

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
8 February 2007 (08.02.2007)

PCT

(10) International Publication Number  
**WO 2007/014946 A1**

(51) International Patent Classification:  
C07K 7/02 (2006.01) A61P 25/28 (2006.01)  
A61K 38/03 (2006.01)

(21) International Application Number:  
PCT/EP2006/064885

(22) International Filing Date: 1 August 2006 (01.08.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
05016866.5 3 August 2005 (03.08.2005) EP

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

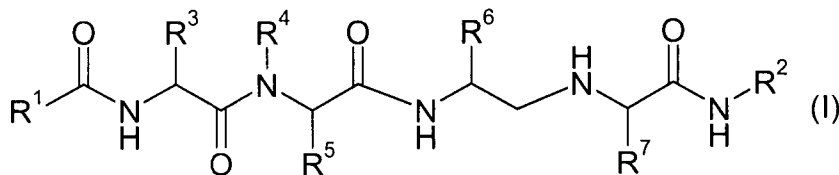
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED ETHANE-1,2-DIAMINES FOR THE TREATMENT OF ALZHEIMER'S DISEASE II



(57) Abstract: The invention relates to a compound of the formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are defined as in the specification and claims and to its use for treating or preventing Alzheimer's disease and other similar diseases.



WO 2007/014946 A1

## **Substituted Ethane-1,2-Diamines For The Treatment of Alzheimer's Disease II**

### BACKGROUND OF THE INVENTION

#### 1. TECHNICAL FIELD

5 The invention relates to novel substituted ethylene diamines and to their use for treating or preventing Alzheimer's disease and other similar diseases.

#### 2. BACKGROUND INFORMATION

Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily  
10 associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgement, and orientation. As the disease progresses, motor, sensory, and linguistic abilities are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

15

Alzheimer's disease is characterized by two major pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment know as A beta. Individuals with AD exhibit characteristic beta-amyloid deposits in the brain (beta amyloid plaques) and in cerebral  
20 blood vessels (beta amyloid angiopathy) as well as neurofibrillary tangles. Neurofibrillary tangles occur not only in Alzheimer's disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

25 Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD.

Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral  
30 Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurodegenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be

a causative precursor or factor in the development of disease. Deposition of A beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U. S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp2, am Memapsin2. See, for example, Sindha et al., 1999, Nature 402 : 537-554 and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A beta) plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, Neuron 6: 487-498. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. See, for example, Seubert et al., 1992, Nature 359: 325-327.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD, see for example Vassar, R. 2002, Adv. Drug Deliv. Rev. 54, 1589-1602 In vivo processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A beta

production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3,1-19.

BACE1 knockout mice fail to produce A beta, and present a normal phenotype. When  
5 crossed with transgenic mice that overexpress APP, the progeny show reduced amounts of  
A beta in brain extracts as compared with control animals (Luo et. al., 2001 *Nature  
Neuroscience* 4: 231-232). This evidence further supports the proposal that inhibition of  
beta-secretase activity and reduction of A beta in the brain provides a therapeutic method  
for the treatment of AD and other beta amyloid disorders.

10

The International patent application WO00/47618 identifies the beta-secretase enzyme and  
methods of its use. This publication also discloses oligopeptide inhibitors that bind the  
enzyme's active site and are useful in affinity column purification of the enzyme. In  
addition, WO00/77030 discloses tetrapeptide inhibitors of beta-secretase activity that are  
15 based on a statine molecule.

Various pharmaceutical agents have been proposed for the treatment of Alzheimer's  
disease but without any real success. US Patent 5,175,281 discloses aminosteroids as being  
useful for treating Alzheimer's disease. US Patent 5,502,187 discloses bicyclic heterocyclic  
20 amines as being useful for treating Alzheimer's disease.

EP 652 009 A1 discloses inhibitors of aspartyl protease which inhibit beta amyloid peptide  
production in cell culture and in vivo. The compounds which inhibit intracellular beta-  
amyloid peptide production are useful in treating Alzheimer's disease.

25

WO00/69262 discloses a new beta-secretase and its use in assays to screen for potential  
drug candidates against Alzheimer's disease.

WO01/00663 discloses memapsin 2 (human beta-secretase) as well as catalytically active  
30 recombinant enzyme. In addition, a method of identifying inhibitors of memapsin 2, as  
well as two inhibitors are disclosed. Both inhibitors that are disclosed are peptides.

WO01/00665 discloses inhibitors of memapsin 2 that are useful in treating Alzheimer's disease.

- 5 WO 03/057721 discloses substituted amino carboxamides for the treatment of Alzheimer's disease.

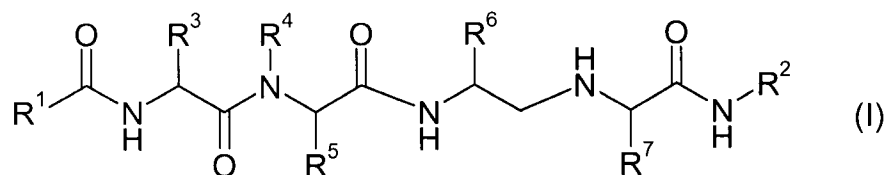
At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical  
10 agents with sufficient plasma and/or brain stability capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta secretase-mediated cleavage of APP, that are effective inhibitors of A beta production, and/or are  
15 effective to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

#### BRIEF SUMMARY OF THE INVENTION

20 Surprisingly, it has been found that substituted ethane-1,2-diamines of formula (I) show superior inhibition of beta secretase-mediated cleavage of APP and sufficient plasma stability.

Thus the invention relates in a first embodiment to compounds of group 1 according to  
25 formula (I)



wherein

R<sup>1</sup> represents

- 5 a) a C<sub>1-4</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,  
 wherein one non terminal methylene group of the C<sub>1-4</sub>-alkyl-group is  
 optionally replaced by a nitrogen or a oxygen atom, and  
 wherein the C<sub>1-4</sub>-alkyl- or the C<sub>3-6</sub>-cycloalkyl-group is substituted by one or  
 more substituents independently selected from the group consisting of HO-  
 10 CO-, HO-PO<sub>2</sub>- and HO-SO<sub>2</sub>-,  
 b) an aryl-group,  
 wherein the aryl-group is optionally substituted by one or more substituents  
 independently selected from the group consisting of halogen, C<sub>1-3</sub>-alkyl-,  
 HO-, HO-CO- and HO-SO<sub>2</sub>-, or  
 15 c) a heteroaryl-group,  
 wherein the heteroaryl-group is optionally substituted by one or more  
 substituents independently selected from the group consisting of halogen,  
 C<sub>1-3</sub>-alkyl-, HO-, HO-CO- and HO-SO<sub>2</sub>-

- 20 R<sup>2</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-  
 cycloalkyl-C<sub>1-5</sub>-alkyl-, heterocyclyl-, heterocyclyl-C<sub>1-5</sub>-alkyl-, aryl-, aryl-C<sub>1-5</sub>-  
 alkyl-, heteroaryl-, heteroaryl-C<sub>1-5</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-5</sub>-alkenyl-,  
 heterocyclyl-C<sub>2-5</sub>-alkenyl-, aryl-C<sub>2-5</sub>-alkenyl-, heteroaryl-C<sub>2-5</sub>-alkenyl-, C<sub>3-8</sub>-  
 cycloalkyl-C<sub>2-5</sub>-alkynyl-, heterocyclyl-C<sub>2-5</sub>-alkynyl-, aryl-C<sub>2-5</sub>-alkynyl- or a  
 25 heteroaryl-C<sub>2-5</sub>-alkynyl-group,  
 each of said groups may be substituted by one or more substituents  
 independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, HO-C<sub>1-3</sub>-  
 alkyl-, HO-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-, C<sub>1-3</sub>-alkyl-O-CO-C<sub>1-3</sub>-alkyl-,  
 C<sub>1-3</sub>-alkyl-O-, halogen-, carboxy-, formyl-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N-  
 30 , (R<sup>8</sup>)<sub>2</sub>N-C<sub>1-3</sub>-alkyl-, (R<sup>8</sup>)<sub>2</sub>N-CO-, (R<sup>8</sup>)<sub>2</sub>N-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-CO-  
 N(R<sup>8</sup>)-, (R<sup>8</sup>)<sub>2</sub>N-SO<sub>2</sub>-, C<sub>1-3</sub>-alkyl-SO<sub>2</sub>- and C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-N(R<sup>8</sup>)-,

- 5  $R^3$  represents a  $C_{1-8}$ -alkyl-,  $C_{2-8}$ -alkenyl-,  $C_{2-8}$ -alkynyl-,  $C_{1-8}$ -alkyl-O- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl-,  $C_{3-8}$ -cycloalkyl- $C_{1-3}$ -alkyl-,  $C_{1-3}$ -alkyl-S- $C_{1-3}$ -alkyl-, aryl-, aryl- $C_{1-4}$ -alkyl-, heteroaryl- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkenyl-, heterocyclyl- $C_{2-3}$ -alkenyl-, aryl- $C_{2-3}$ -alkenyl-, heteroaryl- $C_{2-3}$ -alkenyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkynyl-, heterocyclyl- $C_{2-3}$ -alkynyl-, aryl- $C_{2-3}$ -alkynyl- or a heteroaryl- $C_{2-3}$ -alkynyl-group, each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-,  $(R^8)_2N$ - and  $(R^8)_2N$ -CO-,
- 10  $R^4$  represents hydrogen, a  $C_{1-6}$ -alkyl-,  $C_{2-6}$ -alkenyl-,  $C_{2-6}$ -alkynyl- or a  $C_{3-8}$ -cycloalkyl- $C_{1-3}$ -alkyl-group, each of said groups may be optionally substituted by one or more fluor atoms,
- 15  $R^5$  represents a  $C_{1-8}$ -alkyl-,  $C_{2-8}$ -alkenyl-,  $C_{2-8}$ -alkynyl-,  $C_{1-8}$ -alkyl-O- $C_{1-3}$ -alkyl-,  $C_{1-3}$ -alkyl-S- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl-,  $C_{3-8}$ -cycloalkyl- $C_{1-3}$ -alkyl-, aryl-, aryl- $C_{1-4}$ -alkyl-, heteroaryl- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkenyl-, heterocyclyl- $C_{2-3}$ -alkenyl-, aryl- $C_{2-3}$ -alkenyl-, heteroaryl- $C_{2-3}$ -alkenyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkynyl-, heterocyclyl- $C_{2-3}$ -alkynyl-, aryl- $C_{2-3}$ -alkynyl- or a heteroaryl- $C_{2-3}$ -alkynyl-group, each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-,  $(R^8)_2N$ - and  $(R^8)_2N$ -CO-,
- 20  $R^6$  represents a  $C_{1-8}$ -alkyl-,  $C_{2-8}$ -alkenyl-,  $C_{2-8}$ -alkynyl-,  $C_{1-8}$ -alkyl-O- $C_{1-3}$ -alkyl-,  $C_{1-3}$ -alkyl-S- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl-,  $C_{3-8}$ -cycloalkyl- $C_{1-3}$ -alkyl-, aryl-, aryl- $C_{1-4}$ -alkyl-, heteroaryl- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkenyl-, heterocyclyl- $C_{2-3}$ -alkenyl-, aryl- $C_{2-3}$ -alkenyl-, heteroaryl- $C_{2-3}$ -alkenyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkynyl-, heterocyclyl- $C_{2-3}$ -alkynyl-, aryl- $C_{2-3}$ -alkynyl- or a heteroaryl- $C_{2-3}$ -alkynyl-group,
- 25

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

5 R<sup>7</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl-, heteroaryl-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkenyl-, heterocyclyl-C<sub>2-3</sub>-alkenyl-, aryl-C<sub>2-3</sub>-alkenyl-, heteroaryl-C<sub>2-3</sub>-alkenyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkynyl-, heterocyclyl-C<sub>2-3</sub>-alkynyl-, aryl-C<sub>2-3</sub>-alkynyl- or a heteroaryl-C<sub>2-3</sub>-alkynyl-group,  
10 each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>8</sup> each independently of one another represents hydrogen, a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, heterocyclyl-, heterocyclyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-3</sub>-alkyl-, heteroaryl-, heteroaryl-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkenyl-, heterocyclyl-C<sub>2-3</sub>-alkenyl-, aryl-C<sub>2-3</sub>-alkenyl-, heteroaryl-C<sub>2-3</sub>-alkenyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkynyl-, heterocyclyl-C<sub>2-3</sub>-alkynyl-, aryl-C<sub>2-3</sub>-alkynyl- or a heteroaryl-C<sub>2-3</sub>-alkynyl-group,  
15 each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-, halogen-, carboxy-, hydroxy-, nitro-, cyano-, H<sub>2</sub>N- and H<sub>2</sub>N-SO<sub>2</sub>-,  
20

25 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

Furthermore, the invention relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a  
30 pharmaceutically acceptable carrier or diluent.

Another aspect of the present invention is the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in treating a patient who has, or in preventing a patient from getting, a disease or condition associated with an abnormal processing of the amyloid precursor protein and/or aggregation of the Abeta peptide and/or condition induced by the Abeta peptide. Conditions are selected from Alzheimer's disease, diffuse Lewy body type of Alzheimer's disease, Down's syndrome, MCI ("Mild Cognitive Impairment"), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, Cerebral Amyloid Angiopathy, Traumatic Brain Injury, , Dementia, Parkinson's Syndrome, Pancreatitis, inclusion body myositis (IBM) or central or peripheral amyloid diseases.

Furthermore the invention relates to a method for inhibiting  $\beta$ -secretase activity, comprising exposing said  $\beta$ -secretase to an effective inhibitory amount of a compound of formula (I).

The present invention provides compounds, compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP).

More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A beta peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A beta peptide.

Therefore, a further object of the invention relates to the the use of a compound according to the present invention for the manufacture of a medicament for the treatment or prevention of diseases and conditions which can be modified by inhibition of  $\beta$ -secretase.

The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with

Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia  
5 associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD.

The compounds of the invention possess beta-secretase inhibitory activity.

10 The inhibitory activities of the compounds of the invention are readily demonstrated, for example, using one or more of the assays described herein or known in the art.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of formula (I) that are useful in treating and  
15 preventing Alzheimer's disease.

Some expressions used hereinbefore and below to describe the compounds according to the invention will now be defined more fully.

20 The term alkyl in the present invention denotes, unless otherwise stated, a unbranched or branched hydrocarbon group having 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, most preferably 1 to 5 carbon atoms, especially 1, 2 or 3 carbon atoms. Examples are methyl, ethyl, propyl, butyl, pentyl, hexyl, etc. Unless otherwise stated the above terms propyl, butyl, pentyl, hexyl, heptyl, octyl also include all the possible isomeric forms like  
25 n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, n-hexyl, iso-hexyl, etc. In some cases common abbreviations are also used to denote the above mentioned alkyl groups, such as Me for methyl, Et for ethyl etc.

The term alkyl includes, if not otherwise stated, also such alkyl groups which are mono- or  
30 polysubstituted by fluorine. Examples include: trifluoromethyl, trifluoromethoxy,

difluoromethoxy, perfluoroethyl, perfluoropropyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoroethoxy, 1,1,1-trifluoroprop-2-yl, etc.

Preferred fluorinated alkyl groups are fluoromethyl, difluoromethyl and trifluoromethyl.

- 5 The term halogen generally denotes fluorine, chlorine, bromine or iodine particularly F, Cl and Br.

The term alkenyl denotes, unless otherwise stated, branched or unbranched hydrocarbon groups having from 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, most preferably 2  
10 to 4 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, allyl, 1-butenyl, 1-pentenyl, 1-hexenyl and the like.

The term alkynyl denotes, unless otherwise stated, branched or unbranched hydrocarbon groups having from 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, most preferably 2  
15 to 4 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, propargyl, butynyl, pentynyl and the like.

The term cycloalkyl (including those which are part of other groups, especially cycloalkyl-alkyl- or cycloalkoxy-) denotes, unless otherwise stated, saturated carbocyclic groups with  
20 3 to 12 carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system. Preferably the cycloalkyl group is monocyclic with 3 to 8 carbon atoms, most preferably 3, 4, 5 or 6 carbon atoms, especially 3 or 6 carbon atoms. Examples are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl etc. Most preferred is cyclopropyl and cyclohexyl.

25

The term aryl group, unless otherwise stated, denotes an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed aromatic rings (e.g. naphthyl, anthryl). Examples are: phenyl, biphenyl, 1-naphthyl, 2-naphthyl, anthracenyl, phenanthrenyl. A particularly preferred meaning of "aryl" is phenyl.

30

The term heteroaryl group, unless otherwise stated, denotes one or more aromatic or

unsaturated ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and 1, 2, 3, or 4 heteroatoms selected from nitrogen, oxygen, or sulfur. The term heteroaryl group embraces also heteroaryl groups containing a nitrogen atom in the ring substituted with an oxygen atom (heteroaryl N-oxides). Typical

5 heteroaryl N-oxides are pyridin-2-yl N-oxide, pyridin-3-yl N-oxide, pyridin-4-yl N-oxide, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyll N-oxide, indazolyl N-oxide,

10 benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, tetrazolyl N-oxide. Further examples for heteroaryl groups are: thiophenyl, pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyll, indazolyl,

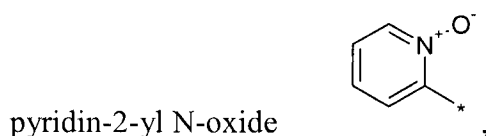
15 benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranlyl,

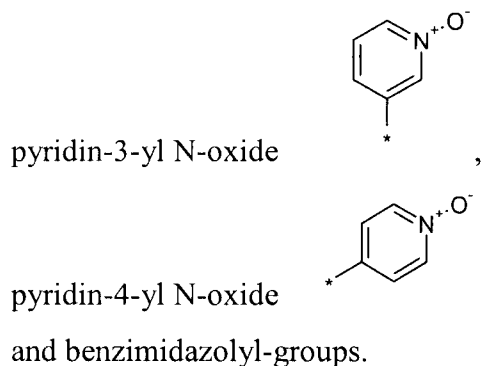
isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl,

20 benzotetrahydrofuranlyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranlyl, benzothiopyranlyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, tetrahydroquinolinyl, dihydroquinolinyl,

25 dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, benzothiopyranlyl S-oxide, benzothiopyranlyl S,S-dioxide, benzo[1,3]dioxol.

Preferred heteroaryl groups are





- 5 The term heterocyclyl group, unless otherwise stated, denotes one or more saturated carbocyclic ring systems of 3-, 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least 1, 2, 3, or 4 heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl,
- 10 homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, morpholinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, azepanyl, diazepanyl,
- 15 tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. An especially preferred heterocyclyl group is morpholinyl.

Terms such as cycloalkyl-alkyl-, heterocyclyl-alkyl-, aryl-alkyl-, heteroaryl-alkyl- refer to alkyl groups, as defined above, which are substituted with a cycloalkyl, heterocyclyl, aryl

20 or heteroaryl group. Examples of aryl-alkyl-groups are benzyl or 2-phenylethyl. Examples for cycloalkyl-alkyl-groups are cyclopropylmethyl-, cyclohexylmethyl or cyclopentylethyl.

Many of the terms given above may be used repeatedly in the definition of a formula or group and in each case have one of the meanings given above, independently of one

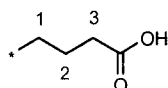
25 another.

The term "optionally substituted" used in this application indicates that the group thus designated is either unsubstituted or mono- or polysubstituted by the substituents specified. If the group in question is polysubstituted, the substituents may be identical or different.

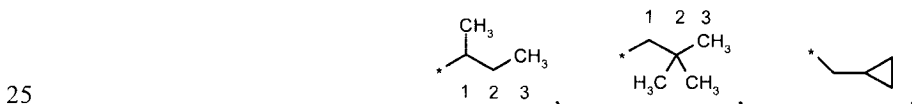
- 5 The compounds of the present invention contain asymmetric carbon atoms and may be present in the form of one of the possible isomers or as a mixture thereof, e.g. depending on the number, absolute and relative configurations of the asymmetric carbon atoms as pure isomers, such as antipodes and/or diastereoisomers, or as isomeric mixtures, such as enantiomeric mixtures, e.g. racemates, diastereoisomeric mixtures or racemic mixtures; the  
 10 invention relates to both the pure isomers and all the possible isomeric mixtures, and is to be understood as such hereinbefore and hereinafter, even if stereochemical details are not specifically mentioned in each case.

The symbol “-“ in general represents a bond between two atoms in a chain and the point of attachment of a group to the rest of the molecule as defined. For example, an aryl-C<sub>1-3</sub>-alkyl-group indicates an arylalkyl-group (e.g. 2-phenylethyl-) wherein the phenyl group is attached to the ethyl group and the ethyl group is attached to the rest of the molecule. The  
 15 numeration of the atoms of a substituent starts with the atom which is closest to the rest of the molecule to which the substituent is attached.

- 20 For example, the term “3-carboxypropyl-group” represents the following substituent:



wherein the carboxy group is attached to the third carbon atom of the propyl group. The terms “1-methylpropyl-“, “2,2-dimethylpropyl-“ or “cyclopropylmethyl-“ group represent the following groups:



The asterisk is used in sub-formulas to indicate the bond which is connected to the rest of the molecule as defined.

In a preferred embodiment the present invention relates to compounds of group 2 according to formula (I), wherein

5 R<sup>1</sup> represents

a) a C<sub>1-4</sub>-alkyl-group,

wherein the C<sub>1-4</sub>-alkyl- is substituted by one or more substituents

independently selected from the group consisting of HO-CO- and HO-SO<sub>2</sub>-,

b) an aryl-group,

10 optionally substituted by one or more substituents independently selected from the group consisting of fluoro, HO- and HO-CO-, or

c) a heteroaryl-group,

optionally substituted by one or more substituents independently selected from the group consisting of fluoro, chloro, Me, HO- and HO-CO-.

15

R<sup>2</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-5</sub>-alkyl-, heterocyclyl-, heterocyclyl-C<sub>1-5</sub>-alkyl-, aryl-, aryl-C<sub>1-5</sub>-alkyl-, heteroaryl- or a heteroaryl-C<sub>1-5</sub>-alkyl-group,

each of said groups may be substituted by one or more substituents

20 independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, HO-C<sub>1-3</sub>-alkyl-, HO-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-, C<sub>1-3</sub>-alkyl-O-, halogen-, carboxy-, formyl-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N-, (R<sup>8</sup>)<sub>2</sub>N-C<sub>1-3</sub>-alkyl-, (R<sup>8</sup>)<sub>2</sub>N-CO-, (R<sup>8</sup>)<sub>2</sub>N-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-CO-N(R<sup>8</sup>)-, (R<sup>8</sup>)<sub>2</sub>N-SO<sub>2</sub>-, C<sub>1-3</sub>-alkyl-SO<sub>2</sub>- and C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-N(R<sup>8</sup>)-,

25

R<sup>3</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,

each of said groups may be optionally substituted by one or more

30 substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>4</sup> represents hydrogen, a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl- or a C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-group,  
each of said groups may be optionally substituted by one or more fluor  
5 atoms,

R<sup>5</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl- and heteroaryl-C<sub>1-3</sub>-alkyl-,  
10 each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>6</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,  
15 each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>7</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,  
20 each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>8</sup> each independently of one another represents hydrogen, a C<sub>1-6</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, heterocyclyl-, heterocyclyl-C<sub>1-3</sub>-alkyl-,  
25 aryl-, aryl-C<sub>1-3</sub>-alkyl-, heteroaryl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,

30

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-, halogen-, carboxy-, hydroxy-, nitro-, cyano-, H<sub>2</sub>N- and H<sub>2</sub>N-SO<sub>2</sub>-,

5

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

In a further preferred embodiment the present invention relates to compounds of group 3 according to formula (I), wherein

10

R<sup>1</sup> represents

- a) a HO-CO-(CH<sub>2</sub>)<sub>n</sub>- or a HO-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-group wherein n is 1, 2, 3 or 4, or
- b) a quinolinyl N-oxide, isoquinolinyl N-oxide, pyridin-2-yl N-oxide, pyridin-3-yl N-oxide, pyridin-4-yl N-oxide, or

15

- c) a phenyl group,

wherein the phenyl group is optionally substituted by one or more substituents independently selected from the group consisting of halogen and hydroxy-,

20

R<sup>8</sup> each independently of one another represents hydrogen or a C<sub>1-6</sub>-alkyl-group, wherein the C<sub>1-6</sub>-alkyl-group may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-O-, halogen, carboxy-, hydroxy-, nitro-, cyano- and H<sub>2</sub>N-,

25

and wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are defined as for the compounds of group 1 or 2, or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

In a further preferred embodiment the present invention relates to compounds of group 4 according to formula (I), wherein

30

R<sup>1</sup> represents

- a) HO-CO-(CH<sub>2</sub>)<sub>n</sub>-group, wherein n is 1, 2, 3 or 4,  
b) a pyridin-2-yl N-oxide, pyridin-3-yl N-oxide, pyridin-4-yl N-oxide, or  
c) a phenyl group,

5 wherein the phenyl group is optionally substituted by one or more substituents independently selected from the group consisting of halogen and hydroxy,

R<sup>8</sup> each independently of one another represents hydrogen or a C<sub>1-6</sub>-alkyl-group, wherein the C<sub>1-6</sub>-alkyl-group may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-  
10 O- and fluor,

and wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are defined as for the compounds of group 1 or 2, or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
15 thereof.

In a further preferred embodiment the present invention relates to compounds of group 5 according to formula (I), wherein

R<sup>1</sup> represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-2-yl N-oxide, pyridin-3-yl N-oxide, pyridin-  
20 4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

R<sup>8</sup> each independently of one another represents hydrogen or a C<sub>1-6</sub>-alkyl-group,  
25 and wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are defined as for the compounds of group 1 or 2, or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

In a further preferred embodiment the present invention relates to compounds of group 6 according to formula (I), wherein

R<sup>1</sup> represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

5

R<sup>8</sup> each independently of one another represents hydrogen or a C<sub>1-3</sub>-alkyl-group,

and wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are defined as for the compounds of group 1 or 2, or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

10

In a further preferred embodiment the present invention relates to compounds of group 7 according to formula (I), wherein

R<sup>2</sup> represents a C<sub>1-5</sub>-alkyl-, C<sub>2-5</sub>-alkenyl-, C<sub>2-5</sub>-alkynyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-5</sub>-alkyl-, phenyl-C<sub>1-5</sub>-alkyl- or a heteroaryl-C<sub>1-5</sub>-alkyl-group

15

wherein the C<sub>1-5</sub>-alkyl-group may be optionally substituted by one or more fluoro atoms, and

wherein the phenyl group may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, nitro-, halogen, hydroxy-, carboxy-, (R<sup>8</sup>)<sub>2</sub>N-, (R<sup>8</sup>)<sub>2</sub>N-C<sub>1-3</sub>-alkyl-, (R<sup>8</sup>)<sub>2</sub>N-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-CO-N(R<sup>8</sup>)-, C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-, (R<sup>8</sup>)<sub>2</sub>N-CO-, HO-C<sub>1-3</sub>-alkyl-, HO-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO- and C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-N(R<sup>8</sup>)-,

20

R<sup>3</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, phenyl-, phenyl-C<sub>1-4</sub>-alkyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,

25

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-,

30

R<sup>4</sup> represents hydrogen or a C<sub>1-4</sub>-alkyl-group  
optionally substituted with one or more Fluor atoms,

5 R<sup>5</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-,  
phenyl-, phenyl-C<sub>1-4</sub>-alkyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl- or  
a C<sub>3-6</sub>-cycloalkyl-group,

each of said groups may be optionally substituted by one or more  
substituents independently selected from the group consisting of halogen,  
carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-,

10

R<sup>6</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-,  
phenyl-, phenyl-C<sub>1-4</sub>-alkyl-, heteroaryl-C<sub>1-3</sub>-alkyl, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-  
alkyl-S-C<sub>1-3</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,

each of said groups may be optionally substituted by one or more  
substituents independently selected from the group consisting of halogen,  
15 carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-,

15

R<sup>7</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-,  
phenyl-, phenyl-C<sub>1-4</sub>-alkyl-group, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-  
20 alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,

each of said groups may be optionally substituted by one or more  
substituents independently selected from the group consisting of halogen,  
carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-groups,

20

25 and wherein R<sup>1</sup> and R<sup>8</sup> are defined as for the compounds of group 1, 2, 3, 4, 5 or 6,  
or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
thereof.

In a further preferred embodiment the present invention relates to compounds of group 8 according to formula (I), wherein

R<sup>2</sup> represents a C<sub>1-3</sub>-alkyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, phenyl-C<sub>1-3</sub>-alkyl- or a pyridyl-C<sub>1-3</sub>-alkyl-group

5            wherein the C<sub>1-3</sub>-alkyl-group may be optionally substituted by one or more fluoro atoms, and

             wherein the phenyl group may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, nitro-, hydroxy-, carboxy-, H<sub>2</sub>N-, H<sub>2</sub>N-CH<sub>2</sub>-, H<sub>2</sub>N-CO-CH<sub>2</sub>-, Me-CO-NH-  
10            , Me-SO<sub>2</sub>-, H<sub>2</sub>N-CO-, HO-CH<sub>2</sub>-, HOCO-CH<sub>2</sub>-, Me-OCO-CH<sub>2</sub>-, Me-OCO-, and Me-SO<sub>2</sub>-NH-,

R<sup>3</sup> represents a C<sub>1-5</sub>-alkyl-group,

15            R<sup>4</sup> represents hydrogen,

R<sup>5</sup> represents a C<sub>1-5</sub>-alkyl- or a phenyl-C<sub>1-2</sub>-alkyl-group,

R<sup>6</sup> represents a C<sub>1-4</sub>-alkyl- or a phenyl-C<sub>1-2</sub>-alkyl-group,

20

R<sup>7</sup> represents a C<sub>1-5</sub>-alkyl- or a phenyl-C<sub>1-2</sub>-alkyl-group,

             wherein the alkyl-group may be optionally substituted by one or more substituents independently selected from the group consisting of carboxy-, hydroxy-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-groups,

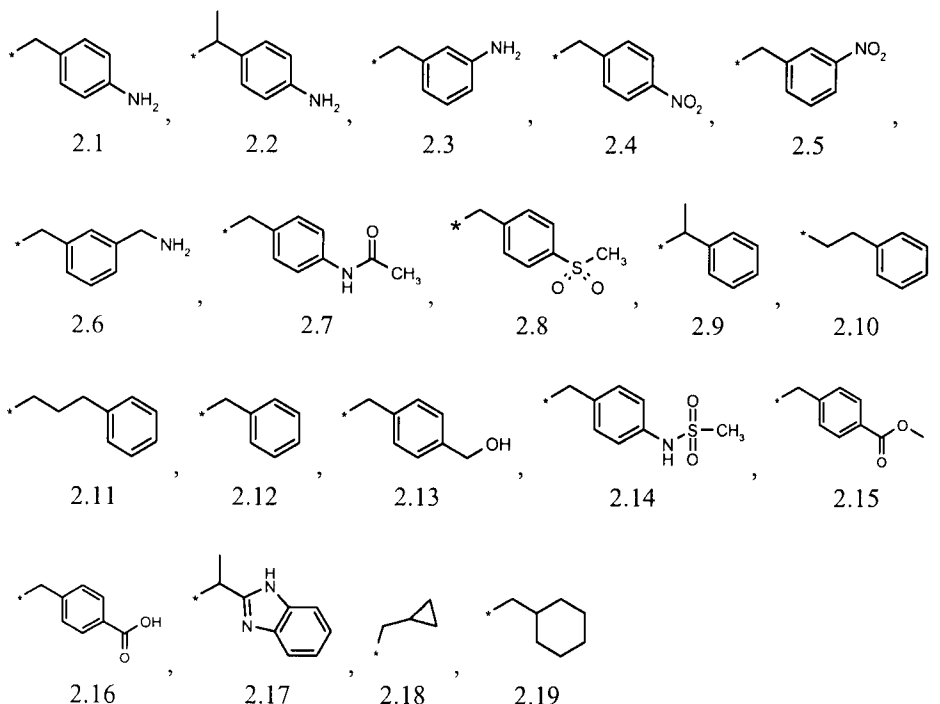
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and wherein R<sup>1</sup> is defined as for the compounds of group 1, 2, 3, 4, 5 or 6, or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

In a further preferred embodiment the present invention relates to compounds of group 9 according to formula (I), wherein

$R^2$  represents an ethyl-, n-propyl- or a 2-methylpropyl-group,  
or a substituent selected from the group consisting of

5



10

15

$R^3$  represents a  $C_{1-5}$ -alkyl-group,

20  $R^4$  represents hydrogen,

$R^5$  represents a  $C_{1-5}$ -alkyl- or a phenyl- $C_{1-2}$ -alkyl-group,

$R^6$  represents a  $C_{1-4}$ -alkyl- or a phenyl- $C_{1-2}$ -alkyl-group,

25

$R^7$  represents a  $C_{1-5}$ -alkyl- or a phenyl- $C_{1-2}$ -alkyl-group,

wherein the alkyl-group may be optionally substituted by one or more substituents independently selected from the group consisting of carboxy-, hydroxy-,  $H_2N$ - and  $H_2N-CO$ -groups,

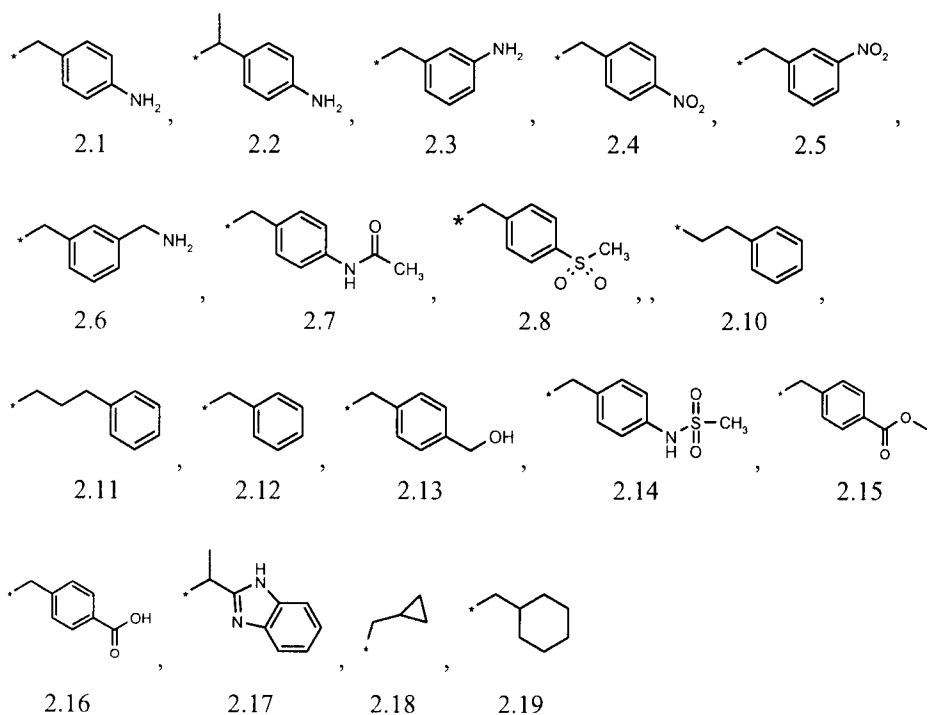
and wherein R<sup>1</sup> is defined as for the compounds of group 1, 2, 3, 4, 5 or 6 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

5

In a further preferred embodiment the present invention relates to compounds of group 10 according to formula (I), wherein

R<sup>2</sup> represents an ethyl-, n-propyl- or a 2-methylpropyl-group, or a substituent selected from the group consisting of

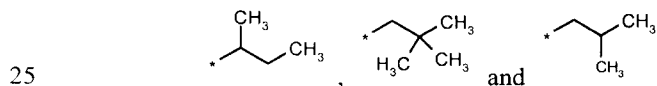
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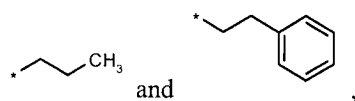
20

R<sup>3</sup> represents a substituent selected from the group consisting of

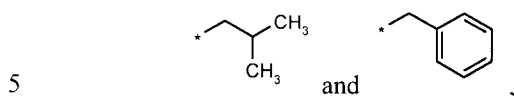


R<sup>4</sup> represents hydrogen,

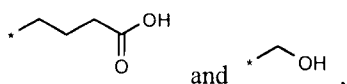
R<sup>5</sup> represents a substituent selected from the group consisting of



R<sup>6</sup> represents a substituent selected from the group consisting of



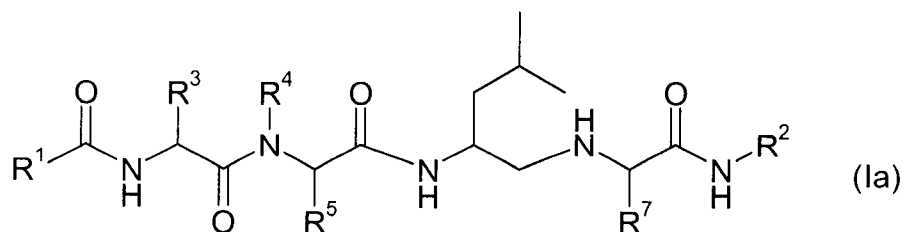
R<sup>7</sup> represents a methyl-, ethyl-, n-propyl- or a n-butyl-group,  
or a substituent selected from the group consisting of



10

and wherein R<sup>1</sup> is defined as for the compounds of group 1, 2, 3, 4, 5 or 6,  
or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
thereof.

15 In a more preferred embodiment the present invention refers to compounds according to  
formula (Ia)



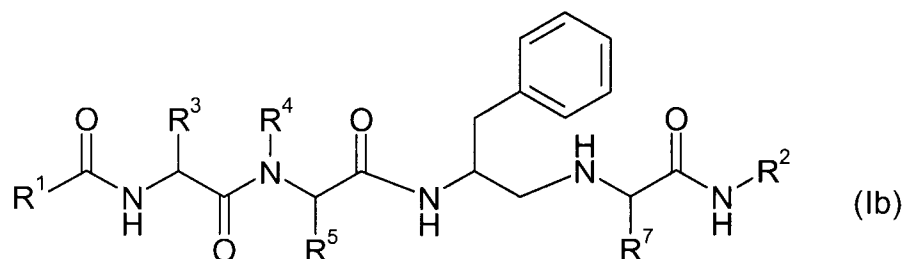
wherein

20 R<sup>1</sup> represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or  
 a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group, and

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> are defined as for the compounds of group 1, 2, 3, 4, 5, 6, 7, 8, 9  
or 10,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

- 5 In another more preferred embodiment the present invention refers to compounds according to formula (Ib)

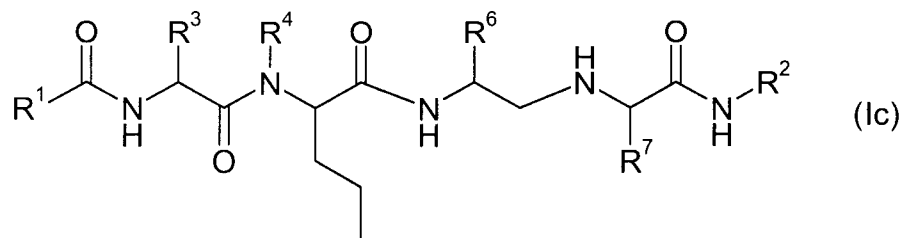


wherein

- R<sup>1</sup> represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a  
 10 4-hydroxy-2,3,5,6-tetrafluorophenyl-group, and  
 R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>7</sup> and R<sup>8</sup> are defined as for the compounds of group 1, 2, 3, 4, 5, 6, 7, 8, 9  
 or 10,  
 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
 thereof.

15

- In another more preferred embodiment the present invention refers to compounds according to formula (Ic)

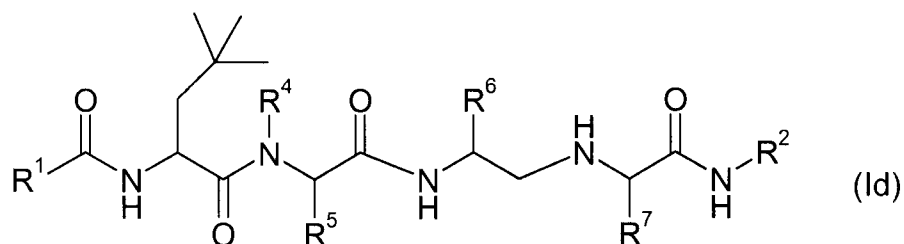


wherein

- 20 R<sup>1</sup> represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or  
 a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group, and  
 R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are defined as for the compounds of group 1, 2, 3, 4, 5, 6, 7, 8, 9  
 or 10,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

In another more preferred embodiment the present invention refers to compounds according to formula (Id)



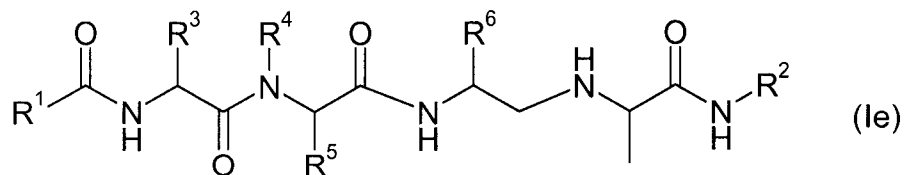
wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group, and

10  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are defined as for the compounds of group 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

15 In another more preferred embodiment the present invention refers to compounds according to formula (Ie)



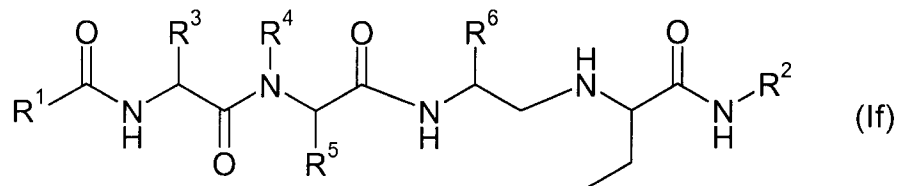
wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group, and

20  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^8$  are defined as for the compounds of group 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

In another more preferred embodiment the present invention refers to compounds according to formula (If)

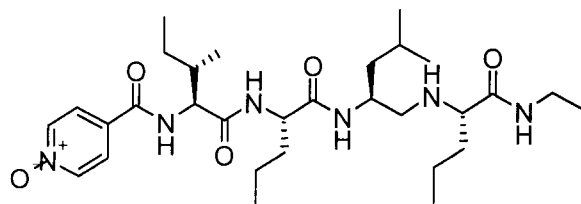


wherein

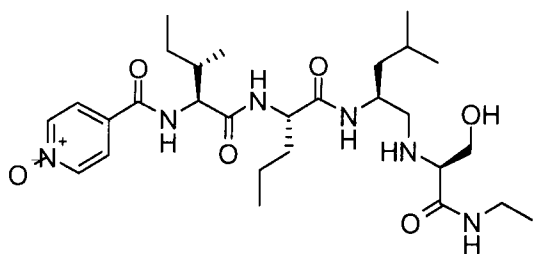
- 5 R<sup>1</sup> represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group, and  
 R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>8</sup> are defined as for the compounds of group 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,  
 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
 10 thereof.

Most preferred are the compounds of formulae (1) through (58):

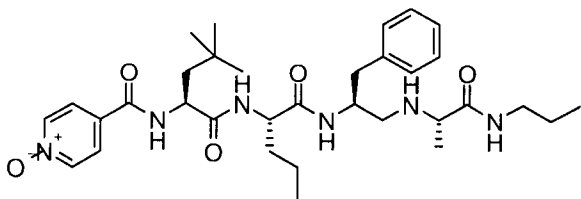
Compound	Compound No.	Example No
	(1)	1.1
	(2)	1.2



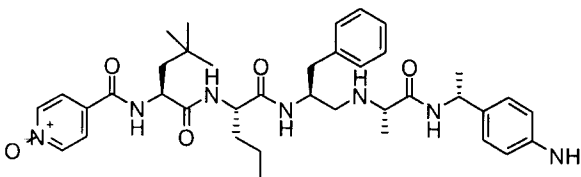
(3) 1.3



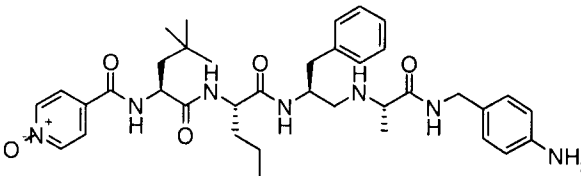
(4) 1.4



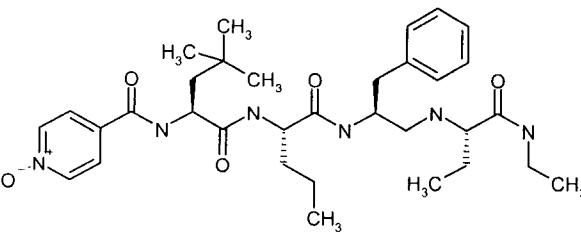
(5) 3.9



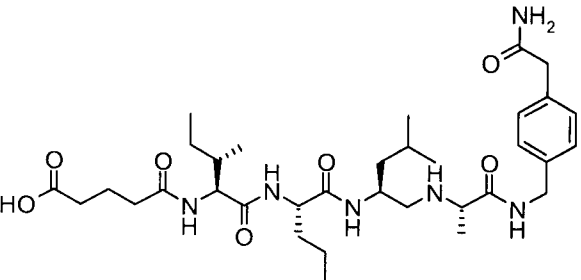
(6) 5



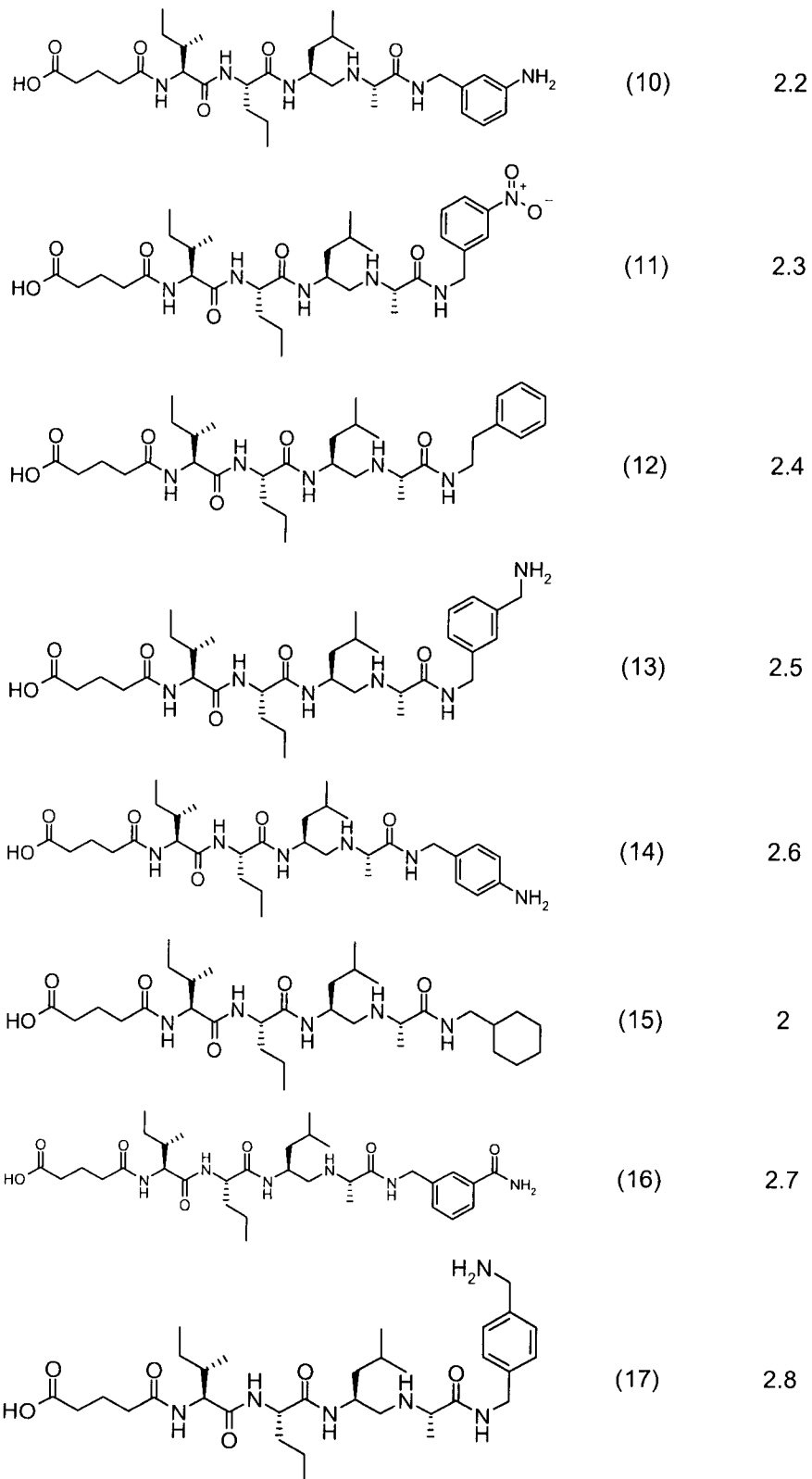
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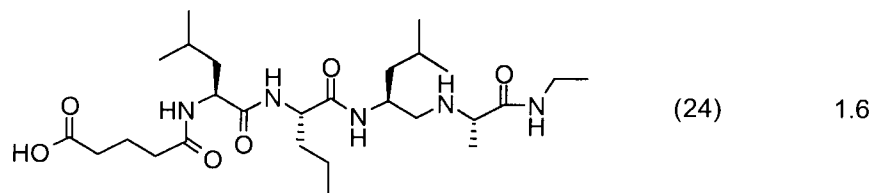
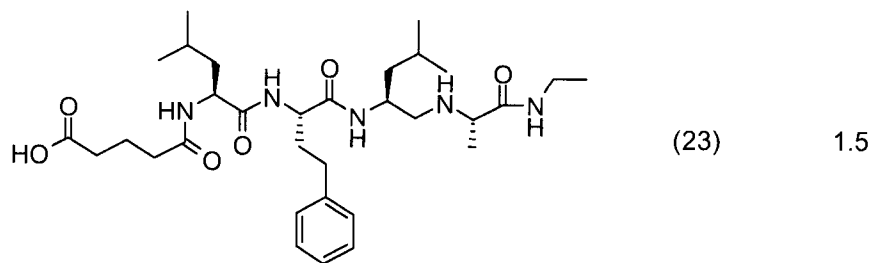
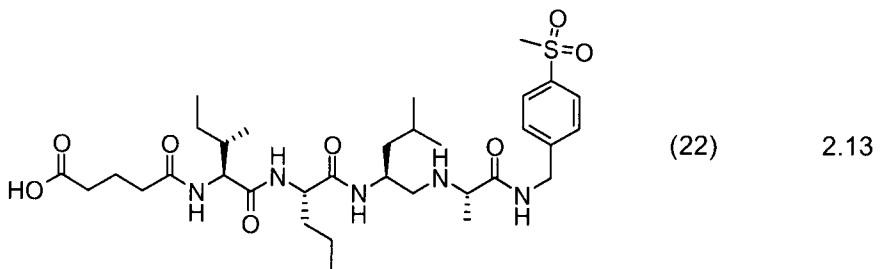
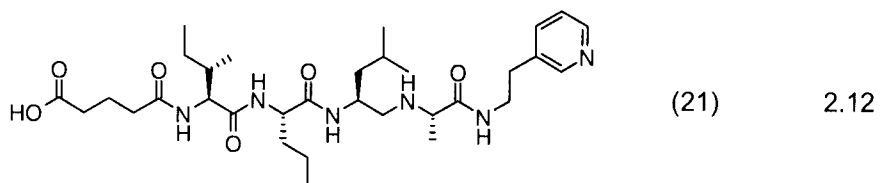
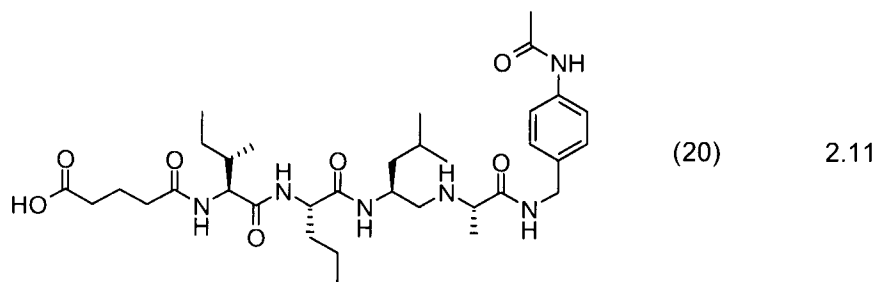
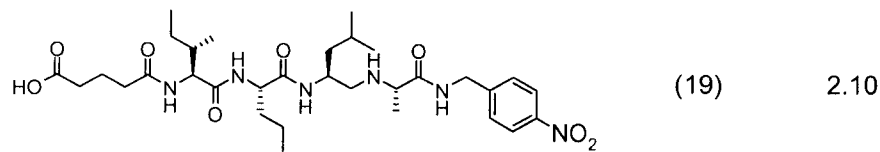
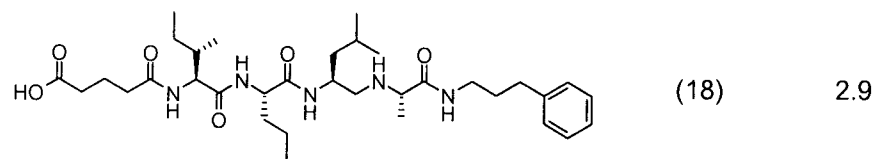


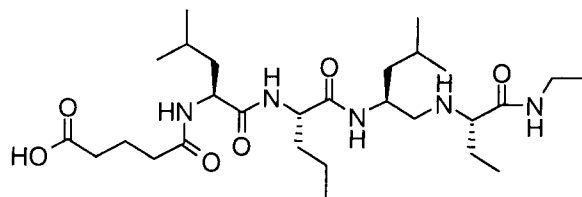
(8) 9



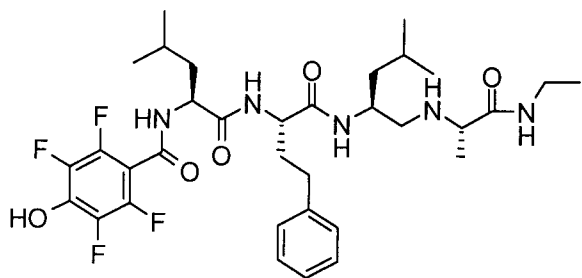
(9) 2.1



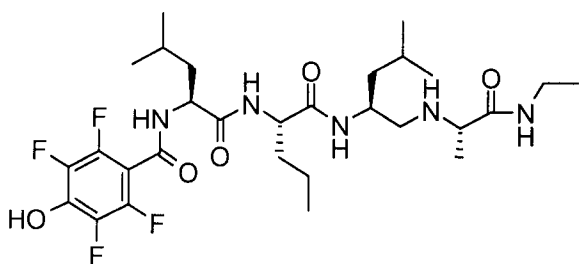




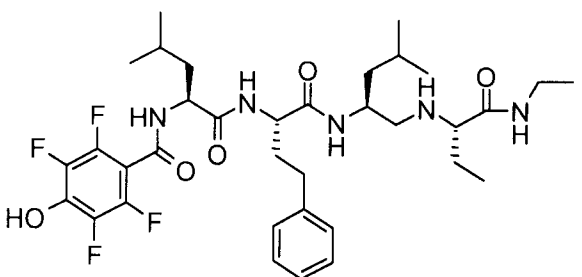
(25) 1.7



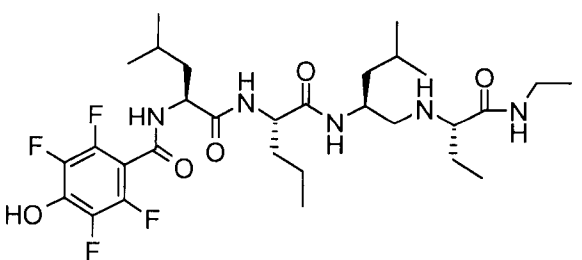
(26) 1.8



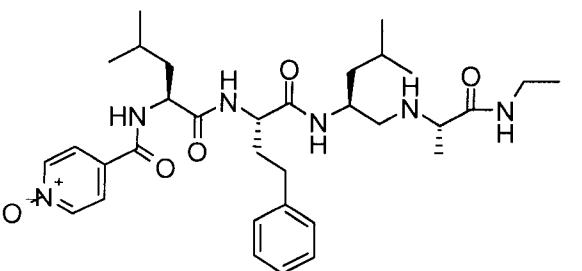
(27) 1.9



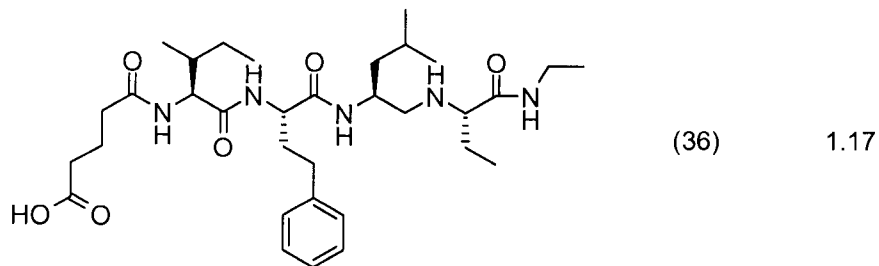
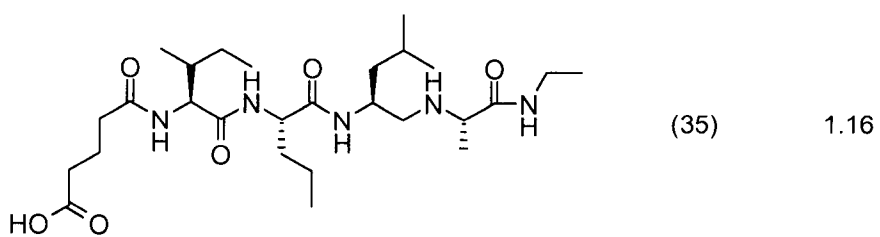
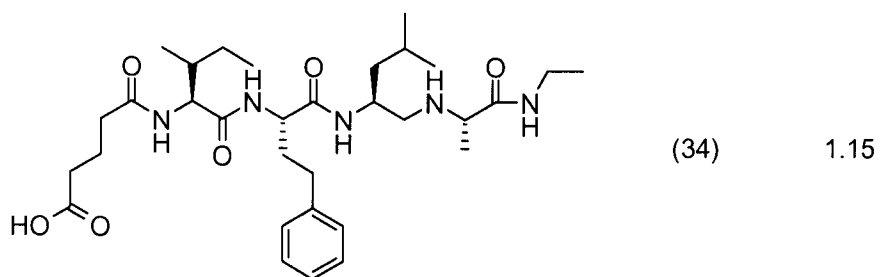
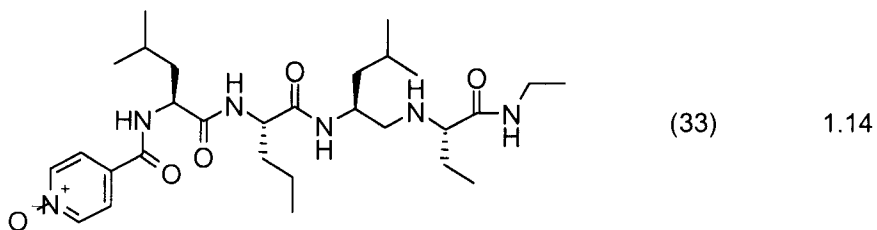
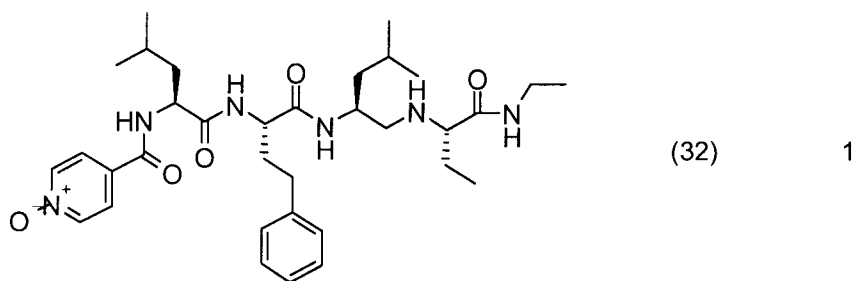
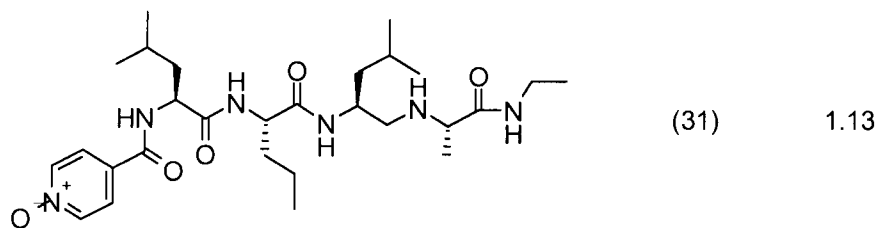
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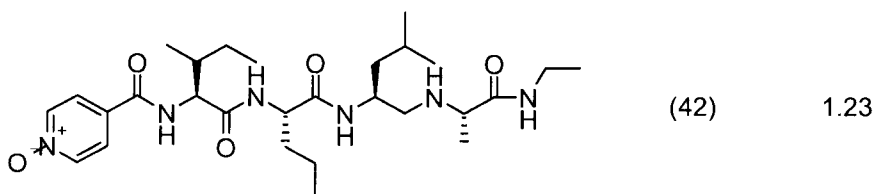
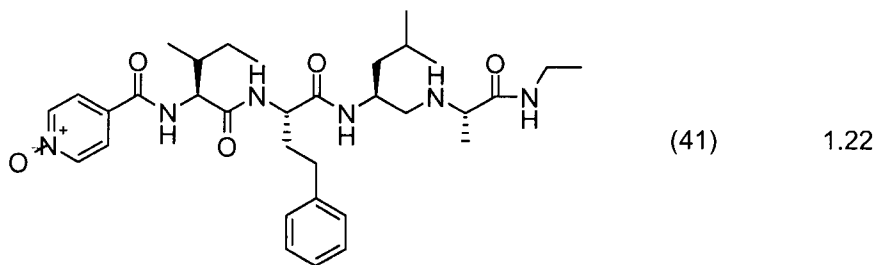
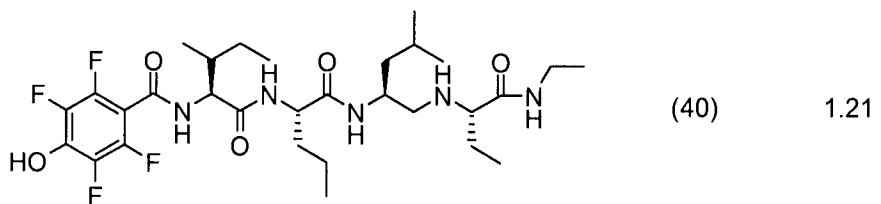
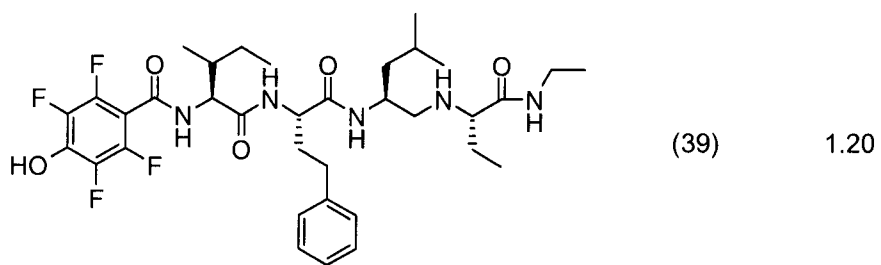
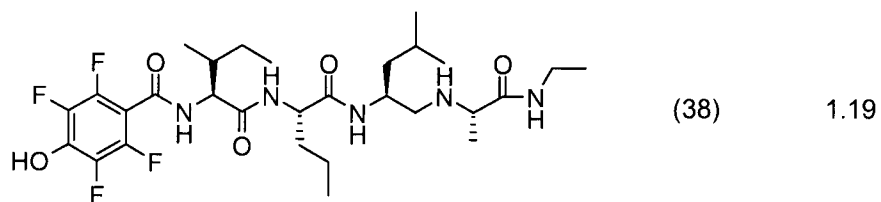
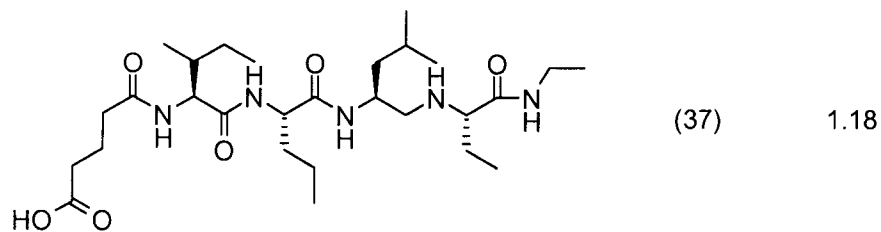


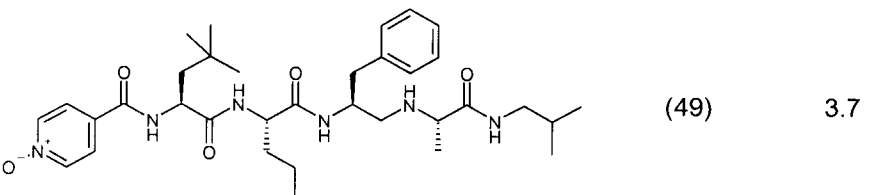
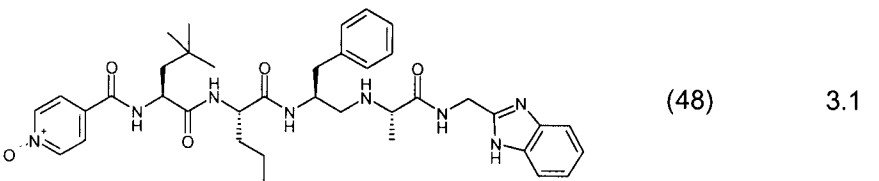
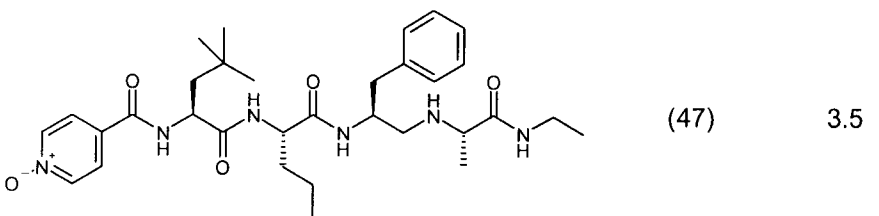
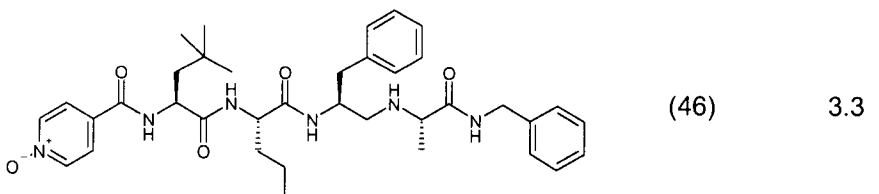
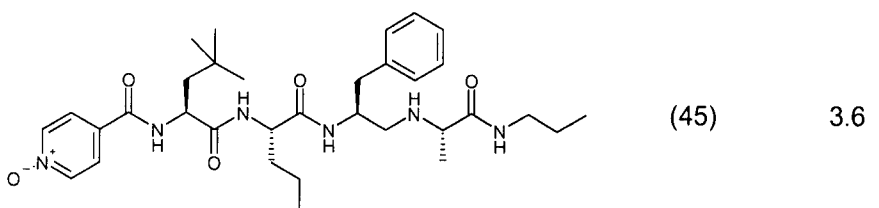
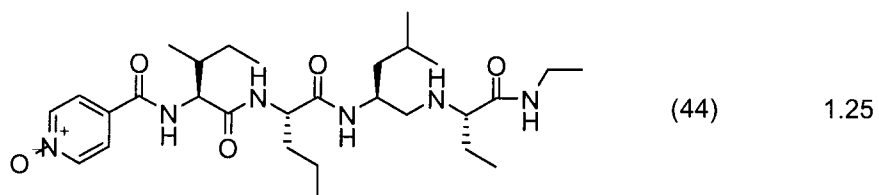
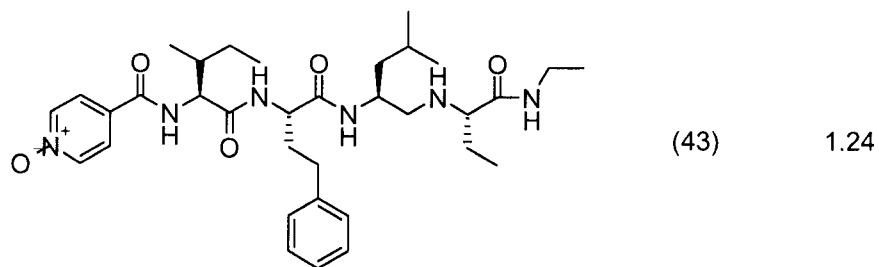
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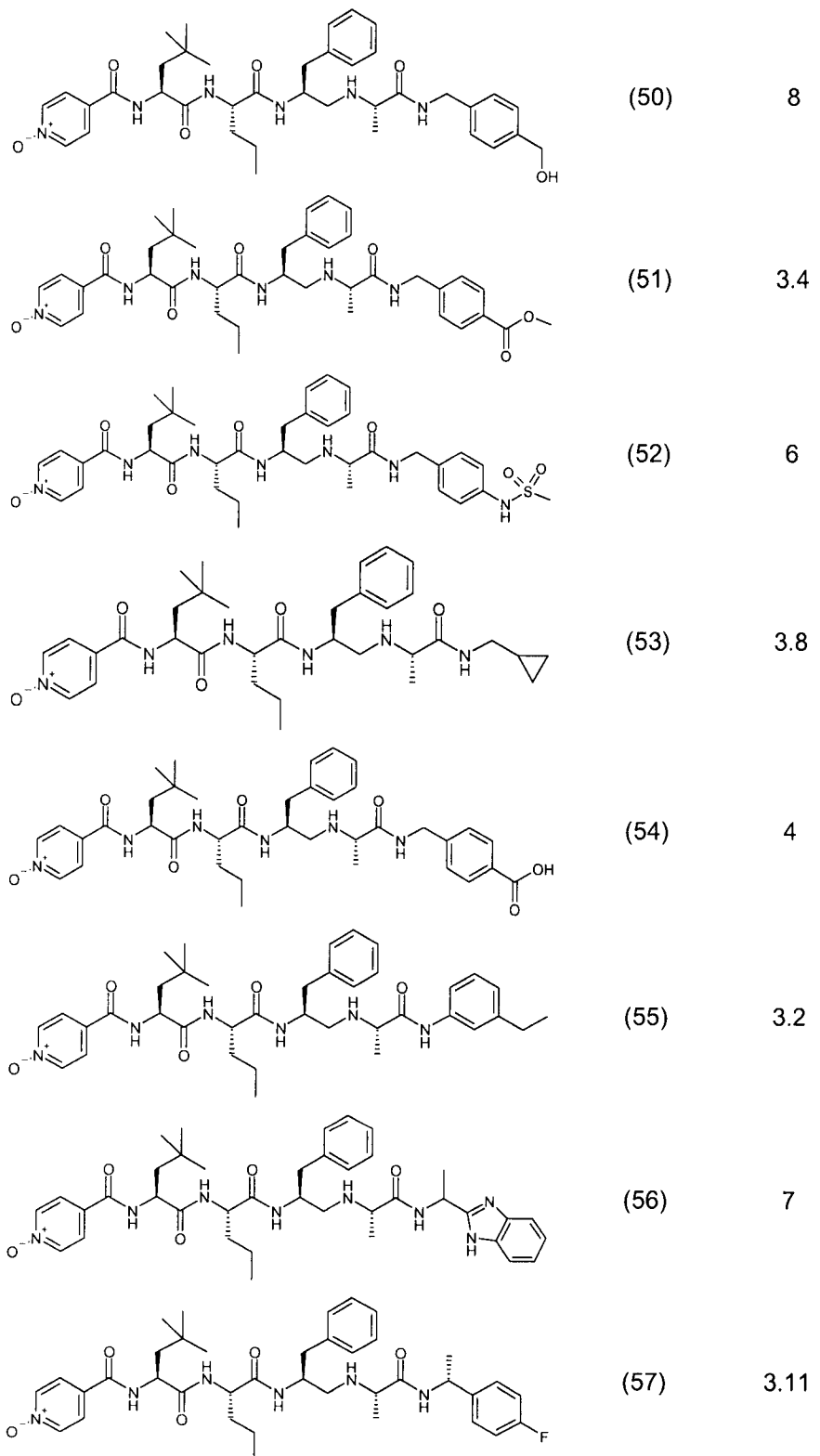


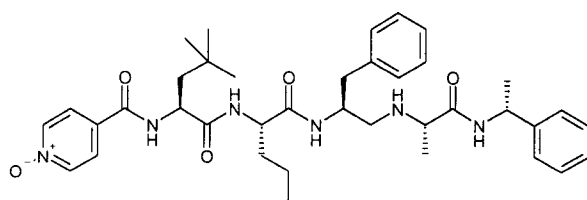
(30) 1.12











(58)

3.10

The compounds of the present invention are made by methods well known to those skilled in the art from starting compounds known to those skilled in the art. The process chemistry is well known to those skilled in the art. The following reaction schemes illustrate the peptide synthesis of the compounds according to the present invention.

One skilled in the art will appreciate that these are all well known reactions in organic chemistry (Houben-Weyl – Methods of Organic Chemistry, Vol E22, Synthesis of Peptides and Peptidomimetics, M. Goodman, A. Felix, L. Moroder, C. Toniolo Eds., Georg Thieme Verlag Stuttgart, New York). A chemist skilled in the art, knowing the chemical structure of the biologically active compounds according to formula (I) of the invention would be able to prepare them by known methods from known starting materials without any additional information. The explanation below therefore is not necessary but is deemed helpful to those skilled in the art who desire to make the compounds of the present invention.

Schema A illustrates the solid-phase peptide synthesis of compounds of formula (I)

As a polymer commercially available [3-{{[Ethyl-Fmoc-amino]-methyl}}-indol-1-yl]-acetyl AM resin (Indol resin, Novabiochem) is used. After cleavage of the Fmoc-group with piperidine in DMF (step a) the first amino acid is coupled with standard methods of peptide chemistry, e.g. HATU/HOBt (step b). After deprotection of the Fmoc-group (step b) the next amino acid (Fmoc-Abu) is coupled with a suitable peptide coupling reagent such as DIC/HOBt (step c). After cleavage of the Fmoc-group (step c) a reductive alkylation with Fmoc-leucinal in presence of NaCNBH<sub>3</sub> as reducing agent is performed (step d). The resulting secondary amine group is capped with (Boc)<sub>2</sub>O. The peptide

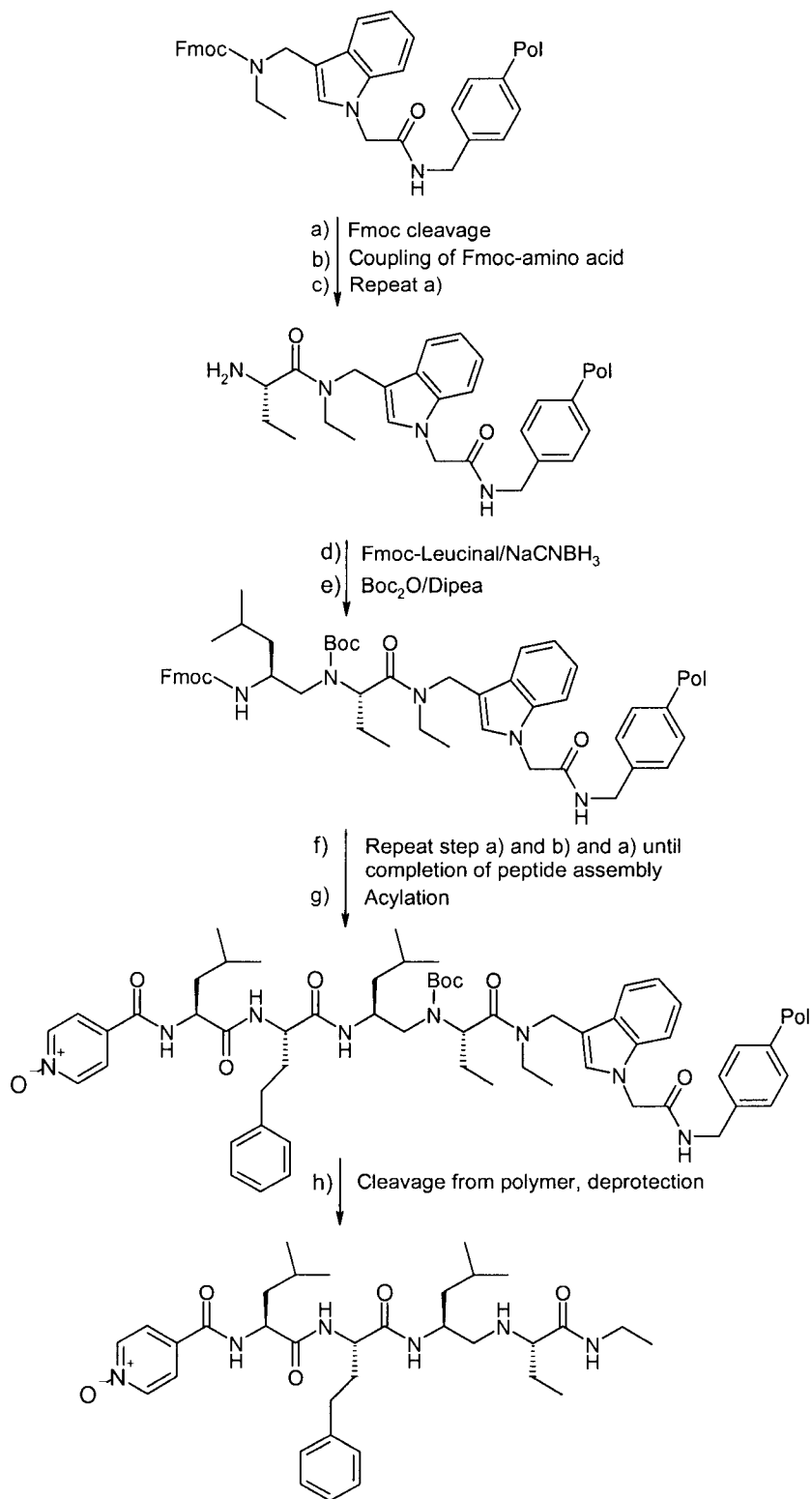
assembly has been completed applying step a), b) and c) and using the respective amino acids Fmoc-homoPhe and Fmoc-Leu . The introduction of the N-terminal capping group can be achieved by standard acylation methods.(step g). The C-terminal peptide N-ethylamide is cleaved from the polymer by reaction with acids e.g. trifluoroacetic acid.

5

The synthesis protocol allows the incorporation of different residues in the position  $R^1$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  of formula (I)

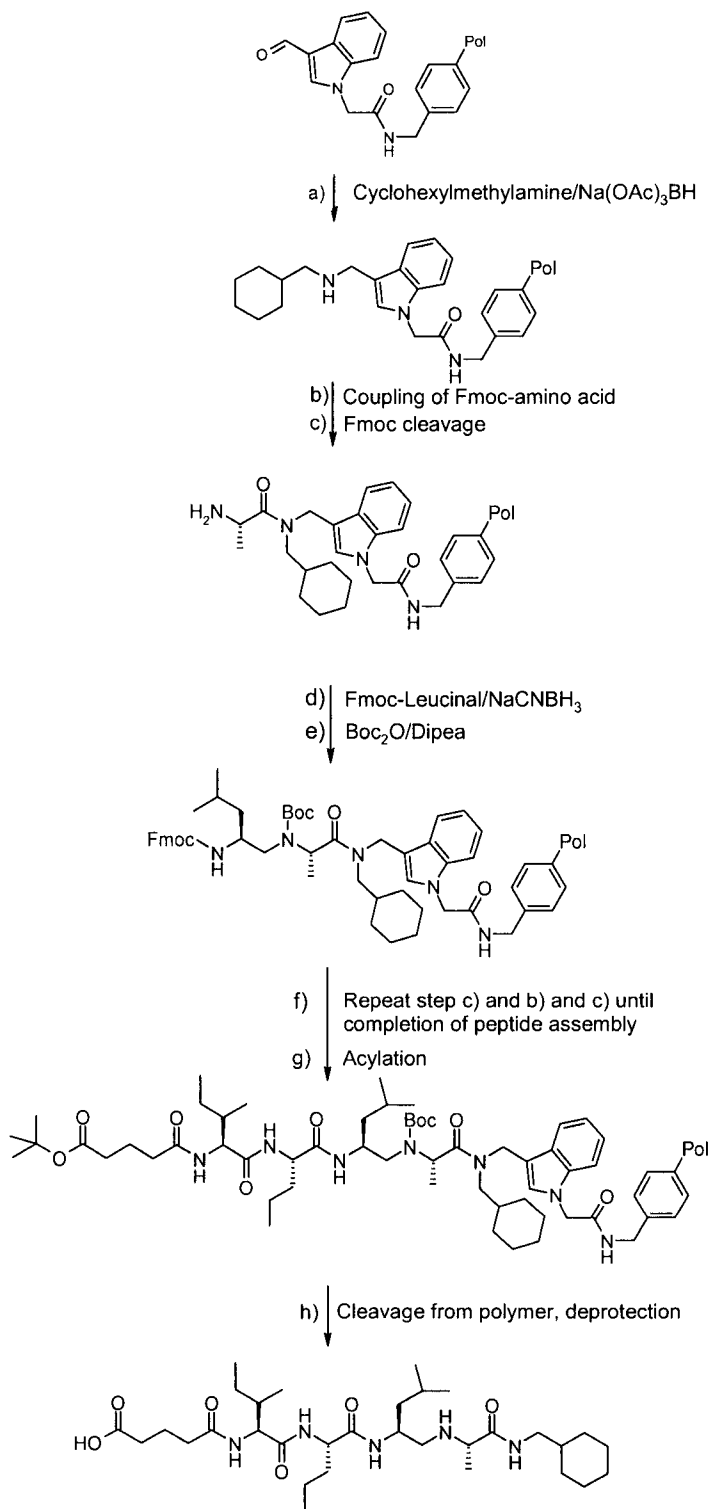
Scheme A (Example No 1)

10



Scheme B illustrates the synthesis of peptides with variations of the C-terminal amide part. For this purpose a commercially available (Formylindolyl)acetamidomethylpolystyrene resin is used. In the first reaction the aldehyde group has been reductively alkylated with cyclohexymethylamine in presence of NaCNBH<sub>3</sub> (step a). The further peptide assembly  
5 and the cleavage from the polymer has been done as described in schema A.

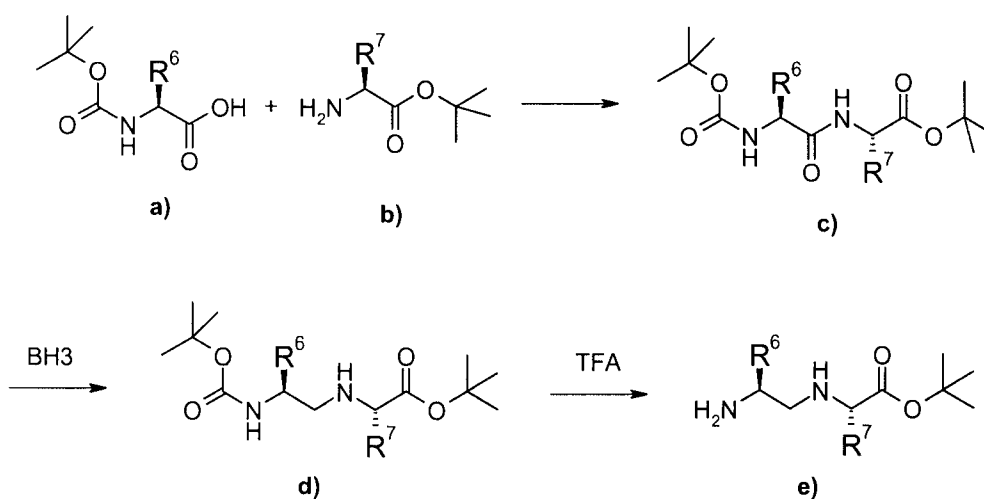
Scheme B (Example No 2)



The compounds of the invention can be synthesized by solution phase chemistry according to the general synthesis schemes outlined as follows. This method allows the variation of R1, R2, R3, R4, R5, R6, and R7 by usage of the respective amino acids, carboxylic acids  
5 or amines.

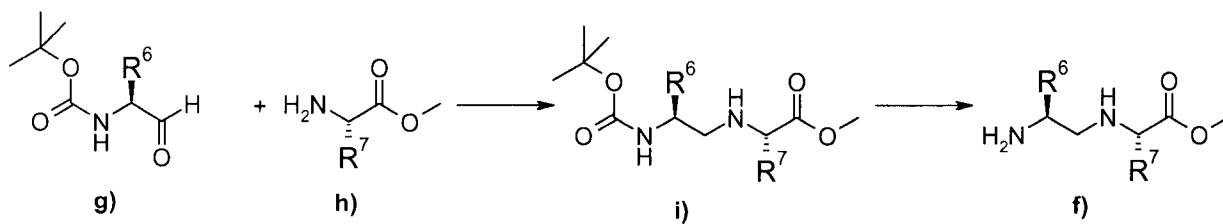
The central core **e**) was assembled as shown in scheme C. The Boc-protected amino acid **a**) was coupled with the amino acid *t*-butylester **b**) using standard peptide coupling conditions, in particular TBTU/DIPEA, to yield the diprotected dipeptide **c**). Reduction of  
10 **c**) with borane dimethylsulfide complex gave the diamine **d**). Boc-deprotection gave after careful chromatography the monoprotected product **e**).

#### Scheme C



15 In an alternative procedure the monoprotected dipeptide **f**) was prepared as shown in scheme D:

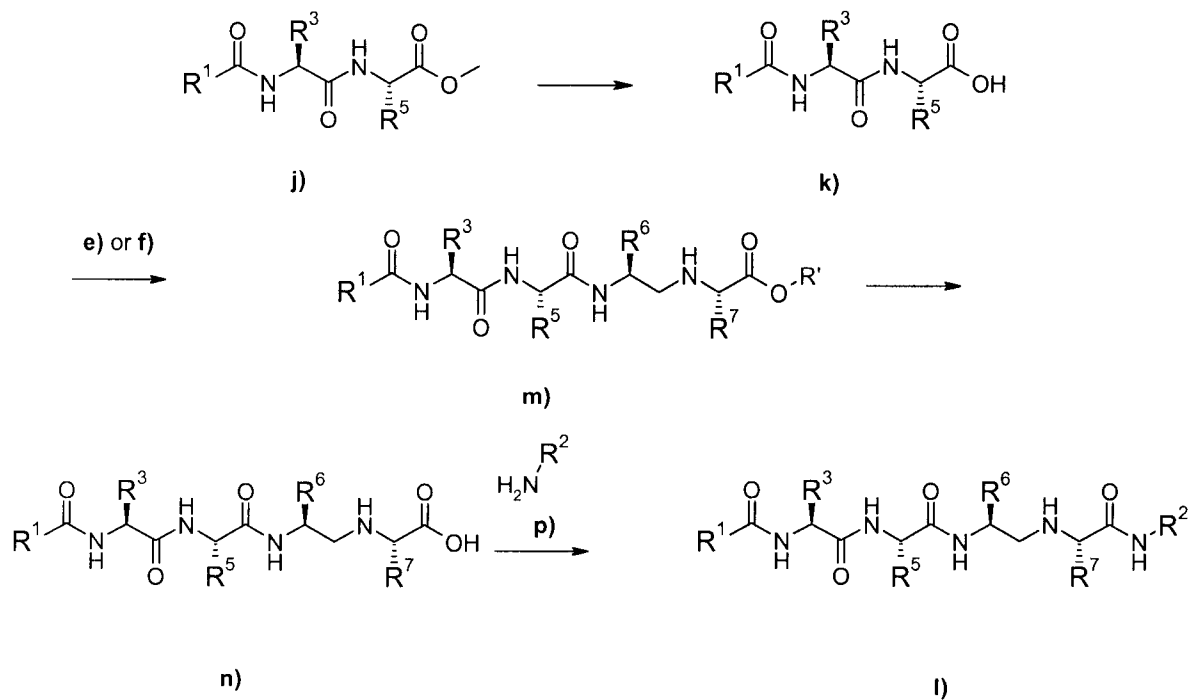
#### Scheme D:



- Reductive alkylation of the Boc-protected amino acid aldehyde **g)** which was obtained by Dees/Martin oxidation of the corresponding amino acid alcohol, with the amino acid ester **h)** gave the diprotected diamine **i)**, which was Boc-deprotected to yield the monoprotected product **f)**.

The final products **l)** were obtained according to scheme E:

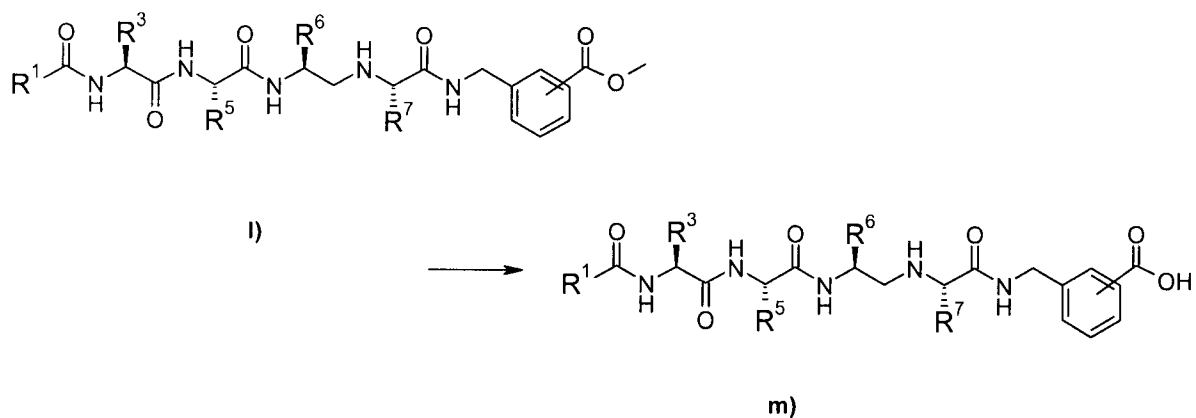
10 Scheme E:



The N-terminal part **k**) was assembled using standard peptide coupling procedures and Boc-deprotection steps starting from the Boc-protected amino acid ester bearing R<sup>5</sup>. Subsequently, the ester **j**) was hydrolyzed to yield the free acid **k**). Diamine **e**) or **f**) was coupled with the N-terminal part **k**) using standard peptide coupling conditions, in particular TBTU/DIPEA. After hydrolysis of the ester **m**) either using LiOH in the case of the methyl ester or TFA in the case of the *t*-butyl ester, the resulting acid was coupled with the corresponding amine **p**) to give the amide **l**).

In some cases the C-terminal R<sub>2</sub> needed to be liberated from a protected precursor in the last step to yield the final product **m**). Scheme F illustrated an example. The ester **l**) is hydrolyzed to yield the free acid **m**).

Scheme F:

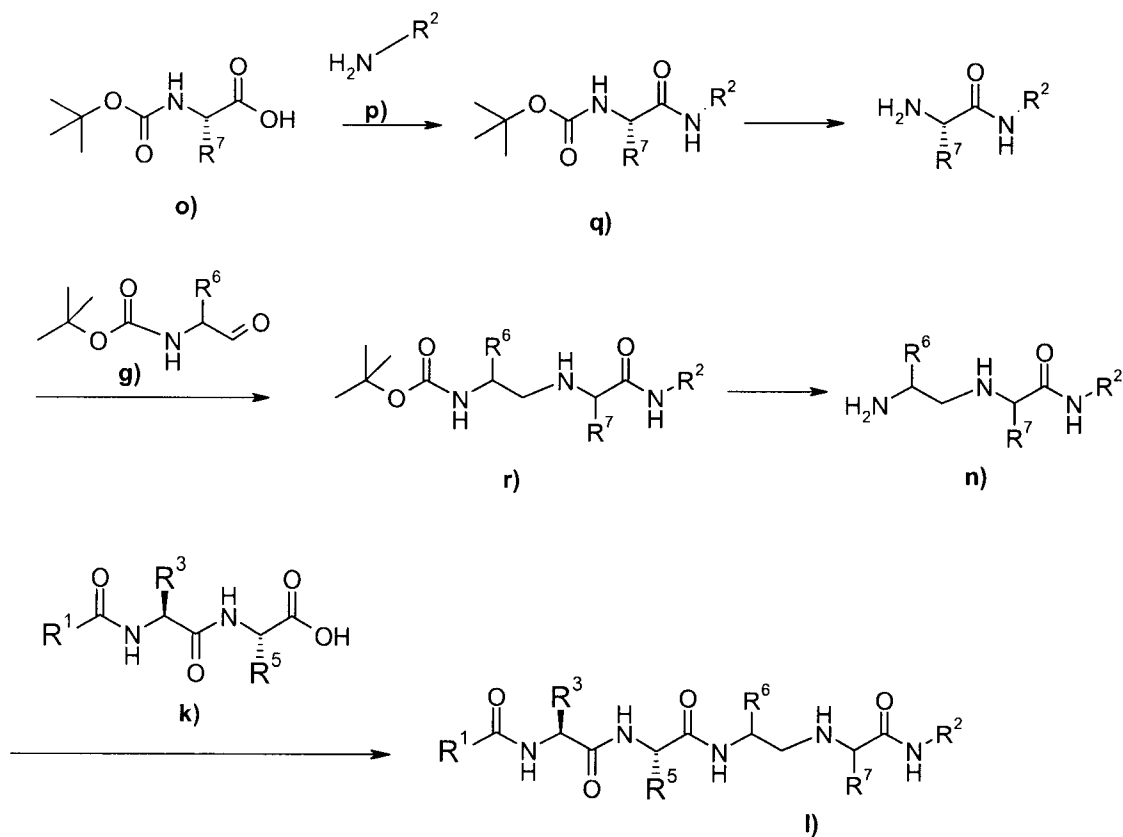


15

20

In an alternative procedure the final compounds were obtained according to scheme G.

Scheme G:



5

Thus, in the first step of the synthesis of the C-terminal part **n)** the amide **q)** assembled by a standard peptide coupling procedure using a Boc-protected amino acid **o)** and the amine **p)**. Boc-deprotection of **q)** and reductive alkylation with the corresponding Boc-protected amino acid aldehyde **g)** gave dipeptide amide **r)**. Boc-deprotection of **r)** and coupling with the N-terminal part **k)** gave the final product **l)**.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are hereby incorporated by reference for all purposes. The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

15

- All temperatures are in degrees Celsius,  
(M+H)<sup>+</sup> refers to the positive ion of a parent plus a hydrogen atom,  
Abu refers to 2-aminobutyric acid
- 5 BOC refers to 1,1-dimethylethoxy carbonyl or t-butoxycarbonyl,  
BOP refers to benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluoro-  
phosphate,  
Bzl refers to benzyl,  
CBZ refers to benzyloxycarbonyl,
- 10 CDI refers to 1,1'-carbonyldiimidazole,  
Chromatography (column and flash chromatography) refers to purification/separation of  
compounds expressed as (support, eluent). It is understood that the appropriate fractions  
are pooled and concentrated to give the desired compound (s),  
CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm
- 15 (8) downfield from TMS,  
DIC refers to dicyclohexyl carbodiimide,  
DIPAMP refers to (R,R)-1,2-Ethanediybis[(2-methoxyphenyl)phenylphosphine]  
DCM refers to dichloromethane,  
Dipea refers to diisopropylethylamine,
- 20 DIPEA refers to diisopropylethylamine,  
DMF refers to dimethylformamide,  
EDC refers to ethyl-1- (3-dimethylaminopropyl) carbodiimide or 1- (3- dimethylamino-  
propyl)-3-ethylcarbodiimide hydrochloride,  
EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom
- 25 bombardment,  
Ether refers to diethyl ether, unless specified otherwise,  
Fmoc refers to 9-fluorenylmethyl carbonate,  
HATU refers to O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-  
phosphate,
- 30 HBTU refers to 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-  
phosphate,

- HOAc refers to acetic acid,  
HOBt refers to 1-hydroxy benzotriazole hydrate,  
HRMS refers to high resolution mass spectrometry,  
IR refers to infrared spectroscopy,  
5 MPLC refers to middle pressure liquid chromatography,  
MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit,  
NBS refers to N-bromosuccinimide,  
NMM refers to N-methylmorpholine,  
NMP refers to N-methylpyrrolidone,  
10 NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (d) downfield from TMS,  
psi refers to pounds/in<sup>2</sup>,  
RF refers to retention factor,  
RT refers to retention time,  
15 Saline refers to an aqueous saturated sodium chloride solution,  
Sta refers to (3S, 4S)-4-amino-3-hydroxy-6-methyl-heptanoic acid,  
TBTU refers to 1-[Bis(dimethylamino)methylen]-1-H-benzotriazolim-tetrafluoroborate-3-oxide,  
tBu refers to tert.-butyl,  
20 TFA refers to trifluoroacetic acid  
THF refers to tetrahydrofurane  
TMOF refers to trimethylorthoformate.

Pharmaceutically acceptable refers to those properties and/or substances which are  
25 acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is  
30 weight/volume (wt/v).

## EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent.

5

The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both  
10 as to reactants and as to reaction conditions and techniques.

The products were analyzed by analytical HPLC-MS and/or NMR.

HPLC-conditions 1: Column: Waters Xterra MS, C18, 2.1 x 50 mm, 3.5  $\mu$ m

Column Temperature ( $^{\circ}$ C): 60.0

15 Flowrate 1.0 ml/min.

Solvent A: Water + 0.1% TFA. Solvent B: MeCN + 0.1% TFA. Gradient: from 95% A to 2% A in 4.0 min

HPLC-conditions 2: Column: Waters Xterra MS. C18. 4.6 x 50mm. 3.5 $\mu$ m

20 Columntemp ( $^{\circ}$ C): 40.0

Flowrate 1 ml/min.

Solvent A: Water + 0.1% TFA. Solvent B: MeCN + 0.1% TFA.

Gradient: from 95% A to 2% A in 5.1 min

25 HPLC-conditions 3: Column: Waters Xterra MS, C18, 2.1 x 50 mm, 3.5  $\mu$ m

Column Temperature ( $^{\circ}$ C): 25.0

Flowrate 0.4 ml/min.

Solvent A: Water + 0.1% TFA. Solvent B: MeCN + 0.1% TFA.

Gradient: from 95% A to 2% A in 5.1 min

30

HPLC-conditions 4: Column: Varian Microsorb 100, C18, 4.6 x 50 mm, 3.0  $\mu$ m

Column Temperature (°C): 25.0

Flowrate 1.0 ml/min.

Solvent A: Water + 0.1% TFA. Solvent B: MeCN + 0.1% TFA.

Gradient: from 95% A to 2% A in 4.5 min

5 HPLC-conditions 5: Column: Varian Microsorb , C18, 21.2 x 250 mm, 8.0 µm

Column Temperature (°C): 25.0

Flowrate 20.0 ml/min.

Solvent A: Water + 0.1% TFA. Solvent B: MeCN + 0.1% TFA.

Gradient: from 90% A to 50% A in 20.0 min

10

HPLC-conditions 6: Column: Waters Xterra MS, C18, 4.6 x 30 mm, 2.5 µm

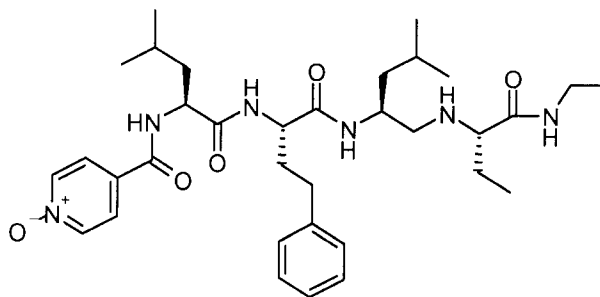
Column Temperature (°C): 25.0

Flowrate 1.0 ml/min.

Solvent A: Water + 0.1% TFA. Solvent B: MeCN + 0.1% TFA.

15 Gradient: from 95% A to 2% A in 4.4 min

### Example 1:



20 The compound was synthesized by standard solid phase peptide synthesis using a [3-  
((ethyl-Fmoc-amino)-methyl)-1-indol-yl]acetyl AM resin (277 mg, 0.2 mmol)  
(Novabiochem).

Fmoc-deprotections were performed by a 2 and 20 minute treatment with 30% piperidine  
25 in DMF. The coupling of the first amino acid was performed by with HATU (5 equiv.),  
HOBt (5 equiv.), Dipea (5 equiv.) and Fmoc-protected amino acid (5 equiv.) in DMF as

solvent for 16 hours. The coupling of the first amino acid was repeated once. Coupling of the other amino acids were achieved with TBTU as coupling reagent (5 equiv.), HOBt (5 equiv.), Dipea (15 equiv.) and the amino acid (5 equiv.) with DMF as solvent.

- 5 After coupling of Fmoc-2-aminobutyric acid and Fmoc-deprotection the amino group was reductively alkylated with freshly prepared Fmoc-leucinal (3.5 equiv.) and NaCNBH<sub>3</sub> (10.5 equiv.) in DMF/HOAc (99:1, 2 ml) for 16 hours. After the alkylation the resin was carefully washed with DMF/HOAc (99:1), DMF, 5% Dipea in DMF and DMF. The resulting secondary amino group was protected by reaction with Boc<sub>2</sub>O (10 equiv.) and  
10 Dipea (10 equiv.) in DMF for 16 hours.

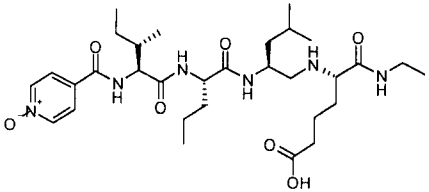
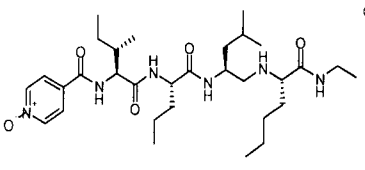
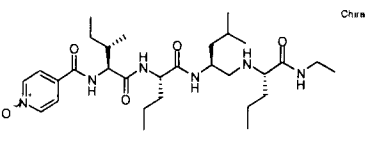
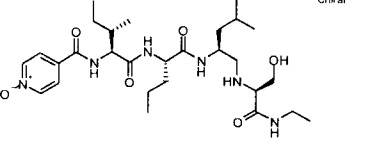
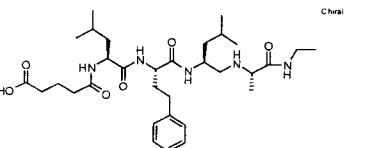
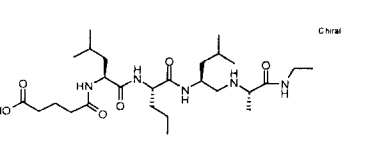
The following Fmoc-amino acids were coupled until completion of the peptide chain as described above. The terminal acetylation was performed with 4-nicotinic acid N-oxide (5 eq.), TBTU (5 eq.), HOBt (5 eq.), Dipea (15 eq.) in DMF as solvent.

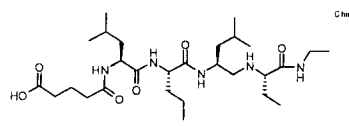
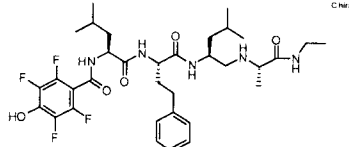
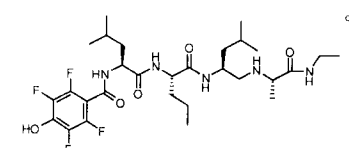
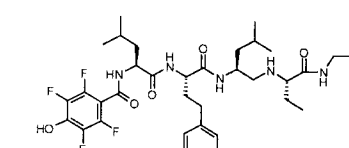
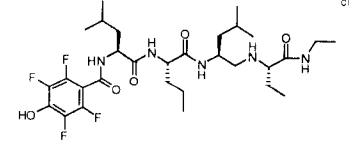
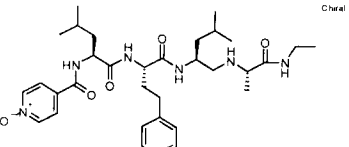
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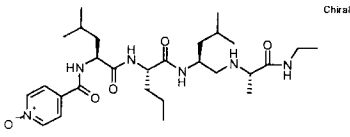
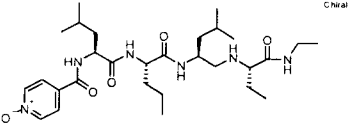
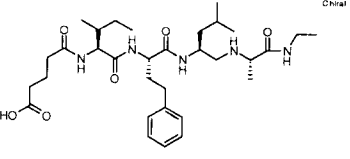
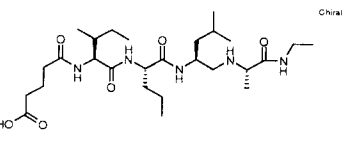
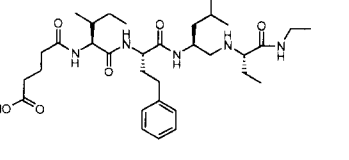
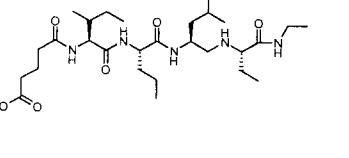
The cleavage from the resin was achieved by treatment with TFA/water (95:5) for 1 hour. The TFA solution was evaporated under reduced pressure and diethyl ether was added for precipitation of the peptide. The precipitate was dissolved in acetonitrile/water and purified by preparative reversed phase HPLC. The purified product was lyophilized . Yield 90 mg  
20 (59 %).

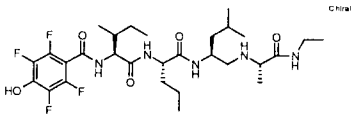
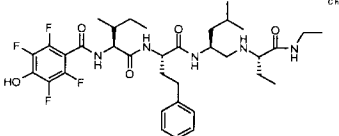
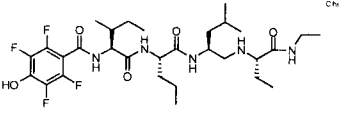
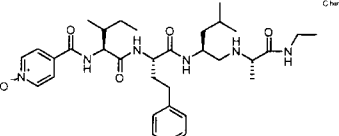
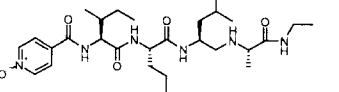
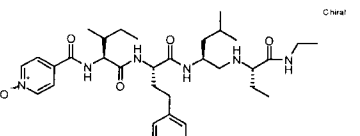
The product was analyzed by analytical HPLC-MS and NMR. The analytical data were in agreement with the structure. Found [M+H]<sup>+</sup> 625.4; RT = 4.58 min (HPLC-conditions 3). The examples No. 1.1 to 1.25 were synthesized analogously. The analytical data were in  
25 agreement with the structures.

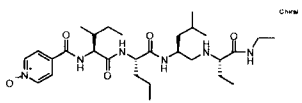
Example No.	Formula	Mass Spectra [M+H] <sup>+</sup>	HPLC-Retention Time

<p>1.1</p>		<p>621.3</p>	<p>RT=2.07 min, HPLC-conditions 1</p>
<p>1.2</p>		<p>591.4</p>	<p>RT=2.38 min, HPLC-conditions 1</p>
<p>1.3</p>		<p>577.4</p>	<p>RT=2.26 min, HPLC-conditions 1</p>
<p>1.4</p>		<p>565.4</p>	<p>RT=1.99 min, HPLC-conditions 1</p>
<p>1.5</p>		<p>604.3</p>	<p>RT=4.60 min, HPLC-conditions 3</p>
<p>1.6</p>		<p>542.3</p>	<p>RT=4.32 min, HPLC-conditions 3</p>

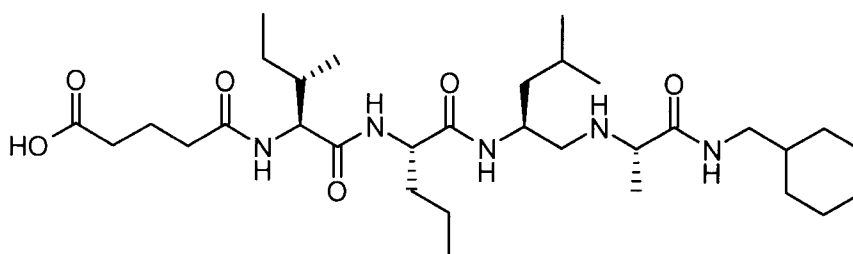
<p>1.7</p>	 <p>Chiral</p>	<p>556.4</p>	<p>RT=4.40 min, HPLC-conditions 3</p>
<p>1.8</p>	 <p>Chiral</p>	<p>682.3</p>	<p>RT=4.95 min, HPLC-conditions 3</p>
<p>1.9</p>	 <p>Chiral</p>	<p>620.3</p>	<p>RT=4.68 min, HPLC-conditions 3</p>
<p>1.10</p>	 <p>Chiral</p>	<p>696.3</p>	<p>RT=4.99 min, HPLC-conditions 3</p>
<p>1.11</p>	 <p>Chiral</p>	<p>634.3</p>	<p>RT=4.77 min, HPLC-conditions 3</p>
<p>1.12</p>	 <p>Chiral</p>	<p>611.3</p>	<p>RT=4.55 min, HPLC-conditions 3</p>

<p>1.13</p>		<p>549.3</p>	<p>RT=4.14 min, HPLC-conditions 3</p>
<p>1.14</p>		<p>563.3</p>	<p>RT=4.22 min, HPLC-conditions 3</p>
<p>1.15</p>		<p>604.4</p>	<p>RT=4.63 min, HPLC-conditions 3</p>
<p>1.16</p>		<p>542.3</p>	<p>RT=4.27 min, HPLC-conditions 3</p>
<p>1.17</p>		<p>618.3</p>	<p>RT=4.67 min, HPLC-conditions 3</p>
<p>1.18</p>		<p>556.4</p>	<p>RT=4.32 min, HPLC-conditions 3</p>

<p>1.19</p>		<p>620.3</p>	<p>RT=4.70 min, HPLC-conditions 3</p>
<p>1.20</p>		<p>696.3</p>	<p>RT=4.96 min, HPLC-conditions 3</p>
<p>1.21</p>		<p>634.3</p>	<p>RT=4.76 min, HPLC-conditions 3</p>
<p>1.22</p>		<p>611.3</p>	<p>RT=4.39 min, HPLC-conditions 3</p>
<p>1.23</p>		<p>549.3</p>	<p>RT=4.17 min, HPLC-conditions 3</p>
<p>1.24</p>		<p>625.3</p>	<p>RT=4.49 min, HPLC-conditions 3</p>

1.25		563.3	RT=4.23 min, HPLC-conditions 3
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### Example 2



- 5 The compound was synthesized by standard solid phase peptide synthesis using a 3-(formylindolyl)acetamidomethylpolystyrene resin (100 mg, 0.11 mmol) (Merckbiosciences).

For the first reductive alkylation the resin was washed with 1,2-dichloroethane/TMOF  
 10 (2:1) and then reacted with a solution of cyclohexylmethylamine (10 equiv.) in 1,2-dichloroethane/TMOF 1:1 (1 ml). After 5 minutes solid  $\text{Na}(\text{OAc})_3\text{BH}$  (10 equiv.) and 1,2-dichloroethane/TMOF 2:1 (1 ml) was added and the suspension was shaken overnight at room temperature. The resin was carefully washed with DMF, MeOH, THF and DCM.

15 Fmoc-deprotections were performed by a 2 and 20 minute treatment with 30% piperidine in DMF. The resin was then carefully washed with DMF. The coupling amino acids was performed with TBTU (5 equiv.), HOBt (5 equiv.), Dipea (10 equiv.) and Fmoc-protected amino acid (5 equiv.) in DMF as solvent overnight.

20 After coupling of the first amino acid and Fmoc-deprotection the amino group was reductively alkylated with freshly prepared Fmoc-leucinal (3.5 equiv.) and  $\text{NaCNBH}_3$  (10.5 equiv.) in DMF/HOAc (99:1, 2 ml) for 2.25 hours. After the alkylation the resin was

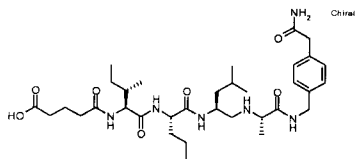
carefully washed with DMF/HOAc (99:1), DMF, 5% Dipea in DMF and DMF. The resulting secondary amino group was protected by reaction with  $\text{Boc}_2\text{O}$  (10 equiv.) and Dipea (10 equiv.) in DMF for 16 hours.

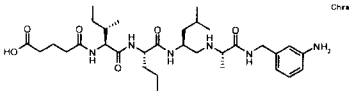
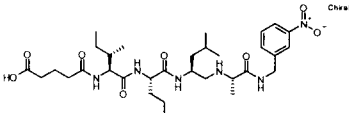
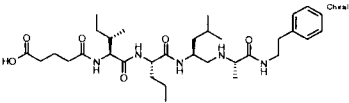
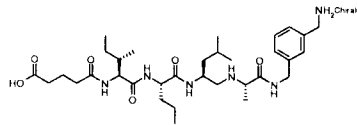
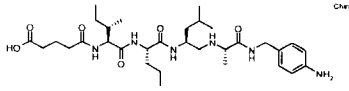
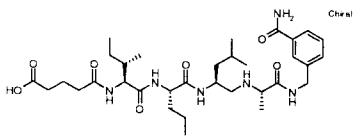
- 5 The following Fmoc-amino acids and the N-terminal carboxylic acid were coupled until completion of the peptide chain as described above.

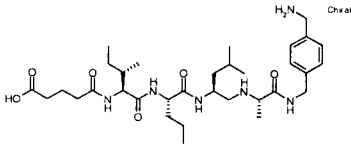
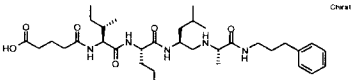
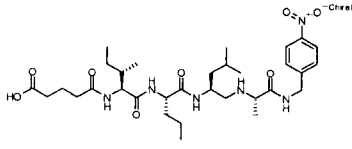
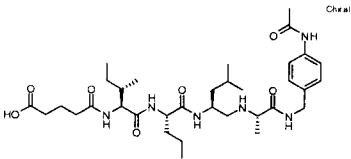
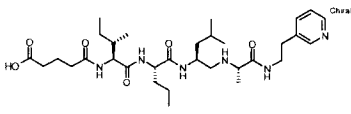
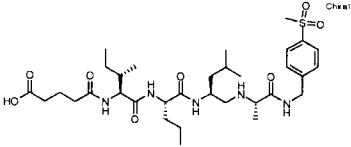
The cleavage from the resin was achieved by treatment with TFA/DCM (5:95) for 2 hour. The solution was evaporated and treated with TFA/water (95:5) for 1 hour. The TFA  
 10 solution was evaporated under reduced pressure and diethyl ether was added for precipitation of the peptide. The precipitate was dissolved in acetonitrile/water and purified by preparative reversed phase HPLC. The purified product was lyophilized .

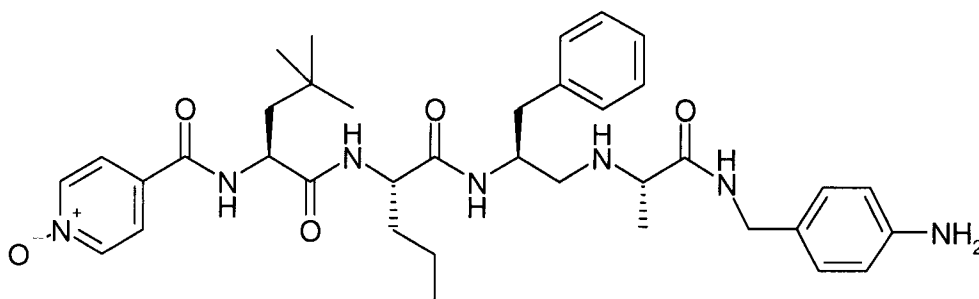
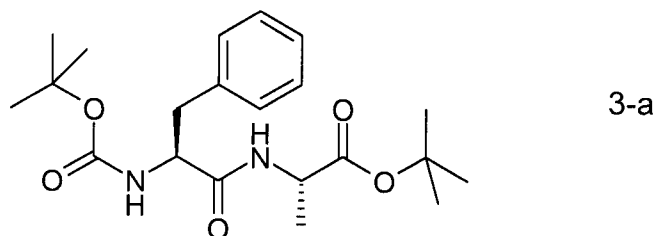
The product was analyzed by analytical HPLC-MS and NMR. The analytical data were in  
 15 agreement with the structure. Found  $[\text{M}+\text{H}]^+$  610.6; RT = 4.26 min (HPLC-conditions 2) .

The examples 2.1 to 2.13 were synthesized analogously. The analytical data were in agreement with the structures.

Example No.	Formula	Mass Spectra $[\text{M}+\text{H}]^+$	HPLC-Retention Time
2.1		661.5	RT=3.60 min, HPLC-conditions 2

<p>2.2</p>		<p>619.6</p>	<p>RT=3.34 min, HPLC-conditions 2</p>
<p>2.3</p>		<p>649.5</p>	<p>RT=4.08 min, HPLC-conditions 2</p>
<p>2.4</p>		<p>618.6</p>	<p>RT=4.1 min, HPLC-conditions 2</p>
<p>2.5</p>		<p>633.6</p>	<p>RT=3.34 min, HPLC-conditions 2</p>
<p>2.6</p>		<p>619.6</p>	<p>RT=3.36 min, HPLC-conditions 2</p>
<p>2.7</p>		<p>647.5</p>	<p>RT=3.60 min, HPLC-conditions 2</p>

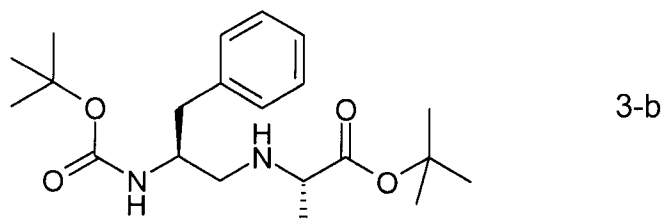
<p>2.8</p>		<p>633.6</p>	<p>RT=3.32 min, HPLC-conditions 2</p>
<p>2.9</p>		<p>632.6</p>	<p>RT=4.29 min, HPLC-conditions 2</p>
<p>2.10</p>		<p>649.5</p>	<p>RT=4.08 min, HPLC-conditions 2</p>
<p>2.11</p>		<p>661.6</p>	<p>RT=3.69 min, HPLC-conditions 2</p>
<p>2.12</p>		<p>619.6</p>	<p>RT=3.34 min, HPLC-conditions 2</p>
<p>2.13</p>		<p>682.5</p>	<p>RT=3.77 min, HPLC-conditions 2</p>

**Example 3:**5 a) Preparation of **3-a**:

- 10 5.0 g (18.8 mmol) (S)-2-*tert*-Butoxycarbonylamino-3-phenyl-propionic acid, 3.4 g (18.8 mmol) (S)-2-Amino-propionic acid-*tert*-butylester-hydrochloride and 6.8 ml (37.7 mmol) DIPEA were dissolved in 20 ml THF. 6.1 g (18.8 mmol) TBTU and 2.6 g (18.8 mmol) HOBt were added. The reaction mixture was stirred at room temperature for 4 hours, diluted with NaHCO<sub>3</sub> solution and extracted with ethylacetate. The combined organic
- 15 phases were concentrated and the residue was purified by flash chromatography (silica gel, dichloromethane/ethanol 98:2) to yield 5.8 g (78 %) **3-a**.

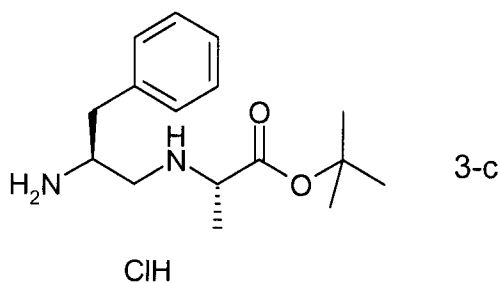
ES-MS (M+H)<sup>+</sup> = 393

RT(HPLC-conditions 6) = 3.42 min

20 b) Preparation of **3-b**:

2.9 g (7.4 mmol) **3-a** were dissolved in 10 ml THF and 14.8 ml (29.6 mmol) 2N Boron-dimethylsulfide-complex were added under ice cooling. The mixture was stirred at room temperature over night and carefully diluted with methanol under ice cooling. The reaction was extracted with NaHCO<sub>3</sub> solution and ethylacetate, the combined organic phases were dried, concentrated and the residue was purified by chromatography (Flashmaster, 50 g column, dichloromethane/ethanol 100:0 to 95:5) to yield 1.9 g (68 %) **3-b**.

c) Preparation of **3-c**:



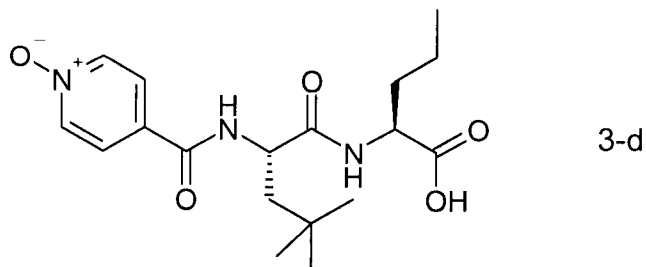
10

2.9 g (4.6 mmol) **3-b** in 10 ml ethylacetate were treated with 535  $\mu$ l 4N HCl in 1,4-Dioxane and stirred for 6 hours at room temperature. The mixture was concentrated to yield quantitative **3-c**.

15

RT(HPLC-conditions 6) = 2.13 min

d) Preparation of **3-d**:



20

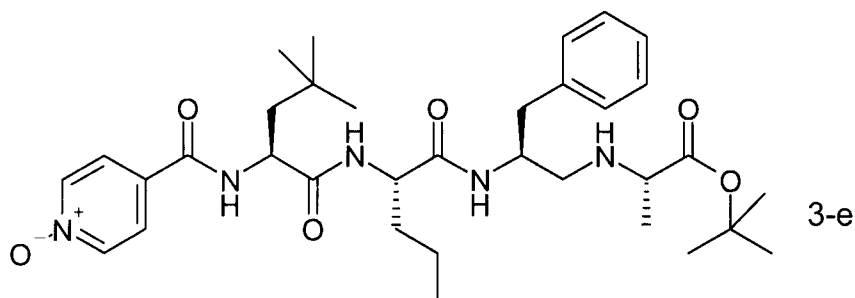
850 mg (2.2 mmol) (S)-2-((S)-4,4-Dimethyl-2-[(1-oxy-pyridine-4-carbonyl)-amino]-pentanoylamino)-pentanoic acid methyl ester in 5 ml methanol were treated with 5 ml (25.0 mmol) 5N LiOH and stirred at room temperature over night. The reaction was concentrated, made acidic with 4N HCl and extracted with a mixture of

25

methanol/dichloromethane. The combined organic phases were dried and concentrated to yield 700 mg (86 %) **3-d**.

ES-MS (M+H)<sup>+</sup> = 366

5 e) Preparation of **3-e**:

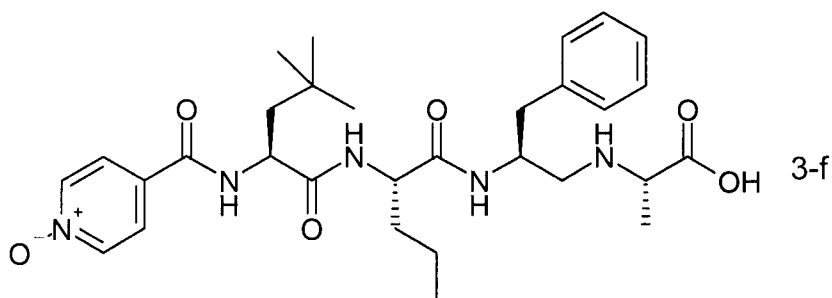


In analogy to the preparation of **3-a** 150 mg (0.54 mmol) **3-c** and 197 mg (0.54 mmol) **3-d** yielded 245 mg (73%) **3-e**.

RT(HPLC-conditions 6) = 2.76 min

10

f) Preparation of **3-f**:



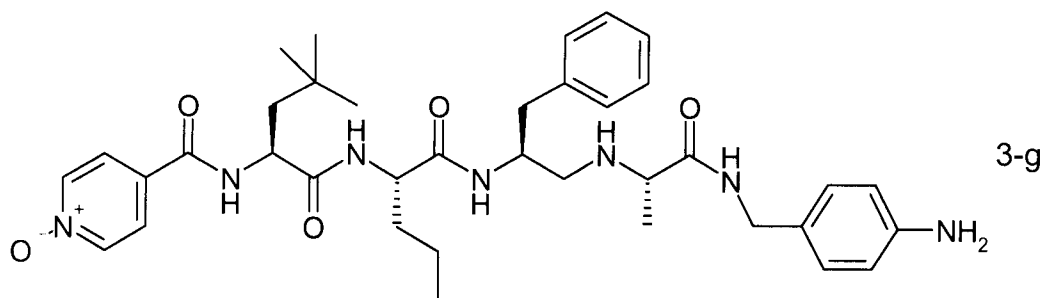
580 mg (0.9 mmol) **3-e** in 5 ml dichloromethane were treated with 500 μl (6.5 mmol) TFA and stirred at 50°C for 5 hours. The mixture was concentrated and the residue was purified by chromatography (Flashmaster, 20 g column, dichloromethane/ethanol 100:0 to 95:5) to yield 580 mg (88 %) **3-f**.

ES-MS (M+H)<sup>+</sup> = 570

RT(HPLC-conditions 6) = 2.35 min

20

g) Preparation of **3-g**:



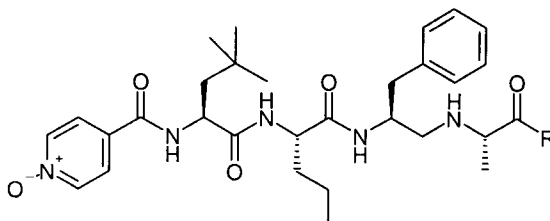
In analogy to the preparation of **3-a** 75 mg (0.13 mmol) **3-f** and 15  $\mu$ l (0.13 mmol) 4-aminomethyl-phenylamine yielded 14 mg (16%) **3-g**.

5

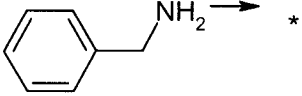
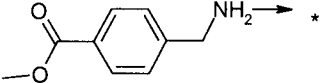
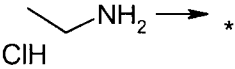

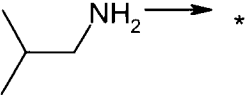
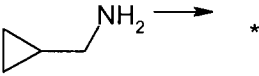
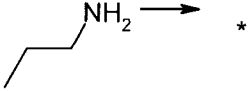
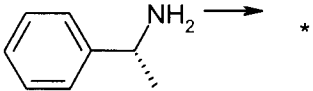
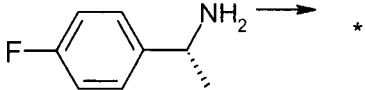
ES-MS (M+H)<sup>+</sup> = 674  
 RT(HPLC-conditions 6) = 2.28 min

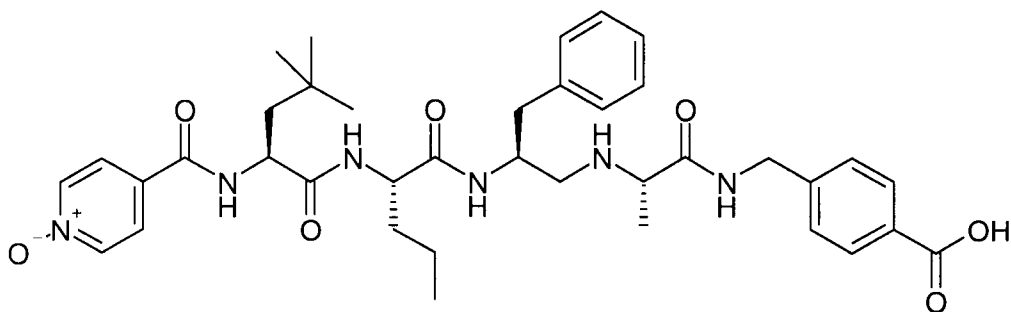
In analogy to the preparation of **3-g** the follow-up examples were prepared using **3-f** and the according amount of amines:

10

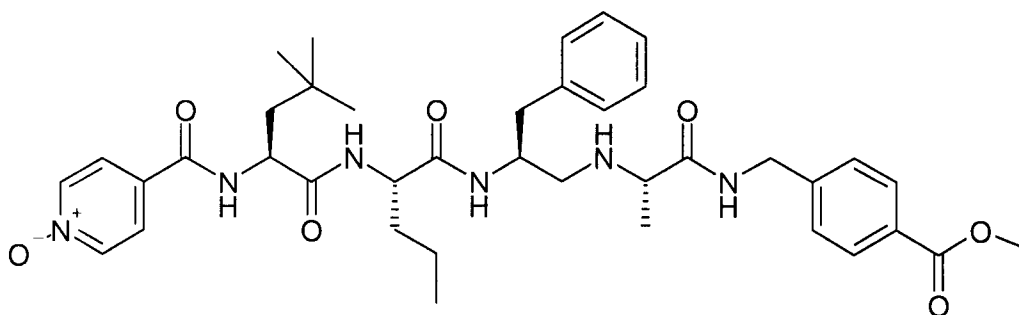


Example	R	mass spectrum	retention time (methode)
3.1		699 [M+H] <sup>+</sup>	4.01min (HPLC-conditions 4)
3.2		673 [M+H] <sup>+</sup>	2.85 min (HPLC-conditions 6)

3.3		659 [M+H] <sup>+</sup>	2.63 min (HPLC-conditions 6)
3.4		717 [M+H] <sup>+</sup>	2.66 min (HPLC-conditions 6)
3.5		597 [M+H] <sup>+</sup>	4.06 min (HPLC-conditions 4)
3.6		611 [M+H] <sup>+</sup>	2.50 min (HPLC-conditions 6)
3.7		623 [M+H] <sup>+</sup>	2.62 min (HPLC-conditions 6)
3.8		623 [M+H] <sup>+</sup>	2.55 min (HPLC-conditions 6)
3.9		611 [M+H] <sup>+</sup>	2.50 min (HPLC-conditions 6)
3.10		673 [M+H] <sup>+</sup>	2.69 min (HPLC-conditions 6)
3.11		691 [M+H] <sup>+</sup>	2.70 min (HPLC-conditions 6)

**Example 4:**

5

a) Preparation of **4-a**:

4-a

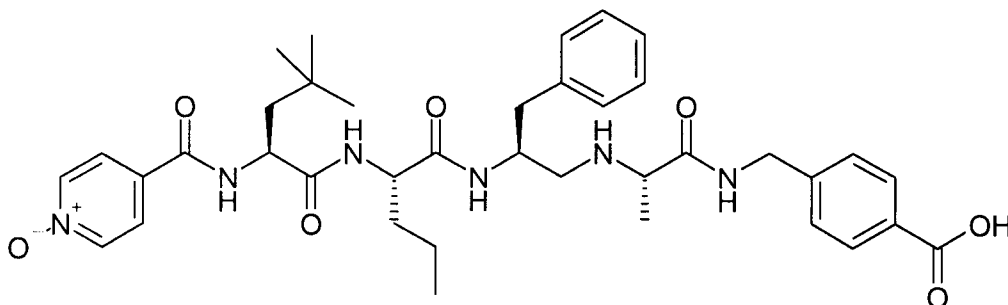
10

In analogy to the preparation of **3-a** 100 mg (0.18 mmol) **3-f** and 29  $\mu$ l (0.18 mmol) 4-aminomethyl-benzoic acid methyl ester yielded 46.0 mg (37%) **4-a**.

ES-MS (M+H)<sup>+</sup> = 717

RT(HPLC-conditions 6) = 2.66 min

15

b) Preparation of **4-b**:

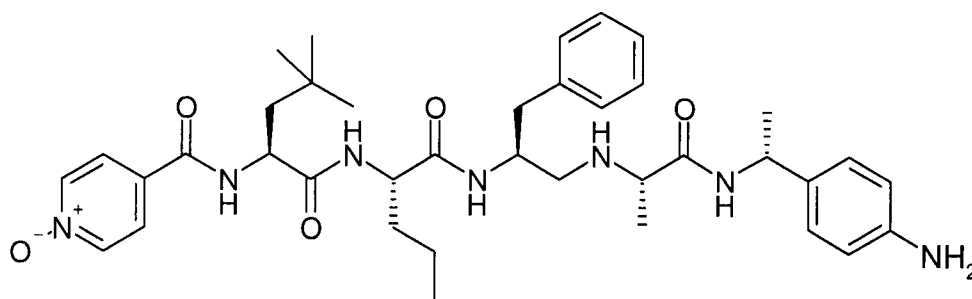
4-b

36 mg (0.05 mmol) **4-a** in 2 ml methanol were treated with 300  $\mu$ l (1.0 mmol) 8% LiOH and stirred at room temperature over night. The mixture was made acidic with 4N HCl, extracted with ethylacetate, dried and concentrated to yield 13 mg (37%) **4-b**.

ES-MS (M+H)<sup>+</sup> = 703

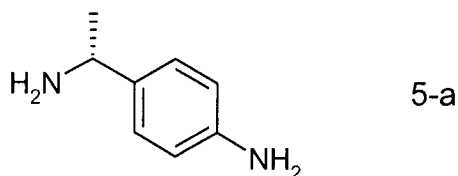
5 RT(HPLC-conditions 4) = 4.05 min

**Example 5:**



10

a) Preparation of **5-a**:

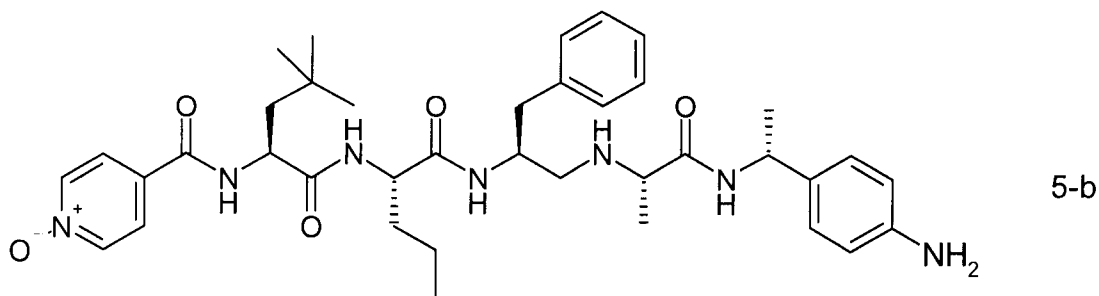


15 1.9 g (9.4 mmol) (R)-1-(4-Nitro-phenyl)-ethylamine-hydrochloride in 50 ml ethylacetate were treated with 7.4 g (32.8 mmol) tin-(II)-chloride-dihydrate and stirred at room temperature over night. The mixture was made basic with NH<sub>3</sub> and filtered. The filtrate was extracted with water, the organic phase was dried and concentrated to yield 794 mg (62%) **5-a**.

ES-MS (M+H)<sup>+</sup> = 136

20 RT(HPLC-conditions 6) = 1.37 min

b) Preparation of **5-b**:

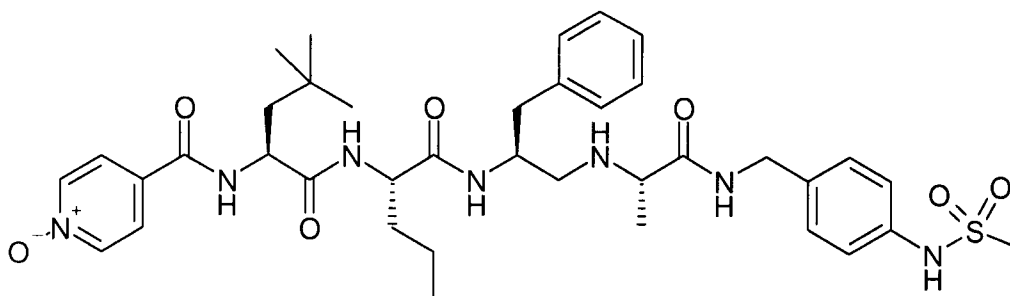


In analogy to the preparation of **3-a** 125 mg (0.18 mmol) **3-f** and 24 mg (0.18 mmol) **5-a**  
 5 yielded 4.0 mg (3%) **5-b**.

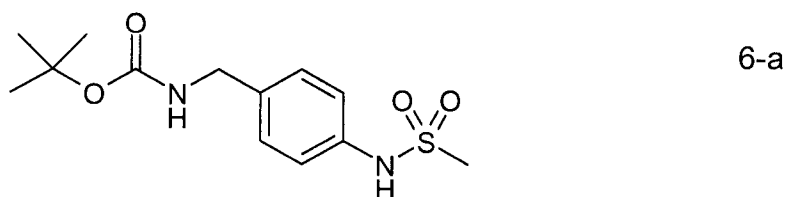
ES-MS (M+H)<sup>+</sup> = 688

RT(HPLC-conditions 6) = 2.37 min

10 **Example 6:**



15 a) Preparation of **6-a**:

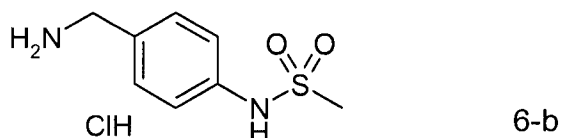


20 1.0 g (4.5 mmol) (4-Amino-benzyl)-carbamic acid-*tert*-butylester were suspended in 30 ml dichloromethane and 363 ml (4.5 mmol) pyridine were added. The mixture was cooled to 0°C and 352 μl (4.5 mmol) methanesulfonylchloride were added slowly. The reaction was stirred at room temperature over night, filtered and the filtrate was concentrated. The

residue was purified by chromatography (Flashmaster, 20 g column, cyclohexane/ethylacetate 50:50 to 100:0) to yield 640 mg (47%) **6-a**.

RT(HPLC-conditions 6) = 2.71 min

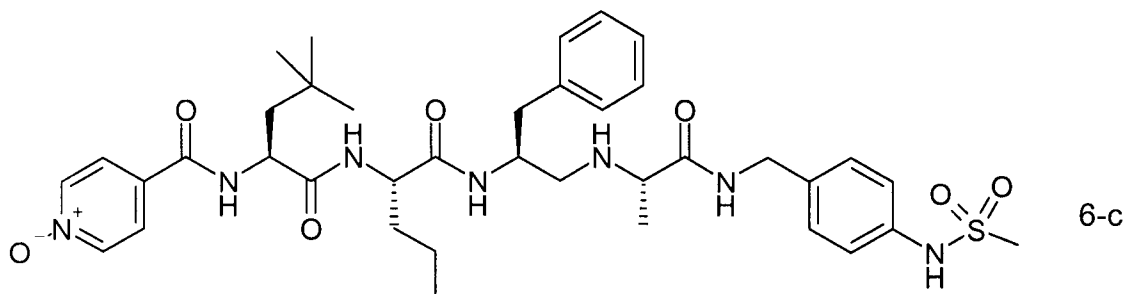
5 b) Preparation of **6-b**:



640 mg (2.1 mmol) **6-a** were treated with a mixture of dichloromethane/TFA 1:1, the mixture was stirred at room temperature over night and concentrated to yield quantitatively **6-b**.

ES-MS (M+H)<sup>+</sup> = 201

15 c) Preparation of **6-c**:

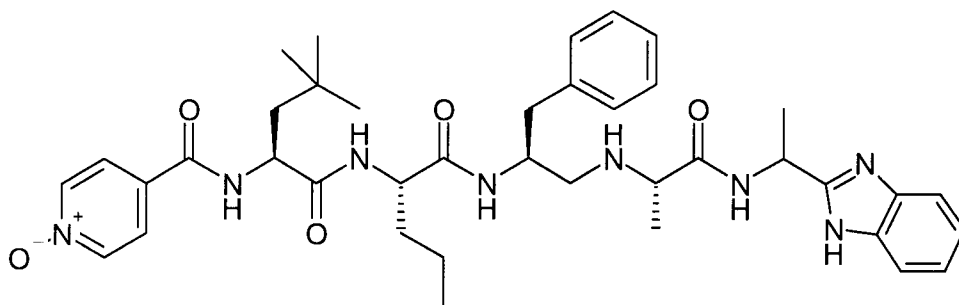


In analogy to the preparation of **3-a** 100 mg (0.18 mmol) **3-f** and 42 mg (0.18 mmol) **6-b** yielded 29.0 mg (22%) **6-c**.

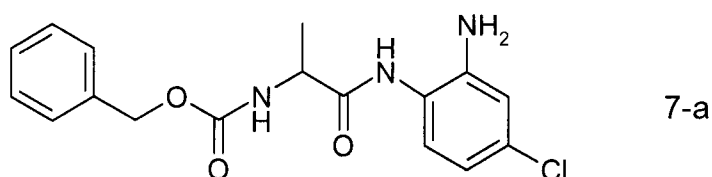
20 ES-MS (M+H)<sup>+</sup> = 752

RT(HPLC-conditions 6) = 2.47 min

25 **Example 7:**



5 a) Preparation of 7-a:



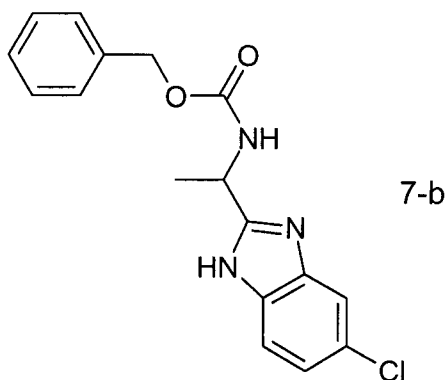
To a solution of 6.0 g (42.1 mmol) 4-chloro-benzene-1,2-diamine and 4.9 ml (44.4 mmol) 4-methylmorpholine in 25 ml DMF the mixture of 4.5 g (20.1 mmol) L-alanine-*tert*-butylester-hydrochloride and 3.6 g (22.2 mmol) CDI in 25 ml DMF was added. The  
 10 reaction was stirred at room temperature over night, concentrated, diluted with dichloromethane and water. The insoluble solid was filtered, the two phases of the filtrate were separated and the water phase was extracted two times with dichloromethane. The combined organic phase were dried and concentrated. The residue was purified by flash  
 15 column (silica gel, dichloromethane/ethanol 100: 0 to 95:5) to yield 6.0 g (86%) brown crystals 7-a.

ES(-)-MS (M-H)<sup>-</sup> = 346/348 (chloroisotope)

RF = 0.35 (silica gel, dichloromethane/ethanol 19:1)

20

b) Preparation of 7-b:

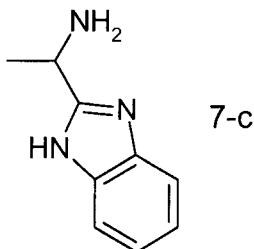


6.0 g (17.3 mmol) **7-a** were treated with 30 ml acetic acid and stirred at room temperature over night. The mixture was concentrated and the residue was purified by flash column  
 5 (silica gel, dichloromethane/ethanol 100: 0 to 98:2) to yield 5.0 g (88%) brown crystals **7-b**.

ES-MS (M+H)<sup>+</sup> = 330/332 (chloroisotope)

RF = 0.40 (silica gel, dichloromethane/ethanol 19:1)

10 c) Preparation of **7-c**:

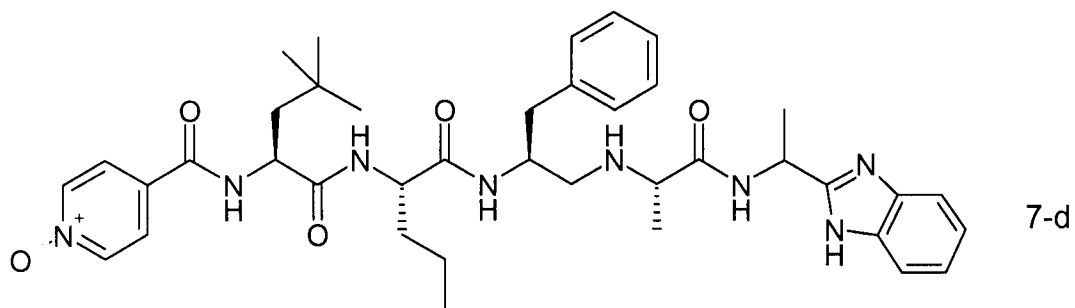


5.0 g (15.2 mmol) **7-b** were dissolved in 100 ml methanol and 40 ml dichloromethane and  
 15 1.0 g Pd/C 10% were added. The mixture was hydrogenated for 1 hour in a Parr-apparatus at room temperature and 50 psi hydrogen-pressure. The catalyst was filtered off, the filtrate was concentrated and the residue was purified by flash column (silica gel, dichloromethane/ethanol/NH<sub>3</sub> 95:5:0.2) to yield 1.1 g (36%) yellow oil **7-c**.

ES-MS (M+H)<sup>+</sup> = 196/198 (chloroisotope)

20 RF = 0.37 (silica gel, dichloromethane/ethanol/NH<sub>3</sub> 4:1:0.2)

d) Preparation of **7-d**:



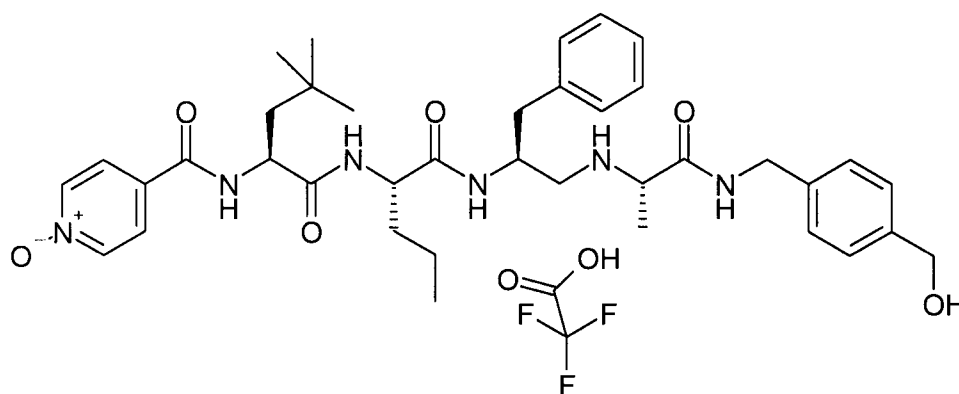
In analogy to the preparation of **3-a** 100 mg (0.18 mmol) **3-f** and 28 mg (0.18 mmol) **7-c** yielded 29.0 mg (22%) **7-d**.

5

ES-MS (M+H)<sup>+</sup> = 713  
 RT(HPLC-conditions 6) = 2.58 min

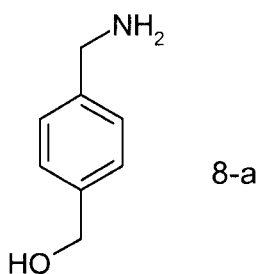
### Example 8:

10



a) Preparation of **8-a**:

15



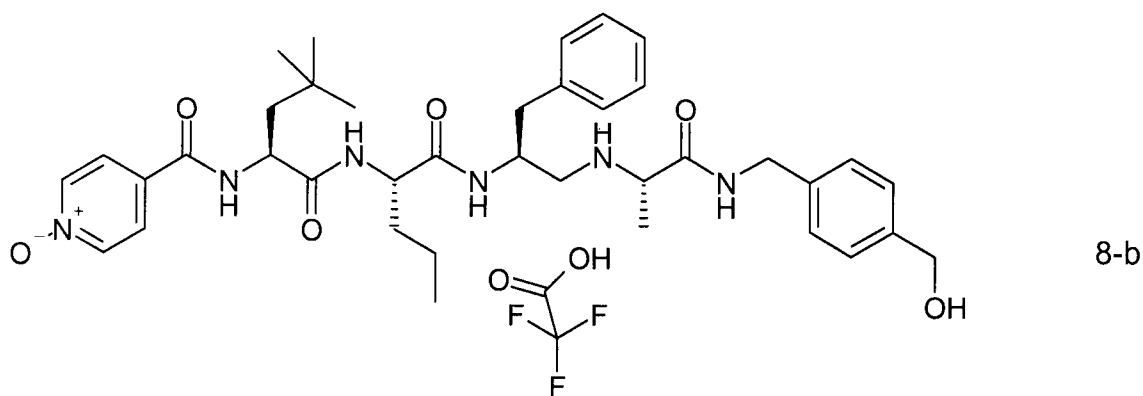
25.0 g (0.2 mol) 4-Formyl-benzonitrile were dissolved in 150 ml methanol and 2 g Pd/C

(10%) were added. The mixture was hydrogenated for 7 hours in a Parr-apparatus at room temperature and 50 psi hydrogen-pressure. The catalyst was filtered off, the filtrate was concentrated and the addition of diethylether led to crystallisation of 22.3 g (87%) **8-a**.

ES-MS (M+H)<sup>+</sup> = 138

5

b) Preparation of **8-b**:



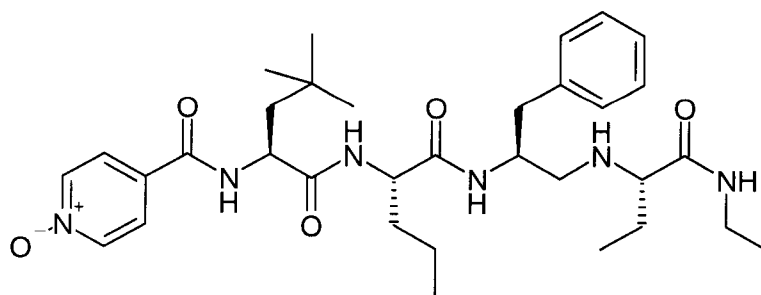
10 In analogy to the preparation of **3-a** 100 mg (0.18 mmol) **3-f** and 24.1 mg (0.18 mmol) **8-a** yielded 36.0 mg (21%) **8-b**.

ES-MS (M+H)<sup>+</sup> = 689

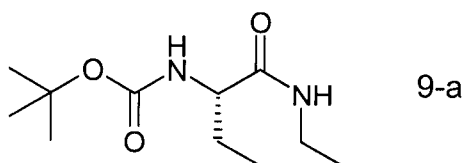
RT(HPLC-conditions 6) = 2.45 min

15

**Example 9:**



20 a) Preparation of **9-a**:

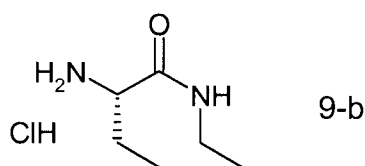


In analogy to the preparation of **3-a** 10.0 g (49.2 mmol) (S)-2-*tert*-butoxycarbonylamino-butyracetic acid and 24.7 ml (49.5 mmol) ethylamine yielded quantitatively **9-a**.

ES-MS (M+H)<sup>+</sup> = 231

5 RT(HPLC-conditions 4) = 2.80 min

b) Preparation of **9-b**:



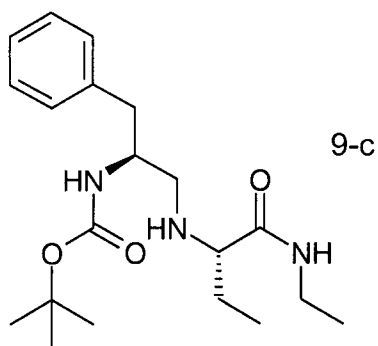
10

11.3 g (49.1 mmol) **2-a** were treated with 25 ml (100 mmol) 4N HCl in 1,4-dioxane and stirred at room temperature over night. The reaction was concentrated to yield quantitatively **9-b**.

ES-MS (M+H)<sup>+</sup> = 131

15 RT(HPLC-conditions 6) = 2.38 min

c) Preparation of **2-c**:



20

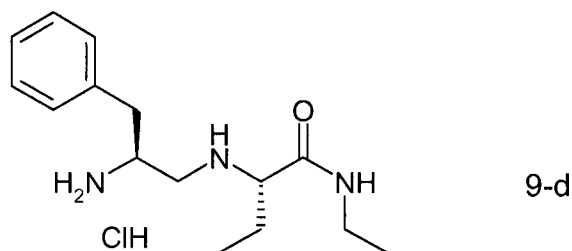
3.0 g (18.0 mmol) **9-b** and 2.4 g (19.0 mmol) DIPEA in 150 ml dichloromethane were stirred 15 minutes at room temperature, then 4.5 g (18.0 mmol) ((S)-1-benzyl-2-oxo-ethyl)-carbamic acid-*tert*-butylester were added and the mixture was cooled to 0°C. After that 3.0 ml (50.0 mmol) acetic acid and 7.6 g (36.0 mmol) sodium triacetoxyborohydride were added and the reaction was stirred at room temperature over night. The mixture was diluted with NaHCO<sub>3</sub> solution and extracted with ethylacetate. The organic phase was concentrated to yield quantitatively **2-c**.

25

ES-MS (M+H)<sup>+</sup> = 264  
 RT(HPLC-conditions 6) = 1.91 min

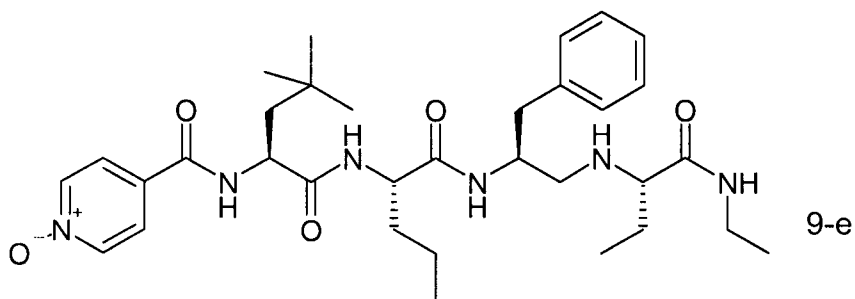
d) Preparation of **9-d**:

5



10 In analogy to the preparation of **9-b** 2.0 g (5.5 mmol) **2-c** yielded quantitatively **9-d**.  
 RT(HPLC-conditions 6) = 1.91 min

e) Preparation of **9-e**:



15

In analogy to the preparation of **3-a** 100.0 mg (0.27 mmol) **3-d** and 82.5 mg (0.27 mmol) **9-d** yielded 17.0 mg (10%) **9-e**.

ES-MS (M+H)<sup>+</sup> = 611  
 20 RT(HPLC-conditions 5) = 18.8 min

**Example A**

Examples of pharmaceutical formulations

5

a)	<u>Tablets</u>	<u>per tablet</u>
	Active substance (Example 1)	50 mg
	Lactose	170 mg
10	Corn starch	260 mg
	Polyvinylpyrrolidone	15 mg
	Magnesium stearate	5 mg
		<hr style="width: 100px; margin: 0 auto;"/> 500 mg

15 The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

20

b)	<u>Tablets</u>	<u>per tablet</u>
	Active substance (Example 1)	40 mg
25	Corn starch	210 mg
	Lactose	65 mg
	Microcrystalline cellulose	40 mg
	Polyvinylpyrrolidone	20 mg
	Sodium-carboxymethyl starch	23 mg
30	Magnesium stearate	<hr style="width: 100px; margin: 0 auto;"/> 2 mg
		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and  
 5 the mixture is compressed to form tablets of a suitable size.

c)	<u>Coated tablets</u>	<u>per coated tablet</u>
	Active substance (Example 1)	5 mg
10	Corn starch	41.5 mg
	Lactose	30 mg
	Polyvinylpyrrolidone	3 mg
	Magnesium stearate	<u>0.5 mg</u>
		80 mg

15 The active substance, corn starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45 °C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm  
 20 are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax..

d)	<u>Capsules</u>	<u>per capsule</u>
25	Active substance (Example 1)	25 mg
	Corn starch	283.5 mg
	Magnesium stearate	<u>1.5 mg</u>
		310 mg

30

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

5 e) Ampoule solution

Active substance (Example 1)	0,5	mg
Sodium chloride	50	mg
Water for inj.	5	ml

10

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 0,5 mg, 2,5 mg and 5,0 mg of active substance.

15

f) Suppositories

Active substance (Example 2)	30	mg
Solid fat	<u>1670</u>	mg
	1700	mg

20

The solid fat is melted. The ground active substance is homogeneously dispersed at 40 °C. It is cooled to 38 °C and poured into slightly chilled suppository moulds.

25

As used herein, the term "treatment" means that the compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

30

The term "prevention" means that the compounds of the present invention are useful when administered to a patient who has not been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The compounds of the invention will slow the development  
5 of disease symptoms, delay the onset of the disease, or prevent the individual from developing the disease at all.

Prevention also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due to age, familial history, genetic or  
10 chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

The compounds of the invention are administered in a therapeutically effective amount.  
15 The therapeutically effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

The compounds of the invention can be administered orally, parenterally, (IV, IM, depo-  
IM, SQ, and depo SQ), sublingually, intranasally, inhalative, intrathecally, topically, or  
20 rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable  
25 pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration or aerosols for inhalative administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

30 About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt thereof is admixed with a physiologically acceptable

vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably formulated in a unit dosage form, each dosage  
5 containing from about 2 to about 100 mg, more preferably about 10 to about 30 mg of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

10

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that  
15 supplement the desired action, or have another action.

The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with one or more different active ingredients.

20 The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

25 The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The compounds and compositions according to the invention can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a  
30 compound inhibitor and a second therapeutic agent for co-administration. The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include

a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampules, 5 vials and the like for parenteral administration; and patches, medipads, creams, and the like for topical administration, and optionally pre-filled inhalators for inhalative administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount 10 administered as well as other factors known to those of skill in the art.

It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the 15 compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can 20 be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be 25 compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets, capsules, lozenges or troches.

Pharmaceutically compatible binding agents and adjuvant materials can be included as part 30 of the composition.

The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and com  
5 starch; a lubricant such as, but not limited to, magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in addition to material of the above  
10 type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives,  
15 dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

20 Methods for preparation of such formulations are known to those skilled in the art.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the  
25 invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

30

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A beta production, to inhibit A beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes.

The invention here is the new compounds of the invention and new methods of using the compounds of the invention. Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for preventing disease or treating patients with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i. e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such agents or approaches include beta-secretase inhibitors; gamma-secretase inhibitors; amyloid aggregation inhibitors (e.g. Alzhemed); directly or indirectly acting neuroprotective compounds; anti-oxidants such as Vitamin E and ginkgolides; anti-

inflammatory agents such as Cox-inhibitors or NSAID's; HMG-CoA Reductase Inhibitors (statins); acetylcholine-esterase inhibitors such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists (e.g. memantine); AMPA agonists; compounds which modulate the release or concentration of neurotransmitters (e.g. NS-2330);  
5 compounds inducing the release of growth hormones (e.g. ibutamoren mesylate and capromorelin); CB-1 receptor antagonists or inverse agonists; antibiotika like minocyclin or rifampicin; PDE-IV and PDE-IX inhibitors; GABA<sub>A</sub> inverse agonists; nicotinic agonists: histamin H3 antagonists, 5 HT-4 agonists or partial agonists; 5HT-6 antagonists; a2-adrenoreceptor antagonists; muscarinic M1 agonists; muscarinic M2 antagonists;  
10 metabotropic glutamaic-receptor 5 positive modulators; and compounds, which modulate receptors oder enzymes in such a way, that the efficacy and/or safety of the compounds of the present invention is increased or side effects are reduced.

Preferred are such combinations comprising one or more of the compounds of the present  
15 invention and one or more additional active ingredient selected from the group consisting Alzhemed, vitamin E, ginkolide, donepezil, rivastigmine, tacrine, galantamine, memantine, NS-2330, ibutamoren mesylate, capromoreline, minocycline and rifampicine.

In the combination of the present invention, the compounds of the present invention and  
20 the above mentioned combination partners may be administered separately (e.g. kit of parts) or together in one pharmaceutical composition (e.g. capsule or tablet). In addition, the administration of one element of the combination of the present invention may be prior to, concurrent to, or subsequent to the administration of the other element of the combination. If the compounds of the present invention and the one or more additional  
25 active ingredient are present in separate formulations these separate formulations may be administered simultaneously or sequentially.

For the treatment or prevention of the above mentioend diseases and conditions the compounds of the invention can be used in combination with immunological approaches,  
30 such as, for example, immunization with A beta peptide or derivatives thereof or administration of anti-A beta peptide antibodies.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compounds of the invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the individual may be taking as is well known to administering physicians who are skilled in this art.

Dosage ranges of the above described combination partners are approximately one fifth to one times the clinically effective ranges required to induce the desired therapeutic effect, respectively when the compounds are used singly.

Therefore, a further object of the invention relates to the the use of a compound according to the present invention in combination with at least one further active ingredient for the manufacture of a medicament for the treatment or prevention of diseases and conditions which can be modified by inhibition of  $\beta$ -secretase.

A further object of the present invention is a medicament comprising a compound according to the present invention and at least one further active ingredient.

The compounds of the invention inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site"). While not wishing to be bound by a particular theory, inhibition of beta-secretase activity is thought to inhibit production of beta amyloid peptide(A beta). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a beta-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate efficacy of the

compound inhibitors of the invention are known. Representative assay systems are described, for example, in U. S. Patents No. 5,942,400, 5,744,346, as well as in the examples below.

5 The enzymatic activity of beta-secretase and the production of A beta can be analyzed in vitro or in vivo, using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, animal models expressing native APP and enzyme, or may utilize transgenic and non-transgenic  
10 animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, fluorometric or chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase  
15 mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

Various forms of beta-secretase enzyme are known, and are available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, recombinant,  
20 and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U. S. Patent No. 5,744,346 and published PCT patent applications W098/22597, WO00/03819, WO01/23533, and WO00/17369, as well as in literature publications (Hussain et. al., 1999, Mol. Cell. Neurosci. 14: 419-427; Vassar et. al., 1999,  
25 Science 286 : 735-741; Yan et. al., 1999, Nature 402: 533-537; Sinha et. al., 1999, Nature40: 537-540; and Lin et. al., 2000, PNAS USA 97 : 1456-1460). Synthetic forms of the enzyme have also been described (W098/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

30

**Determination of BACE activity in vitro**

Activity of BACE can be analyzed by different assay technologies, all incubating a catalytically active form of BACE with a potential substrate in a suitable buffer. The decrease in substrate concentration or the increase in product concentration can be monitored by applying different techniques depending on the nature of the substrate and include but are not limited to HPLC-MS analysis, fluorescence assays, fluorescence quenching assays. The substrate can be a peptide containing an amino acid sequence which is can be hydrolyzed by BACE which may be conjugated with dyes suitable for the detection system chosen or may extend to the protein substrate. As enzyme source, the full-length BACE enzyme can be used as well as the catalytically active ectodomain of the protein. An alternative assay format based on competition of the test compound with a BACE binding compound can be used.

For IC<sub>50</sub> determination different concentrations of compound are incubated in the assay. The relative compound inhibition potency is determined by calculating the concentration of compound that showed a 50% reduction in detected signal compared to the enzyme reaction signal in the control wells with no added compound.

Useful inhibitory compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than 50 micro molar, preferably at a concentration of 10 micro molar or less, more preferably 1 micro molar or less, and most preferably 10 nano molar or less.

In order to obtain the in vitro BACE inhibitory profile of the compounds of the invention they can be tested in the assays as outlined in the examples:

25

**Example BACE assay:**

For each compound being tested, the BACE activity is monitored in a fluorescence quenching assay using the ectodomain of BACE (aa 1-454) fused to a myc-his tag and secreted from HEK293/APP/BACE<sub>ect.</sub> cells into OptiMEM™ (Invitrogen) as enzyme source. The substrate peptide used has the amino acid sequence SEVNLDAEFK and

30

possesses a Cy3-fluorophore at the N-terminus and a Cy5Q-quencher (Amersham) at the C-terminus. The substrate is dissolved at 1mg/ml in DMSO.

The assay is performed in the presence of 10  $\mu$ l OptiMEM containing the ectodomain of BACE, 100  $\mu$ l water containing the desired concentration of compound with a max. conc. of 1% DMSO, 1  $\mu$ M substrate peptide, and 20 mM NaOAc, pH 4.4 in a total assay volume of 200  $\mu$ l in a 96 well plate. The reaction is incubated at 30°C in a fluorimeter and the cleavage of the substrate is recorded as kinetic for 30 min. at ex: 530 nm, em: 590 nm. The water used for preparation of the buffer or compound dilution is of highest purity. Blank wells containing either no inhibitor or no enzyme are included on each plate.

10

The compounds of formula (I) exemplified below as examples 1 to 58 show IC<sub>50</sub> values of less than 20 micro molar.

#### **A $\beta$ secretion assay**

The secretion of A $\beta$  can be monitored in cell lines of different origin. A representative set of such cells include but are not limited to human embryonic kidney 293 cells (HEK293), Chinese hamster ovary cells (CHO), human H4 neuroglialoma cells, human U373-MG astrocytoma glioblastoma cells, murine neuroblastoma N2a cells which are stably or transiently transfected with APP or mutated forms of APP which include but is not limited to the Swedish or London/Indiana mutations. Transfection of the cells can for example be achieved by introducing a pcDNA3 plasmid (Invitrogen) containing the human APP cDNA of interest using a transfection reagent like Lipofectamine (Invitrogen) according to the instructions of the manufacturer.

Secretion of A $\beta$  can also on a routine basis be analyzed from cells producing without genetic modification sufficient amounts of A $\beta$  or by using highly sensitive A $\beta$  detection assays. Cells suitable for an analysis of this kind include but are not limited to human IMR-32 neuroblastoma cells.

Secretion of A $\beta$  from cells can also be analyzed from brain derived cells obtained from embryos or the new born offspring from APP transgenic mice as for example the mice described by Hsiao et al (Hsiao et al 1996 Science 274: 99-102). In addition brain derived cells from other organism such as rat or guinea pig may also be used.

30

Useful inhibitory compounds are effective to inhibit 50% of beta-secretase enzymatic activity in these cellular assays at a concentration of less than 50 micro molar, preferably at a concentration of 10 micro molar or less, more preferably 1 micro molar or less, and most  
5 preferably 10 nano molar or less.

### **Example A $\beta$ secretion assay**

In the following a protocol for the determination of A $\beta$  from U373-MG cells which are stably expressing APP<sub>751</sub> under the control of a CMV promoter is given.

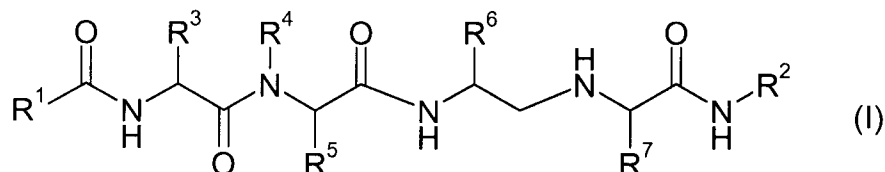
10 The cells can be maintained in a culture medium like DMEM + glucose, sodium pyruvate, glutamine, pyridoxine-HCl, and 10% FCS. The cells are kept in an incubator at 37°C in a water saturated atmosphere of 5% CO<sub>2</sub>. For assaying compounds a confluent cell layer is incubated with compound concentrations in the range of 50  $\mu$ M to 50 pM, originally dissolved in DMSO and for the assay diluted in 150  $\mu$ l of the medium described, for 12-24  
15 hours. The production of A $\beta$  during this period of time in the presence or absence of compound is monitored by sandwich ELISA specific for A $\beta$ 40 and A $\beta$ 42. The antibodies 6E10 (Senetek) and SGY3160 (C. Eckman, Mayo Clinic, Jacksonville, Florida) are used as capture antibodies and immobilized to the plate. Unspecific protein binding is blocked with Block Ace (Serotec) before adding the A $\beta$  containing cell culture supernatant. The  
20 detection antibodies specific for A $\beta$ 40 and A $\beta$ 42 (Nanotools, Germany) are conjugated with alkaline phosphatase which activity is quantified using the substrate CSPD/Sapphire II (Applied Biosystems) according to the manufacturers instructions.  
Potential effects of the compound in altering the A $\beta$  level induced by an unspecific toxicity related mechanism are addressed by the reduction of AlamarBlue (Resazurin) after 60 min.  
25 Potency of non-toxic compounds is determined by calculating the concentration of compound that showed a 50% reduction in the detected signal compared to the cells in the control wells with no added compound.

The compounds of formula (I) exemplified below as examples 1 to 58 show IC<sub>50</sub> values of  
30 less than 10 micro molar.

Various animal models can be used to analyze beta-secretase activity and/or processing of APP to release A beta, as described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for  
5 example, in U. S. Patent Nos: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015"and 5,811,633, and in Games et. al., 1995, Nature 373: 523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of  
10 the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

## CLAIMS:

1. A compound of formula (I)



5

wherein

R<sup>1</sup> represents

- 10 a) a C<sub>1-4</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,  
 wherein one non terminal methylene group of the C<sub>1-4</sub>-alkyl-group is  
 optionally replaced by a nitrogen or a oxygen atom, and  
 wherein the C<sub>1-4</sub>-alkyl- or the C<sub>3-6</sub>-cycloalkyl-group is substituted by one or  
 more substituents independently selected from the group consisting of HO-  
 CO-, HO-PO<sub>2</sub>- and HO-SO<sub>2</sub>-,
- 15 b) an aryl-group,  
 wherein the aryl-group is optionally substituted by one or more substituents  
 independently selected from the group consisting of halogen, C<sub>1-3</sub>-alkyl-,  
 HO-, HO-CO- and HO-SO<sub>2</sub>-, or
- 20 c) a heteroaryl-group,  
 wherein the heteroaryl-group is optionally substituted by one or more  
 substituents independently selected from the group consisting of halogen,  
 C<sub>1-3</sub>-alkyl-, HO-, HO-CO- and HO-SO<sub>2</sub>-

25 R<sup>2</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-  
 cycloalkyl-C<sub>1-5</sub>-alkyl-, heterocyclyl-, heterocyclyl-C<sub>1-5</sub>-alkyl-, aryl-, aryl-C<sub>1-5</sub>-  
 alkyl-, heteroaryl-, heteroaryl-C<sub>1-5</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-5</sub>-alkenyl-,  
 heterocyclyl-C<sub>2-5</sub>-alkenyl-, aryl-C<sub>2-5</sub>-alkenyl-, heteroaryl-C<sub>2-5</sub>-alkenyl-, C<sub>3-8</sub>-

cycloalkyl-C<sub>2-5</sub>-alkynyl-, heterocyclyl-C<sub>2-5</sub>-alkynyl-, aryl-C<sub>2-5</sub>-alkynyl- or a heteroaryl-C<sub>2-5</sub>-alkynyl-group,

each of said groups may be substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, HO-C<sub>1-3</sub>-alkyl-, HO-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-, C<sub>1-3</sub>-alkyl-O-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-, halogen-, carboxy-, formyl-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N-, (R<sup>8</sup>)<sub>2</sub>N-C<sub>1-3</sub>-alkyl-, (R<sup>8</sup>)<sub>2</sub>N-CO-, (R<sup>8</sup>)<sub>2</sub>N-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-CO-N(R<sup>8</sup>)-, (R<sup>8</sup>)<sub>2</sub>N-SO<sub>2</sub>-, C<sub>1-3</sub>-alkyl-SO<sub>2</sub>- and C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-N(R<sup>8</sup>)-,

R<sup>3</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl-, heteroaryl-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkenyl-, heterocyclyl-C<sub>2-3</sub>-alkenyl-, aryl-C<sub>2-3</sub>-alkenyl-, heteroaryl-C<sub>2-3</sub>-alkenyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkynyl-, heterocyclyl-C<sub>2-3</sub>-alkynyl-, aryl-C<sub>2-3</sub>-alkynyl- or a heteroaryl-C<sub>2-3</sub>-alkynyl-group,

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>4</sup> represents hydrogen, a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl- or a C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-group,

each of said groups may be optionally substituted by one or more fluor atoms,

R<sup>5</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl-, heteroaryl-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkenyl-, heterocyclyl-C<sub>2-3</sub>-alkenyl-, aryl-C<sub>2-3</sub>-alkenyl-, heteroaryl-C<sub>2-3</sub>-alkenyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>2-3</sub>-alkynyl-, heterocyclyl-C<sub>2-3</sub>-alkynyl-, aryl-C<sub>2-3</sub>-alkynyl- or a heteroaryl-C<sub>2-3</sub>-alkynyl-group,

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

- 5  $R^6$  represents a  $C_{1-8}$ -alkyl-,  $C_{2-8}$ -alkenyl-,  $C_{2-8}$ -alkynyl-,  $C_{1-8}$ -alkyl-O- $C_{1-3}$ -alkyl-,  $C_{1-3}$ -alkyl-S- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl-,  $C_{3-8}$ -cycloalkyl- $C_{1-3}$ -alkyl-, aryl-, aryl- $C_{1-4}$ -alkyl-, heteroaryl- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkenyl-, heterocyclyl- $C_{2-3}$ -alkenyl-, aryl- $C_{2-3}$ -alkenyl-, heteroaryl- $C_{2-3}$ -alkenyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkynyl-, heterocyclyl- $C_{2-3}$ -alkynyl-, aryl- $C_{2-3}$ -alkynyl- or a heteroaryl- $C_{2-3}$ -alkynyl-group, each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-,  $(R^8)_2N$ - and  $(R^8)_2N$ -CO-,
- 10  $R^7$  represents a  $C_{1-8}$ -alkyl-,  $C_{2-8}$ -alkenyl-,  $C_{2-8}$ -alkynyl-,  $C_{1-8}$ -alkyl-O- $C_{1-3}$ -alkyl-,  $C_{1-3}$ -alkyl-S- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl-,  $C_{3-8}$ -cycloalkyl- $C_{1-3}$ -alkyl-, aryl-, aryl- $C_{1-4}$ -alkyl-, heteroaryl- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkenyl-, heterocyclyl- $C_{2-3}$ -alkenyl-, aryl- $C_{2-3}$ -alkenyl-, heteroaryl- $C_{2-3}$ -alkenyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkynyl-, heterocyclyl- $C_{2-3}$ -alkynyl-, aryl- $C_{2-3}$ -alkynyl- or a heteroaryl- $C_{2-3}$ -alkynyl-group, each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-,  $(R^8)_2N$ - and  $(R^8)_2N$ -CO-,
- 15  $R^8$  each independently of one another represents hydrogen, a  $C_{1-6}$ -alkyl-,  $C_{2-6}$ -alkenyl-,  $C_{2-6}$ -alkynyl-,  $C_{3-8}$ -cycloalkyl-,  $C_{3-8}$ -cycloalkyl- $C_{1-3}$ -alkyl-, heterocyclyl-, heterocyclyl- $C_{1-3}$ -alkyl-, aryl-, aryl- $C_{1-3}$ -alkyl-, heteroaryl-, heteroaryl- $C_{1-3}$ -alkyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkenyl-, heterocyclyl- $C_{2-3}$ -alkenyl-, aryl- $C_{2-3}$ -alkenyl-, heteroaryl- $C_{2-3}$ -alkenyl-,  $C_{3-8}$ -cycloalkyl- $C_{2-3}$ -alkynyl-, heterocyclyl- $C_{2-3}$ -alkynyl-, aryl- $C_{2-3}$ -alkynyl- or a heteroaryl- $C_{2-3}$ -alkynyl-group, each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of  $C_{1-3}$ -alkyl-,  $C_{1-3}$ -alkyl-O-, halogen-, carboxy-, hydroxy-, nitro-, cyano-,  $H_2N$ - and  $H_2N$ - $SO_2$ -,
- 20 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.
- 25
- 30

2. A compound according to claim 1, wherein

R<sup>1</sup> represents

- 5 a) a C<sub>1-4</sub>-alkyl-group,  
wherein the C<sub>1-4</sub>-alkyl- is substituted by one or more substituents  
independently selected from the group consisting of HO-CO- and HO-SO<sub>2</sub>-,
- b) an aryl-group,  
optionally substituted by one or more substituents independently selected  
10 from the group consisting of fluoro, HO- and HO-CO-, or
- c) a heteroaryl-group,  
optionally substituted by one or more substituents independently selected  
from the group consisting of fluoro, chloro, Me, HO- and HO-CO-.

15 R<sup>2</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-  
cycloalkyl-C<sub>1-5</sub>-alkyl-, heterocyclyl-, heterocyclyl-C<sub>1-5</sub>-alkyl-, aryl-, aryl-C<sub>1-5</sub>-  
alkyl-, heteroaryl- or a heteroaryl-C<sub>1-5</sub>-alkyl-group,  
each of said groups may be substituted by one or more substituents  
independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, HO-C<sub>1-3</sub>-  
20 alkyl-, HO-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-,  
C<sub>1-3</sub>-alkyl-O-, halogen, carboxy-, formyl-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N-,  
(R<sup>8</sup>)<sub>2</sub>N-C<sub>1-3</sub>-alkyl-, (R<sup>8</sup>)<sub>2</sub>N-CO-, (R<sup>8</sup>)<sub>2</sub>N-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-CO-  
N(R<sup>8</sup>)-, (R<sup>8</sup>)<sub>2</sub>N-SO<sub>2</sub>-, C<sub>1-3</sub>-alkyl-SO<sub>2</sub>- and C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-N(R<sup>8</sup>)-,

25 R<sup>3</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-  
alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-  
alkyl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,  
each of said groups may be optionally substituted by one or more  
substituents independently selected from the group consisting of halogen,  
30 carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>4</sup> represents hydrogen, a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl- or a C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-group,

each of said groups may be optionally substituted by one or more fluor atoms,

5

R<sup>5</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl- and heteroaryl-C<sub>1-3</sub>-alkyl-,

each of said groups may be optionally substituted by one or more

10 substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

R<sup>6</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,

15

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

20 R<sup>7</sup> represents a C<sub>1-8</sub>-alkyl-, C<sub>2-8</sub>-alkenyl-, C<sub>2-8</sub>-alkynyl-, C<sub>1-8</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-4</sub>-alkyl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, (R<sup>8</sup>)<sub>2</sub>N- and (R<sup>8</sup>)<sub>2</sub>N-CO-,

25

R<sup>8</sup> each independently of one another represents hydrogen, a C<sub>1-6</sub>-alkyl-, C<sub>3-8</sub>-cycloalkyl-, C<sub>3-8</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, heterocyclyl-, heterocyclyl-C<sub>1-3</sub>-alkyl-, aryl-, aryl-C<sub>1-3</sub>-alkyl-, heteroaryl- or a heteroaryl-C<sub>1-3</sub>-alkyl-group,

30

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-,

C<sub>1-3</sub>-alkyl-O-, halogen-, carboxy-, hydroxy-, nitro-, cyano-, H<sub>2</sub>N- and H<sub>2</sub>N-SO<sub>2</sub>-,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

5

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

R<sup>1</sup> represents

- 10 a) a HO-CO-(CH<sub>2</sub>)<sub>n</sub>- or a HO-SO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-group wherein n is 1, 2, 3 or 4, or  
b) a quinolinyl N-oxide, isoquinolinyl N-oxide, pyridin-2-yl N-oxide, pyridin-3-yl N-oxide, pyridin-4-yl N-oxide, or  
c) a phenyl group,  
wherein the phenyl group is optionally substituted by one or more substituents independently selected from the group consisting of halogen  
15 and hydroxy-,

R<sup>8</sup> each independently of one another represents hydrogen or a C<sub>1-6</sub>-alkyl-group,  
wherein the C<sub>1-6</sub>-alkyl-group may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-  
20 O-, halogen, carboxy-, hydroxy-, nitro-, cyano- and H<sub>2</sub>N-,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

25 4. A compound according to claim 1 or 2, wherein

R<sup>1</sup> represents

- a) HO-CO-(CH<sub>2</sub>)<sub>n</sub>-group, wherein n is 1, 2, 3 or 4,  
b) a pyridin-2-yl N-oxide, pyridin-3-yl N-oxide, pyridin-4-yl N-oxide, or  
c) a phenyl group,

wherein the phenyl group is optionally substituted by one or more substituents independently selected from the group consisting of halogen and hydroxy,

5         $R^8$  each independently of one another represents hydrogen or a  $C_{1-6}$ -alkyl-group, wherein the  $C_{1-6}$ -alkyl-group may be optionally substituted by one or more substituents independently selected from the group consisting  $C_{1-3}$ -alkyl-O- and fluor,  
or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
10        thereof.

5. A compound according to claim 1 or 2, wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-2-yl N-oxide, pyridin-3-yl N-oxide, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-  
15        tetrafluorophenyl-group,

$R^8$  each independently of one another represents hydrogen or a  $C_{1-6}$ -alkyl-group.  
or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
thereof.  
20

6. A compound according to claim 1 or 2, wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or  
a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

25         $R^8$  each independently of one another represents hydrogen or a  $C_{1-3}$ -alkyl-group.  
or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
thereof.

7. A compound according to any of the claims 1 to 6, wherein

30         $R^2$  represents a  $C_{1-5}$ -alkyl-,  $C_{2-5}$ -alkenyl-,  $C_{2-5}$ -alkynyl-,  $C_{3-6}$ -cycloalkyl- $C_{1-5}$ -alkyl-,  
phenyl- $C_{1-5}$ -alkyl- or a heteroaryl- $C_{1-5}$ -alkyl-group

wherein the C<sub>1-5</sub>-alkyl-group may be optionally substituted by one or more fluoro atoms, and

wherein the phenyl group may be optionally substituted by one or more substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, nitro-, halogen, hydroxy-, carboxy-, (R<sup>8</sup>)<sub>2</sub>N-, (R<sup>8</sup>)<sub>2</sub>N-C<sub>1-3</sub>-alkyl-, (R<sup>8</sup>)<sub>2</sub>N-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-CO-N(R<sup>8</sup>)-, C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-, (R<sup>8</sup>)<sub>2</sub>N-CO-, HO-C<sub>1-3</sub>-alkyl-, HO-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-O-CO- and C<sub>1-3</sub>-alkyl-SO<sub>2</sub>-N(R<sup>8</sup>)-,

5 R<sup>3</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, phenyl-, phenyl-C<sub>1-4</sub>-alkyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-,

15 R<sup>4</sup> represents hydrogen or a C<sub>1-4</sub>-alkyl-group optionally substituted with one or more Fluor atoms,

20 R<sup>5</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, phenyl-, phenyl-C<sub>1-4</sub>-alkyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-,

25 R<sup>6</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, phenyl-, phenyl-C<sub>1-4</sub>-alkyl-, heteroaryl-C<sub>1-3</sub>-alkyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-,

5 R<sup>7</sup> represents a C<sub>1-6</sub>-alkyl-, C<sub>2-6</sub>-alkenyl-, C<sub>2-6</sub>-alkynyl-, C<sub>1-6</sub>-alkyl-O-C<sub>1-3</sub>-alkyl-, phenyl-, phenyl-C<sub>1-4</sub>-alkyl-group, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl, C<sub>1-3</sub>-alkyl-S-C<sub>1-3</sub>-alkyl- or a C<sub>3-6</sub>-cycloalkyl-group,

each of said groups may be optionally substituted by one or more substituents independently selected from the group consisting of halogen, 10 carboxy-, hydroxy-, cyano-, nitro-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-groups,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

8. A compound according to any of the claims 1 to 6, wherein

15 R<sup>2</sup> represents a C<sub>1-3</sub>-alkyl-, C<sub>3-6</sub>-cycloalkyl-C<sub>1-3</sub>-alkyl-, phenyl-C<sub>1-3</sub>-alkyl- or a pyridyl-C<sub>1-3</sub>-alkyl-group

wherein the C<sub>1-3</sub>-alkyl-group may be optionally substituted by one or more fluoro atoms, and

wherein the phenyl group may be optionally substituted by one or more 20 substituents independently selected from the group consisting of C<sub>1-3</sub>-alkyl-, nitro-, hydroxy-, carboxy-, H<sub>2</sub>N-, H<sub>2</sub>N-CH<sub>2</sub>-, H<sub>2</sub>N-CO-CH<sub>2</sub>-, Me-CO-NH-, Me-SO<sub>2</sub>-, H<sub>2</sub>N-CO-, HO-CH<sub>2</sub>-, HOCO-CH<sub>2</sub>-, Me-OCO-CH<sub>2</sub>-, Me-OCO-, and Me-SO<sub>2</sub>-NH-,

25 R<sup>3</sup> represents a C<sub>1-5</sub>-alkyl-group,

R<sup>4</sup> represents hydrogen,

R<sup>5</sup> represents a C<sub>1-5</sub>-alkyl- or a phenyl-C<sub>1-2</sub>-alkyl-group,

30

R<sup>6</sup> represents a C<sub>1-4</sub>-alkyl- or a phenyl-C<sub>1-2</sub>-alkyl-group,

$R^7$  represents a  $C_{1-5}$ -alkyl- or a phenyl- $C_{1-2}$ -alkyl-group,

wherein the alkyl-group may be optionally substituted by one or more  
substituents independently selected from the group consisting of carboxy-,  
hydroxy-,  $H_2N$ - and  $H_2N$ -CO-groups,

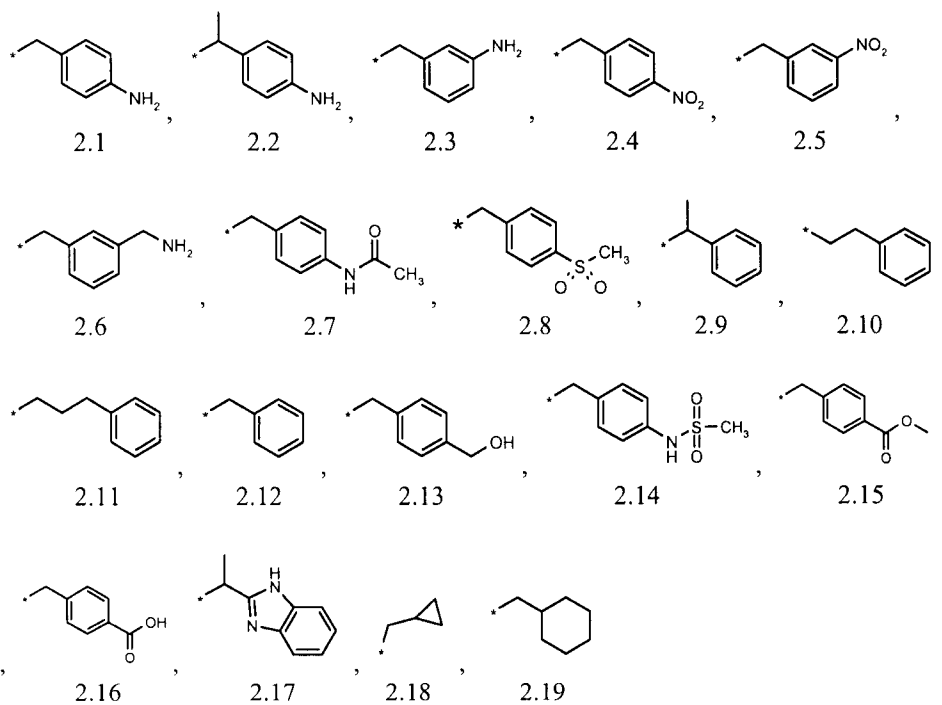
5

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

9. A compound according to one or more of the claims 1 to 6, wherein

10

$R^2$  represents an ethyl-, n-propyl- or a 2-methylpropyl-group,  
or a substituent selected from the group consisting of



20

25  $R^3$  represents a  $C_{1-5}$ -alkyl-group,

$R^4$  represents hydrogen,

$R^5$  represents a  $C_{1-5}$ -alkyl- or a phenyl- $C_{1-2}$ -alkyl-group,

R<sup>6</sup> represents a C<sub>1-4</sub>-alkyl- or a phenyl-C<sub>1-2</sub>-alkyl-group,

R<sup>7</sup> represents a C<sub>1-5</sub>-alkyl- or a phenyl-C<sub>1-2</sub>-alkyl-group,

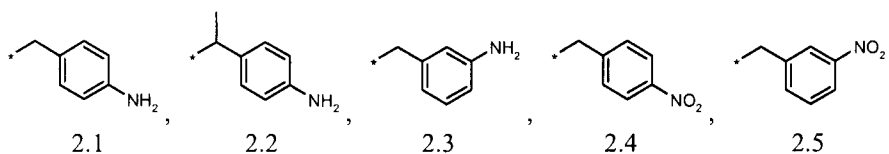
5 wherein the alkyl-group may be optionally substituted by one or more substituents independently selected from the group consisting of carboxy-, hydroxy-, H<sub>2</sub>N- and H<sub>2</sub>N-CO-groups, or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

10

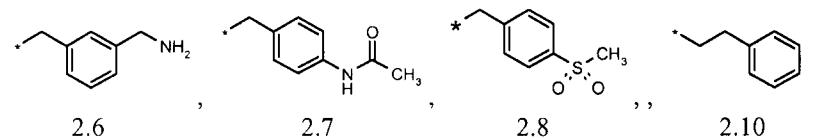
10. A compound according to one or more of the claims 1 to 6, wherein

R<sup>2</sup> represents an ethyl-, n-propyl- or a 2-methylpropyl-group, or a substituent selected from the group consisting of

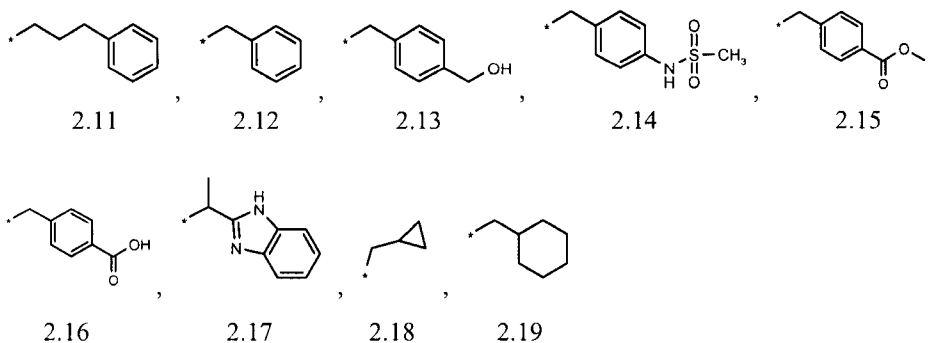
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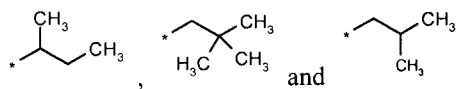
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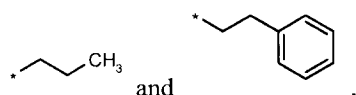


R<sup>3</sup> represents a substituent selected from the group consisting of

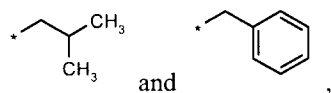


R<sup>4</sup> represents hydrogen,

5 R<sup>5</sup> represents a substituent selected from the group consisting of

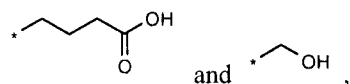


R<sup>6</sup> represents a substituent selected from the group consisting of



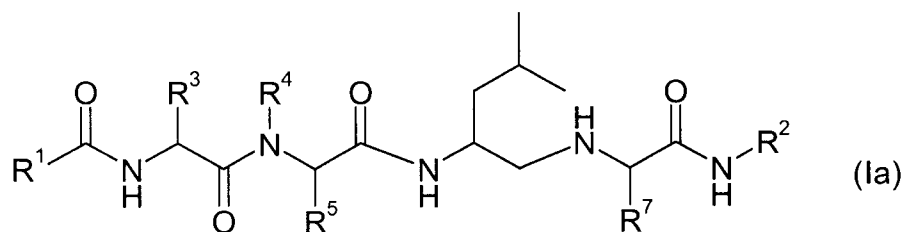
10

R<sup>7</sup> represents a methyl-, ethyl-, n-propyl- or a n-butyl-group,  
 or a substituent selected from the group consisting of



15 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

11. A compound of formula (Ia)



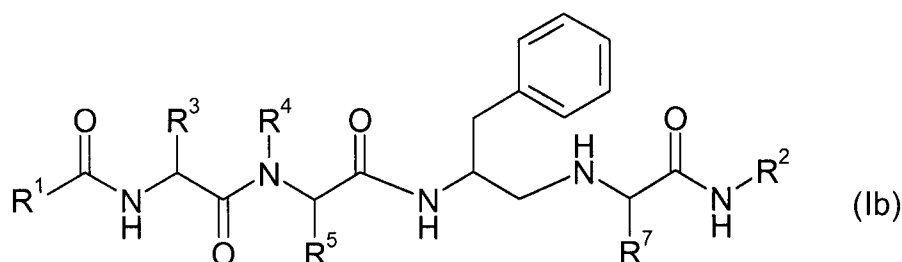
wherein

20 R<sup>1</sup> represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

and  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^7$  and  $R^8$  are defined as in one of the claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,  
or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

5

12. A compound of formula (Ib)



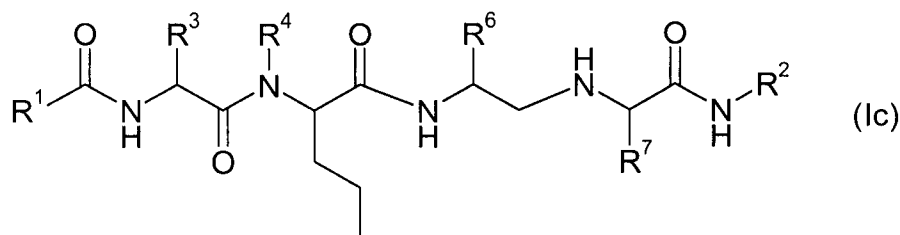
wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or  
10 a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

and  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^7$  and  $R^8$  are defined as in one of the claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,

15 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

13. A compound of formula (Ic)



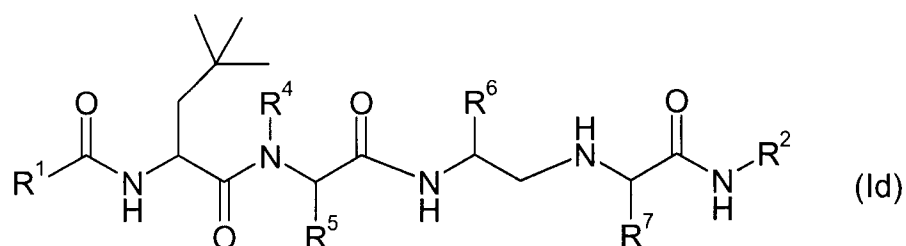
wherein

20  $R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

and  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$ ,  $R^7$  and  $R^8$  are defined as in one of the claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,  
 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

5

14. A compound of formula (Id)

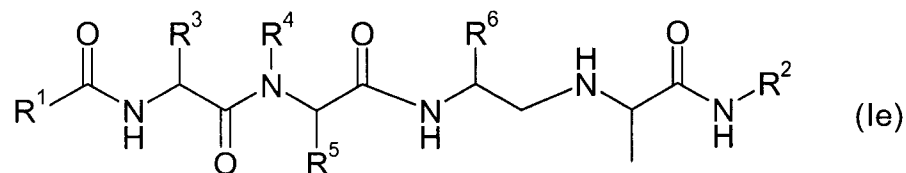


wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or  
 10 a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

and  $R^2$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$  and  $R^8$  are defined as in one of the claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,  
 or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates  
 15 thereof.

15. A compound of formula (Ie)



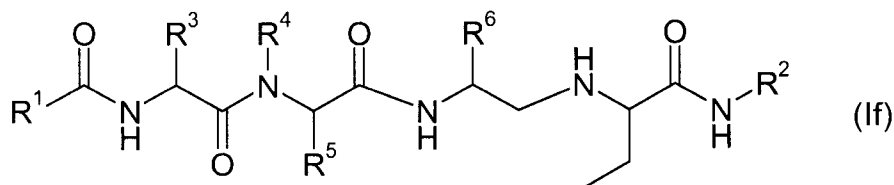
wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or  
 20 a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

and  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^8$  are defined as in one of the claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

16. A compound of formula (If)



5

wherein

$R^1$  represents a HO-CO-(CH<sub>2</sub>)<sub>3</sub>-, pyridin-4-yl N-oxide, phenyl-, 4-hydroxyphenyl- or a 4-hydroxy-2,3,5,6-tetrafluorophenyl-group,

10 and  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$  and  $R^8$  are defined as in one of the claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,

or pharmaceutically acceptable tautomers, enantiomers, diastereomers, salts or solvates thereof.

15 17. A compound according to any of the preceding claims or a pharmaceutically acceptable salt or solvate thereof as a medicament.

18. A pharmaceutical composition comprising a compound according to any of the preceding claims or a pharmaceutically acceptable salt or solvate thereof and a  
20 pharmaceutically acceptable carrier or diluent.

19. A pharmaceutical composition according to claim 18, which comprises one or more additional active ingredient selected from the group consisting of beta-secretase inhibitors; gamma-secretase inhibitors; amyloid aggregation inhibitors; directly or indirectly acting  
25 neuroprotective compounds; anti-oxidants; anti-inflammatory agents; HMG-CoA reductase inhibitors; acetylcholine-esterase inhibitors; NMDA receptor antagonists; AMPA agonists; compounds which modulate the release or concentration of neurotransmitters; compounds inducing the release of growth hormones; CB-1 receptor antagonists or inverse

agonists; antibiotika; PDE-IV and PDE-IX inhibitors, GABA<sub>A</sub> inverse agonists; nicotinic agonists; histamin H3 antagonists; 5 HT-4 agonists or partial agonists; 5HT-6 antagonists;  $\alpha$ 2-adrenoreceptor antagonists; muscarinic M1 agonists; muscarinic M2 antagonists; metabotropic glutamaic-receptor 5 positive modulators.

5

20. A pharmaceutical composition according to claim 18 or 19, which comprises one or more additional agents selected from the group consisting Alzhemed, vitamin E, ginkgolide, donepezil, rivastigmine, tacrine, galantamine, memantine, NS-2330, ibutamoren mesylate, capromoreline, minocycline and rifampicine.

10

21. The use of a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), or (If) according to any of the claims 1 to 17 or a pharmaceutically acceptable salt or solvate thereof or of a pharmaceutical composition according to any one of claims 18 to 21 in the manufacture of a medicamentation for the treatment or prevention of diseases and conditions which can be modified by inhibition of  $\beta$ -secretase.

15

22. The use of a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), or (If) according to any of the claims 1 to 17 or a pharmaceutically acceptable salt or solvate thereof or of a pharmaceutical composition according to any one of claims 18 to 21 in the manufacture of a medicamentation for use in treating a patient who has, or in preventing a patient from getting, a disease or condition selected from Alzheimer's disease, diffuse Lewy body type of Alzheimer's disease, Down's syndrome, MCI ("Mild Cognitive Impairment"), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, Cerebral Amyloid Angiopathy, Traumatic Braininjury, Dementia, Parkinson's Syndrome, Pancreatits, inclusion body myositis (IBM) or central or peripheral amyloid diseases.

20

25

23. A method for inhibiting  $\beta$ -secretase activity, comprising exposing said  $\beta$ -secretase to an effective inhibitory amount of a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie) or (If) of any one of claims 1 to 17.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/064885

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K7/02 A61K38/03 A61P25/28

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)  
C07K A61K A61P

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, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 309 297 A (THE ADMINISTRATORS OF THE TULANE EDUCATIONAL FUND) 29 March 1989 (1989-03-29)	1, 2, 17, 18
Y	* see Bombesin, 9-de-L-alanine-10-[N-(2-aminopropyl)-L-valine]; RN 122036-88-8* the whole document	3-16, 19, 20
X	US 4 743 585 A (HUDSPETH ET AL) 10 May 1988 (1988-05-10)	1, 2, 17, 18
Y	*see RN 118405-36-0 (2,5,8,13,16-Pentaazaheptadecanoic acid, 5, 10-dihydroxy-6-(1H-imidazol-4-ylmethyl)-9, 14-bis(2-methylpropyl)-7,12,15-trioxo-17-phenyl-3-(phenylmethyl)-,1,1-dimethylethyl ester..)*	3-16, 19, 20

 Further documents are listed in the continuation of Box C. 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
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

8 December 2006

Date of mailing of the international search report

14/12/2006

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Bayrak, Sinasi

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/064885

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 750 646 A (COY ET AL) 12 May 1998 (1998-05-12)	1,2,17, 18
Y	*see RN 207616-21-5 (2-14-Bombesin, 9.psi.10(CH2-NH)-12-L-phenylalanine)* the whole document -----	3-16,19, 20
X	US 5 723 578 A (COY ET AL) 3 March 1998 (1998-03-03)	1,2,17, 18
Y	*see RN 115136-04-4 (Bombesin, 9.psi.10(CH2-NH)-14-L-leucinamide-)* the whole document -----	3-16,19, 20
A	WO 01/68120 A (SMITHKLINE BEECHAM P.L.C; SMART, DARREN; STRIJBOS, PAUL) 20 September 2001 (2001-09-20) the whole document -----	1-23

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2006/064885

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 23 is directed to a method of treatment of the human/animal body (insofar as an in vivo application is concerned), the search has been carried out and based on the alleged effects of the composition.
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/064885

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0309297	A	29-03-1989	AT 113961 T	15-11-1994
			AU 2710288 A	18-04-1989
			DE 3852086 D1	15-12-1994
			DE 3852086 T2	18-05-1995
			DK 249489 A	20-07-1989
			ES 2065336 T3	16-02-1995
			FI 892507 A	23-05-1989
			JP 2502016 T	05-07-1990
			JP 2795449 B2	10-09-1998
			NO 892060 A	21-07-1989
			WO 8902897 A1	06-04-1989
US 4743585	A	10-05-1988	AU 8336187 A	16-06-1988
			GR 871770 A1	17-03-1988
			WO 8803927 A2	02-06-1988
US 5750646	A	12-05-1998	NONE	
US 5723578	A	03-03-1998	US 6307017 B1	23-10-2001
WO 0168120	A	20-09-2001	AU 5219101 A	24-09-2001
			EP 1263455 A2	11-12-2002
			JP 2003526674 T	09-09-2003
			US 2004023862 A1	05-02-2004