumulation of amyloid beta-protein in warm blooded mammals, in particular human beings, especially for the treatment of Alzheimer's disease and / or Down's syndrome and / or aging of brain.

15. A pharmaceutical composition comprising one or more compounds according to anyone of claims 1 to 12, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier and optionally one or more adjuvants.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CH2006/000607

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/53 A61P25/28 C07D405/12

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)
A61K C07D

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)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMCATS CHEMICAL ABSTRACT SERVICE, COLUMBUS, OHIO, US; XP002422160 A1877/0078986 A0575/0026531 720397 A0879/0041217 A0879/0041217 A1570/0068441 720399 A1335/0060272 & "AMBINTER STOCK SCREENING COLLECTION" 3 July 2005 (2005-07-03), AMBINTER , PARIS, F-75016, FRANCE -/--	1-7,9,12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"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 February 2007	15/03/2007

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	Damiani, Federica

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY Chemical Library, Supplier: Interchim 6 March 2002 (2002-03-06), XP002422161 retrieved from STN accession no. RN398471-97-1 abstract	1-7,9,12
X	DATABASE REGISTRY Chemical Library, Supplier: AsInEx 17 April 2001 (2001-04-17), XP002422162 retrieved from STN accession no. RN331655-12-0 abstract	1-7,9,12
X	DATABASE REGISTRY Chemical Library, Supplier: Ambinter 28 February 2002 (2002-02-28), XP002422163 retrieved from STN accession no. RN396725-04-5 abstract	1-7,9,12
X	DATABASE REGISTRY Chemical Library, Supplier: SPECS 29 May 2003 (2003-05-29), XP002422164 retrieved from STN accession no. RN521934-50-9 abstract	1-7,9,12
X,P	HUANG DANZHI ET AL: "In silico discovery of beta-secretase inhibitors." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 26 APR 2006, vol. 128, no. 16, 26 April 2006 (2006-04-26), pages 5436-5443, XP002421783 ISSN: 0002-7863 the whole document	1-14
X,P	US 2006/223812 A1 (MANDELKOW ECKHARD [DE] ET AL) 5 October 2006 (2006-10-05) paragraph [0001] table 1 RN 339113-32-5claims 1-30,42,43	1-4,6,7, 10-15
A	GB 2 397 301 A (* DE NOVO PHARMACEUTICALS LTD) 21 July 2004 (2004-07-21) cited in the application page 1 - page 2 page 4 - page 5 claims 1-20	1-15

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INTERNATIONAL SEARCH REPORT

International application No
PCT/CH2006/000607

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 335 339 B1 (ARENAS JAIME E ET AL) 1 January 2002 (2002-01-01) abstract figures 47,69,76,112,144	1-13,15

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Information on patent family members

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GB 2397301 A	21-07-2004	NONE	
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