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(54) **PHOSPHINIC ACID DERIVATIVES, BETA-SECRETASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE**

PHOSPHINSÄUREDERIVATE, INHIBITOREN VON BETA-SEKRETASE ZUR BEHANDLUNG VON ALZHEIMER-KRANKHEIT

DERIVES D'ACIDE PHOSPHINIQUE, INHIBITEURS DE LA BETA-SECRETASE POUR LE TRAITEMENT DE LA MALADIE D'ALZHEIMER

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EP 1 685 142 B1

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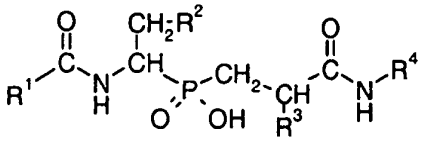
Description

[0001] The invention relates to phosphinic acid derivatives, processes for their preparation, compositions containing said phosphinic acid derivatives and their use in the prevention and treatment of diseases.

[0002] More particularly, the present invention relates to compounds of formula I



(I)

wherein

R^1 is aryl or heteroaryl;
R^2 is (C_1-C_5)-alkyl or phenyl;
R^3 is hydrogen, (C_1-C_5)-alkyl, O-(C_1-C_5)-alkyl or phenyl;
R^4 is (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, phenyl, pyridyl, or indolyl;

and to pharmaceutically acceptable salts thereof.

[0003] The prior art already disclosed some phosphinic peptides, such as in US patent No. 6,630,501 B1; Vassiliou S. et al.: "Phosphinic pseudo-tripeptides as potent inhibitors of matrix metalloproteinases: a structure-activity study" Journal of Medicinal Chemistry, vol. 42, no. 14, 15 July 1999, pages 2610-2620; Yiotakis et al.: "Protection of the hydroxyphosphinyl function of phosphinic dipeptides by Adamantyl. Application to the solid-phase synthesis of phosphinic peptides" Journal of Organic Chemistry, vol. 61, no. 19, 1996, pages 6601-6605; Jiracek J. et al.: "Development of the first potent and selective inhibitor of the zinc endopeptidase neurolysin using a systematic approach based on combinatorial chemistry of phosphinic peptides", Journal of Biological Chemistry, vol. 271, no. 32, 9 August 1996, pages 19606-19611; Vincent Bruno et al.: "Effect of a novel selective and potent phosphinic peptide inhibitor of endopeptidase 3.4.24.16 on neurotensin-induced analgesia and neuronal inactivation" British Journal of Pharmacology, vol. 121, no. 4, 1997, pages 705-710; Yiotakis Athanasios et al.: "Cyclic peptides with a phosphinic bond as potent inhibitors of a zinc bacterial collagenase" Journal of Medicinal Chemistry, vol. 37, no. 17, 1994, pages 2713-2720; and Grobelny D. et al.: "Selective phosphinate transition-state analogue inhibitors of the protease of human immunodeficiency virus" Biochemical and biophysical research communications, vol. 169, no. 3, 1990, pages 1111-1116. All these compounds fall outside the scope of the invention and none of these documents discloses their use for the treatment of Alzheimer's disease.

[0004] Examples for aryl include phenyl which may be unsubstituted or substituted by a substituent selected from OH, halogen, (C_1-C_5)-alkyl, O-(C_1-C_5)-alkyl, pyrrolidonyl and $C(O)NR^5R^6$, wherein R^5 is hydrogen or (C_1-C_5)-alkyl and R^6 is unsubstituted (C_1-C_5)-alkyl or (C_1-C_5)-alkyl substituted by phenyl.

[0005] Examples for heteroaryl include indolyl, quinolinyl, isoquinolinyl and pyridyl. The heteroaryl may be unsubstituted or substituted by (C_1-C_5)-alkyl.

[0006] As used herein, the term "alkyl" denotes a saturated straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Alkyl may be unsubstituted or substituted by a substituent selected from phenyl, COOH, $COOCH_3$ and S-(C_1-C_5)-alkyl.

[0007] The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3 to 7 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

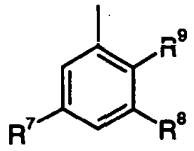
[0008] Examples of halogen include fluorine, chlorine, iodine and bromine.

[0009] The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3 to 7 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0010] Examples of halogen include fluorine, chlorine, iodine and bromine.

[0011] As pharmaceutically acceptable salts there may, e.g., be used the alkali metal or ammonium salts which can be prepared, e.g. by titration of the compounds with inorganic or organic bases, e.g., sodium or potassium hydrogen carbonates, aqueous solutions of sodium or potassium hydroxide or aqueous solutions of ammonia or of amines, e.g. trimethylamine or triethylamine.

[0012] In one embodiment the present invention provides a compound of formula I wherein R^1 is a group of formula (a)



(a)

wherein

R^7 is hydrogen, $(C_1\text{-}C_5)$-alkyl or $O\text{-}(C_1\text{-}C_4)$-alkyl;

R^8 is OH, pyrrolidonyl or $-C(O)NR^5R^6$ wherein R^5 is hydrogen or $(C_1\text{-}C_5)$-alkyl and R^6 is $(C_1\text{-}C_5)$-alkyl or $(C_1\text{-}C_5)$-alkyl substituted by phenyl, and

R^9 is hydrogen or $(C_1\text{-}C_5)$-alkyl.

[0013] In another embodiment the present invention provides a compound of formula I wherein R^1 is a group of formula (a) wherein R^7 is hydrogen or $(C_1\text{-}C_5)$-alkyl; R^8 is $-C(O)NR^5R^6$ wherein R^5 is hydrogen or $(C_1\text{-}C_5)$-alkyl and R^6 is $(C_1\text{-}C_5)$-alkyl or $-CH_2$phenyl; and R^9 is hydrogen.

[0014] In still another embodiment the present invention provides a compound of formula I wherein R^1 is a group of formula (a) wherein R^7 is hydrogen or $(C_1\text{-}C_5)$-alkyl; R^8 is $-C(O)NR^5R^6$ wherein R^5 and R^6 are $(C_1\text{-}C_5)$-alkyl; and R^9 is hydrogen.

[0015] In another embodiment the present invention provides a compound of formula I wherein R^1 is a group of formula (a) wherein R^7 is hydrogen or $O\text{-}(C_1\text{-}C_4)$-alkyl; R^8 is OH or pyrrolidonyl; and R^9 is hydrogen or $(C_1\text{-}C_5)$-alkyl.

[0016] In one embodiment the present invention provides a compound of formula I wherein R^1 is heteroaryl or heteroaryl substituted by $(C_1\text{-}C_5)$-alkyl. In another embodiment the present invention provides a compound of formula I wherein R^1 is indolyl substituted by $(C_1\text{-}C_5)$-alkyl, or quinolinyl. In still another embodiment the present invention provides a compound of formula I wherein R^1 is 1-butyl-indol-6-yl or quinolin-2-yl.

[0017] In one embodiment the present invention provides a compound of formula I wherein R^2 is phenyl which is unsubstituted or substituted with fluorine. In another embodiment the present invention provides a compound of formula I wherein R^2 is $(C_1\text{-}C_5)$-alkyl which is unsubstituted or substituted with $S\text{-}(C_1\text{-}C_5)$-alkyl.

[0018] In one embodiment the present invention provides a compound of formula I wherein R^3 is hydrogen, $(C_1\text{-}C_5)$-alkyl or phenyl. In another embodiment the present invention provides a compound of formula I wherein R^3 is hydrogen, $(C_1\text{-}C_5)$-alkyl which is unsubstituted or substituted by phenyl, COOH or $COOCH_3$; or phenyl. In still another embodiment the present invention provides a compound of formula I wherein R^3 is hydrogen, methyl, ethyl, isopropyl, pnenyl, benzyl, CH_2COOH or CH_2COOCH_3. In still another embodiment the present invention provides a compound of formula I wherein R^3 is methyl.

[0019] In one embodiment the present invention provides a compound of formula I wherein R^4 is unsubstituted $(C_1\text{-}C_6)$-alkyl; $(C_1\text{-}C_6)$-alkyl substituted by one or more substituents selected from halogen, $N[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_3\text{-}C_6)$-rycloalkyl, unsubstituted phenyl, phenyl substituted by one or more $(C_1\text{-}C_5)$-alkyl, and isoxazolyl substituted by one or more $(C_1\text{-}C_5)$-alkyl. In another embodiment the present invention provides a compound of formula I wherein R^4 is unsubstituted $(C_1\text{-}C_6)$-alkyl. In still another embodiment the present invention provides a compound of formula I wherein R^4 is isopropyl, isobutyl, isopentyl or isohexyl. In another embodiment the present invention provides a compound of formula I wherein R^4 is $(C_1\text{-}C_6)$-alkyl substituted by one or more substituents selected from halogen, N[$(C_1\text{-}C_6)$-alkyl]2, $(C_3\text{-}C_6)$-cycloalkyl, unsubstituted phenyl, phenyl substituted by one or more $(C_1\text{-}C_5)$-alkyl, and isoxazolyl substituted by one or more $(C_1\text{-}C_5)$-alkyl. In another embodiment the present invention provides a compound of formula I wherein R^4 is methyl substituted by phenyl or isoxazolyl substituted by methyl; ethyl substituted by cyclohexyl, phenyl or dimethylamino; propyl substituted by phenyl or dimethylphenyl; or butyl substituted by fluorine.

In one embodiment the present invention provides a compound of formula I wherein R^4 is cyclohexyl.

[0020] In one embodiment the present invention provides a compound of formula I wherein R^4 is unsubstituted phenyl or phenyl substituted by OH, $N[(C_1\text{-}C_6)\text{-alkyl}]_2$, unsubstituted $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl substituted by halogen; $O\text{-}(C_1\text{-}C_4)$-alkyl or $COO(C_1\text{-}C_5)$-alkyl.

[0021] In another embodiment the present invention provides a compound of formula I wherein R^4 is phenyl. In another embodiment the present invention provides a compound of formula I wherein R^4 is phenyl substituted by OH, dimethylamino, methyl, isobutyl, trifluoromethyl, methoxy, ethoxy or COOmethyl.

[0022] In one embodiment the present invention provides a compound of formula I wherein R^4 is unsubstituted pyridyl or pyridyl substituted by methyl.

[0023] In one embodiment the present invention provides a compound of formula I wherein

R^1 is a group of formula (a) wherein
R^7 is hydrogen, $(C_1\text{-}C_5)$-alkyl or O-$(C_1\text{-}C_4)$-alkyl;
R^8 is OH, pyrrolidonyl or -C(O)NR^5R^6 wherein R^5 is hydrogen or $(C_1\text{-}C_5)$-alkyl and
R^6 is $(C_1\text{-}C_5)$-alkyl or $(C_1\text{-}C_5)$-alkyl substituted by phenyl, and
R^9 is hydrogen or $(C_1\text{-}C_5)$-alkyl;

R^2 is phenyl which is unsubstituted or substituted with fluorine or is $(C_1\text{-}C_5)$-alkyl which is unsubstituted or substituted with S-$(C_1\text{-}C_5)$-alkyl;

R^3 is hydrogen, $(C_1\text{-}C_5)$-alkyl or phenyl; and

R^4 is unsubstituted $(C_1\text{-}C_6)$-alkyl; $(C_1\text{-}C_6)$-alkyl substituted by one or more substituents selected from halogen, $N[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_3\text{-}C_6)$-rycloalkyl, unsubstituted phenyl, phenyl substituted by one or more $(C_1\text{-}C_5)$-alkyl, and isoxazolyl substituted by one or more $(C_1\text{-}C_5)$-alkyl; cyclohexyl; unsubstituted phenyl or phenyl substituted by OH, $N[(C_1\text{-}C_6)\text{-alkyl}]_2$, unsubstituted $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl substituted by halogen; O-$(C_1\text{-}C_4)$-alkyl or COO $(C_1\text{-}C_5)$-alkyl; unsubstituted pyridyl or pyridyl substituted by methyl.

[0024] In another embodiment the present invention provides a compound of formula I wherein

R^1 is a group of formula (a) wherein
R^7 and R^9 are hydrogen; and
R^8 is -C(O)NR^5R^6 wherein R^5 is hydrogen or $(C_1\text{-}C_5)$-alkyl and R^6 is $(C_1\text{-}C_5)$-alkyl or $(C_1\text{-}C_5)$-alkyl substituted by phenyl;

R^2 is phenyl;

R^3 is hydrogen, $(C_1\text{-}C_5)$-alkyl or phenyl; and

R^4 is unsubstituted $(C_1\text{-}C_6)$-alkyl; $(C_1\text{-}C_6)$-alkyl substituted by one or more substituents selected from halogen, $N[(C_1\text{-}C_6)\text{-alkyl}]_2$, $(C_3\text{-}C_6)$-cycloalkyl, unsubstituted phenyl, phenyl substituted by one or more $(C_1\text{-}C_5)$-alkyl, and isoxazolyl substituted by one or more $(C_1\text{-}C_5)$-alkyl; cyclohexyl; unsubstituted phenyl or phenyl substituted by OH, $N[(C_1\text{-}C_6)\text{-alkyl}]_2$, unsubstituted $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkyl substituted by

halogen; O-$(C_1\text{-}C_4)$-alkyl or COO$(C_1\text{-}C_5)$-alkyl; unsubstituted pyridyl or pyridyl substituted by methyl.

[0025] In one embodiment the present invention provides a compound of formula I wherein

R^1 is indolyl substituted by $(C_1\text{-}C_5)$-alkyl, or quinolinyl;

R^2 is phenyl;

R^3 is $(C_1\text{-}C_5)$-alkyl; and

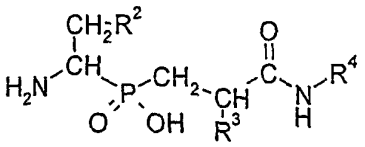
R^4 is phenyl.

[0026] In one embodiment the present invention provides compound of formula I selected from
{(R)-1-[3-(methyl-propyl-carbamoyl)-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinic acid,
{(R)-1-[3-(methyl-pentyl-carbamoyl)-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinic acid,
[(R)-1-(3-dipentylcarbamoyl-benzoylamino)-2-phenyl-ethyl] -(2-phenylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-phenyl-ethyl] -(2-phenylcarbamoyl-propyl)-phosphinic acid,
{(R)-1-[3-(2-oxo-pyrrolidin-1-yl)-5-propoxy-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinic acid,
{(R)-1-[(1-butyl-1H-indole-6-carbonyl)-amino]-2-phenyl-ethyl}-(2-phenylcarbamoylpropyl)-phosphinic acid,
[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]--(2-p-tolylcarbamoyl-butyl)-phosphinic acid,
[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(3-methyl-2-p-tolylcarbamoyl-butyl)-phosphinic acid,
[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl] -(2-phenyl-2-p-tolylcarbamoyl-ethyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S)-2-phenylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-p-tolylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S)-2-p-tolylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((R)-2-p-tolylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl] -(2-isobutylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3-methyl-butylcarbamoyl)-propyl]-phosphinic acid,
[2-(3,3-dimethyl-butylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4,4,4-triffuoro-butylcarbamoyl)-propyl]-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3,3,4,4-tetrafluorobutylcarbamoyl)-propyl] -phosphinic acid,
[(R)- 1-(3- dipropylcarbamoyl- benzoylamino)- 2- phenyl- ethyl]-[2-(2,2,3,3,4,4,4,4- heptafluoro- butylcarbamoyl)-propyl]-phosphinic acid,

(2-cyclohexylcarbamoyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-phosphinic acid,
[2-(2-cyclohexyl-ethylcarbamoyl)-propyl]-{(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl] -phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylarnino)-2-phenyl-ethyl]-[2-(4-hydroxyphenylcarbamoyl)-propyl]-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4-methoxy-phenylcarbamoyl)-propyl] -phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(pyridin-2-ylcarbamoyl)-propyl]-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(5-methyl-pyridin-2-ylcarbamoyl)-propyl]-phosphinic acid and
(2-benzylcarbamoyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenylethyl] -phosphinic acid.

[0027] A further object of the invention are all forms of optically pure enantiomers or diastereomeric mixtures for compounds of formula I.

[0028] In another embodiment the present invention provides a process for the preparation of compounds of formula I comprising reacting a compound of formula II



(II)

wherein

R^2 is (C_1-C_5)-alkyl or phenyl;
R^3 is hydrogen, (C_1-C_5)-alkyl, O-(C_1-C_5)-alkyl or phenyl; and
R^4 is (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, phenyl, pyridyl, or indolyl;

with a compound of formula III

$$R^1\text{-}COR^{10} \qquad \text{(III)}$$

wherein

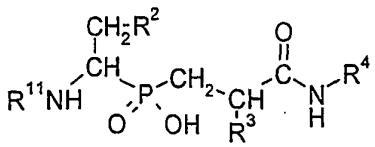
R^1 is aryl or heteroaryl; and
R^{10} is halogen or OH;

and, if desired, converting the resulting compound into a pharmaceutically acceptable salt.

[0029] The reaction may take place in the presence of an activating agent and an additive. Examples for an activating agent include dicyclohexylcarbodiimide and N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride. Examples for an additive include 1-hydroxy-benzotriazole: A base, e.g. a trialkylamine, e.g. triethylamine; maybe present. The reaction may take place in the presence of a solvent, e.g. an ether, e.g. tetrahydrofurane. The temperature may be in the range of from 20°C to 60°C, or of from 20°C to 40°C.

[0030] The compounds of formula III are commercially available or may be prepared according to procedures known to the skilled artisan, e.g. N-methyl-N-propyl-isophthalamic acid, N,N-dipropyl-isophthalamic acid, 5-methyl-N,N-dipropyl-isophthalamic acid, N-pentyl-N-propyl-isophtalamic acid and N,N-dipentyl-isophthalamic acid may be prepared according to a procedure as disclosed in Taylor and Spooner, J. of Agricultural and Food Chemistry, 38:1422-1427 (1990) ; 3-(2-oxo-pyrrolidin-1-yl)-5-propoxy-benzoic acid may be prepared according to the procedure as disclosed in WO 03/045,913; and 1-butyl-indole-6-carboxylic acid may be prepared as disclosed in WO 03/040,096.

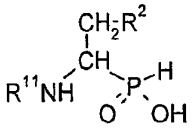
[0031] The compounds of formula II are new and also an embodiment of the present invention. They may be prepared by reacting a compound of formula IV



(IV)

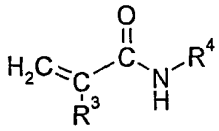
wherein R^{11} is a protecting group, e.g. Boc, and R^2, R^3 and R^4 have the above meanings, with a strong mineral acid, e.g. aqueous HI, HCl or HBr, or with, e.g., trifluoroacetic acid, in a solvent, e.g. CH_2Cl_2, at a temperature in the range of from 20°C to 100°C, or at 20°C.

[0032] The compounds of formula IV are new and also an embodiment of the present invention. They may be prepared by reacting a compound of formula V



(V)

wherein R^{11} and R^2 have the above meanings,
with a compound of formula VI

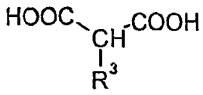


(VI)

wherein R^3 and R^4 have the above meanings.

[0033] Michael addition of the phosphinic acids, i.e. compounds of formula V, to the acrylamides, compounds of formula VI [Liu et al., J. Organomet. Chem. 646:212 (2002)] can be effected in the presence of hexamethyldisilazane at a temperature in the range of from 20°C to 150°C, or at, e.g., 110°C.

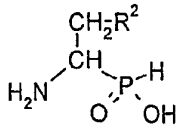
[0034] The compounds of formula VI are known or can be prepared by methods known in the art, e.g. by treatment of the malonic acids, compounds of formula VII



(VII)

with formaldehyde and $HN(Et)_2$ (Liu et al. above) followed by conversion of the acrylic acids to the acrylamides.

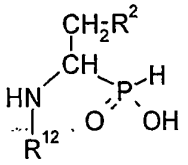
[0035] Compounds of formula V may be prepared by reacting a compound of formula VIII



(VIII)

with a compound of formula R^{11}-O-R^{11}, wherein R^{11} is a protecting group, e.g. Boc, e.g. with $(Boc)_2O$ [Sampson and Bartlett, Biochemistry 30:2255 (1991)] and abase such as an alkylamine, e.g., NEt_3, in a solvent like CH_2Cl_2 or MeOH, at a temperature in the range of from 0°C to 50°C, or, e.g., at 22°C. The compounds of formula V can be resolved using a chiral amine [Sampson and Bartlett, Biochemistry 30:2255 (1991)] such as α-(+)-methylbenzylamine, in a solvent mixture like a ketone and an alcohol, e.g., methylethylketone and MeOH, to give the corresponding salts which can be recrystallized from the same solvent mixture as described above. Desalting affords the enantiomerically pure (>95%) (R)-enantiomers of the compounds of formula V. Novel compounds of formula V, e.g. compounds V-2 and V-5 below, are also an embodiment of the present invention.

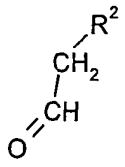
[0036] The compounds of formula VIII can be prepared by reacting a compound of formula IX



(IX)

wherein R^{12} is diphenylmethyl with a strong mineral acid such as HI, HCl or HBr, e.g. aqueous HBr, at a temperature in the range of from 50°C to 100°C, e.g., at 100°C or at 105°C. Novel compounds of formula VIII, e.g. compounds VIII-2 and VIII-4 below, are also an embodiment of the present invention.

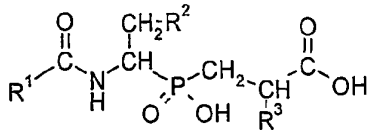
[0037] The compounds of formula IX can be prepared by reacting a compound of formula X



(X)

with a protected amine, e.g. diphenylmethylamine hydrochloride, and phosphinic acid, e.g., 50% aqueous phosphinic acid [Baylis et al., J. Chem. Soc., Perkin Trans. 1:2845 (1984)] in a solvent like water or dioxane, e.g. water, at a temperature in the range of from 50°C to 100°C, e.g., at 100°C. Novel compounds of formula IX, e.g. compounds IX-2 and IX-4 below, are also an embodiment of the present invention.

[0038] In another embodiment the present invention provides a process for the preparation of compounds of formula I comprising reacting a compound of formula XI



(XI)

wherein

R^1 is aryl or heteroaryl;
R^2 is (C_1-C_5)-alkyl or phenyl;
R^3 is hydrogen, (C_1-C_5)-alkyl, O-(C_1-C_5)-akoxy or phenyl;

with a compound of formula XII

$$H_2N\text{-}R^4 \qquad \text{(XII)}$$

wherein

R^4 is (C_1-C_6)-alkyl, (C_3-C_6)-cycloalkyl, phenyl, pyridyl or indolyl,

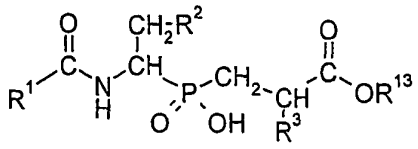
and, if desired, converting the resulting compound into a pharmaceutically acceptable salt.

[0039] The reaction may take place in the presence of an activating agent and an additive. Examples for an activating agent include dicyclohexylcarbodiimide and N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride. Examples for an additive include 1-hydroxy-benzotriazole. Abase, e.g. a trialkylamine, e.g. triethylamine, maybe present. The reaction may take place in the presence of a solvent, e.g. an ether, e.g. tetrahydrofurane. The temperature may be in the range of from 20°C to 60°C, or of from 20°C to 40°C.

[0040] The compounds of formula XII are commercially available or may be prepared according to procedures known

to the skilled artisan, e.g. $H_2N(CH_2)_3CF_3$ may be prepared according to Dijols et al., Biochemistry 41:9286-9292 (2002) ; $H_2N(CH_2)_2CF_2CHF_2$ may be prepared from the corresponding bromide via the phthalimide method according to Jacobs et al., J. Med. Chem. 37:1282 (1994); phenethylamine derivatives may be prepared according to Bailey et al., Can. J. of Chem. 49:3143-51 (1971) and isoxazole derivatives may be prepared according to WO 03/072,535.

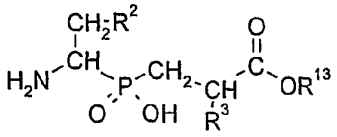
[0041] The compounds of formula XI are new and also an embodiment of the present invention. They may be prepared by hydrolysing a compound of formula XIII



(XIII)

wherein R^{13} is (C_1-C_4)-alkyl, in the presence of a base such as a KOH, NaOH or LiOH, in a solvent like methanol or water, or a mixture of both, at a temperature in the range of from 0°C to 60°C, e.g., at 20°C.

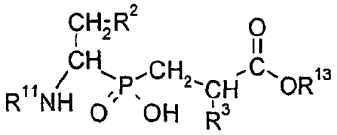
[0042] The compounds of formula XIII are new and also an embodiment of the present invention. They may be prepared by reacting a compound of formula XIV



(XIV)

with a compound of formula III in the presence of an activating agent such as dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride, and an additive such as 1-hydroxy-benzotriazole and a base such as a trialkyl amine, e.g., $N(Et)_3$, in a solvent, such as an ether, e.g., tetrahydrofurane, at a temperature in the range of from 20°C to 60°C, e.g. of from 20°C to 40°C.

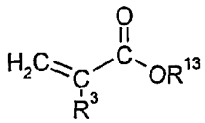
[0043] The compounds of formula XIV are new and also an embodiment of the present invention. They may be prepared by reacting a compound of formula XV



(XV)

wherein R^{11} is a protecting group, e.g. Boc, with a strong mineral acid such as aqueous HI, HCl or HBr, or with, e.g., trifluoroacetic acid, in a solvent like CH_2Cl_2, at a temperature in the range of from 20°C to 100°C, e.g. at 20°C.

[0044] The compounds of formula XV are new and also an embodiment of the present invention. They may be prepared by reacting a compound of formula V with a compound of formula XVI



(XVI)

in the presence of, e.g., hexamethyldisilazane, at a temperature in the range of from 20°C to 150°C, e.g., at 110°C (Michael addition, Liu et al. above).

Examples

[0045] General: Stereo descriptors R and S (according to the CIP-rule) are given in the systematic names. If no descriptors are given mixtures of isomers are obtained. The following abbreviations were used: Boc: t-butyloxycarbonyl; TFA: trifluoroacetic acid

Example S1: Preparation of Starting Compounds of Formula V

(a) Preparation of Compounds of formula IX

[0046] To a suspension of 36.3 g of diphenylmethylamine hydrochloride in 80 ml of water 180 ml of a 50% aqueous solution of H_3PO_2 were added. The mixture was heated to reflux temperature and treated with a solution of 200 mmol of the appropriate compound of formula X in 30 ml of dioxane over 10 min and stirring was continued for 10 min. The suspension was cooled to 65°C, filtered and the solid was washed once with water. The wet solid was stirred with 180 ml of acetone at 0°C for 10 min, the suspension was filtered, the solid was washed once with cold acetone and dried to give the desired compound of formula IX in 50 to 70 % yield.

No.	Compound of formula IX	MS
IX-1	[1-(benzhydryl-amino)-3-methyl-butyl]-phosphinic acid	316.3 $(M-H)^-$
IX-2	[1-(benzhydryl-amino)-3-methylsulfanyl-butyl]-phosphinic acid	348.3 $(M-H)^-$
IX-3	[1-(benzhydryl-amino)-2-phenyl-ethyl]-phosphinic acid	350.3 $(M-H)^-$
IX-4[1)]	[1-(benzhydryl-amino)-2-(3,5-difluoro-phenyl)-ethyl]-phosphinic acid	386.2 $(M-H)^-$

1) The starting aldehyde was prepared as follows: A solution of 5.3 g of 3,5-difluorophenylacetic acid in 40 ml of MeOH and 3 ml of BF_3. Et20 was warmed to 50°C for 1 h. The solution was evaporated, the residue partitioned between Et_2O and aqueous $NaHCO_3$, the organic layer was washed with water, dried and evaporated. The remaining methylester (5.6 g) was dissolved in 240 ml of dry toluene, cooled to -78°C and treated with 45 ml of a 1M solution of diisobutylaluminum hydride in CH_2Cl_2 and stirring was continued at -78°C for 1 h. The mixture was quenched with 30 ml of MeOH and 100 ml of a 50% aqueous solution of sodium-potassium tartrate and extracted with Et_2O. The organic layer was washed with brine, dried and evaporated to give 4.5 g of (3,5-difluorophenyl)-acetaldehyde.

(b) Preparation of compounds of formula VIII

[0047] A suspension of 77.4 mmol of the appropriate compound of formula IX and 210 ml of 48% aqueous HBr was heated to 105°C for 1 h. The mixture was washed several times with Et_2O and the aqueous solution was evaporated to dryness. The resulting solid was dissolved in 465 ml of ethanol. The solution was treated with 29 ml of propylenoxide and the suspension obtained was stirred at 20°C overnight. The suspension was filtered, the solid washed with cold ethanol and dried to give the desired compound of formula VIII in 70 to 95 % yield.

No.	Compound of formula VIII	MS
VIII-1	(1-amino-3-methyl-butyl)-phosphinic acid	150.1 $(M-H)^-$
VIII-2	(1-amino-3-methylsulfanyl-butyl)-phosphinic acid	184.1 $(M+H)^+$
VIII-3	(1-amino-2-phenyl-ethyl)-phosphinic acid	185.9 $(M+H)^+$
VIII-4	[1-amino-2-(3,5-difluoro-phenyl)-ethyl]-phosphinicacid	220.1 $(M-H)^-$

(c) Preparation of compounds of formula V

[0048] To a solution of 2.0 mmol of the appropriate compound of formula VIII in 10 ml of MeOH a solution of 2.2 mmol of $(Boc)_2O$ in 2 ml of MeOH was added at 20°C and stirring was continued for 4 h. The mixture was evaporated and the residue partitioned between AcOEt and aqueous $KHSO_4$ (10%). The organic layer was washed with brine, dried and evaporated to give the crude desired compound of formula V in 80 to 90 % yield. Resolution of the racemate was accomplished by crystallization of 2 mmol of a compound of formula V and 2.2 mmol of α-(+)-methylbenzylamine in 40 ml of methylethylketone followed by recrystallization. The salt obtained was partitioned between aqueous hydrochloric acid and AcOEt to the (R)-enantiomer of a compound of formula V in 30 to 40 % yield and 95 % optical purity.

No.	compound of formula V	MS/α[D]*
V-1	(1-tert-butoxycarbonylamino-3-methyl-butyl)-phosphinic acid	250.1 $(M-H)^-$
V-2	(1-tert-butoxycarbonylamino-3-methylsulfanyl-butyl)- phosphinic acid	282.1 $(M-H)^-$
V-3	(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-phosphinic acid	284.4 (M-H)-
V-4	((R)-1-tert-butoxycarbonylamino-2-phenyl-ethyl)-phosphinic acid	284.1 $(M-H)^-$ α[D] -29.4°
V-5	[1-tert-butoxycarbonylamino-2-(3,5-diffuoro-phenyl)-ethyl]- phosphinic acid	320.4 $(M-H)^-$

*: α[D] (1%, EtOH)

Example S2: Preparation of compounds of formula VI

[0049] A mixture of 28 mmol of the appropriate compound of formula VII and 2.9 ml of diethylamine was treated with 11 ml of formalin and heated to reflux temperature for 1-3 h. The solution was cooled to 20°C diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$. The aqueous layer was acidified to pH = 1 using diluted hydrochloric acid and extracted with CH_2Cl_2. The combined organic layers were dried and evaporated to give the corresponding crude acrylic acid in 70 to 80 % yield. To a solution of 4.3 mmol of the acrylic acid in 7 ml of tetrahydrofurane 560 mg of p-toluidine, 1.8 ml of NEt_3, 950 mg of 1-hydroxybenzotriazole and 1.28 g of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride were subsequently added and the suspension was stirred at 20°C for 1-3 h. The mixture was partitioned between aqueous sat. NH_4Cl and AcOEt, the organic layer was washed with 0.5 N aqueous NaOH, dried and evaporated. The crude material was chromatographed on silica using n-heptane/AcOEt to give the desired compound of formula VI in 50 to 70 % yield.

No.	Compound of formula VI	MS
VI-1	N-phenylmethacrylamide	
VI-2	2-methylene-N-p-tolyl-butyramide	190.3 $(M+H)^+$
VI-3	3-methyl-2-methylene-N-p-tolyl-butyramide	204.1 $(M+H)^+$
VI-4	2-benzyl-N-p-tolyl-acrylamide	252.1 $(M+H)^+$
VI-5	3-phenylcarbamoyl-but-3-enoic acid methyl ester	219.7 $(M)^+$
VI-6	N-(3-ethoxy-phenyl)-acrylamide	
VI-7	N-(3-trifluoromethyl-phenyl)-acrylamide	
VI-8	N-(5-methyl-pyridin-2-yl)-acrylamide	
VI-9	N-(4-tert-butyl-phenyl)-acrylamide	
VI-10	N-(4-dimethylamino-phenyl)-acrylamide	
VI-11	N-(4-hydroxy-phenyl)-acrylamide	
VI-12	4-acryloylamino-benzoic acid methyl ester	
VI-13	N-(3,4-dimethoxy-phenyl)-acrylamide	
VI-14	N-(3,5-dimethoxy-phenyl)-acrylamide	
VI-15	N-(3,4,5-trimethoxy-phenyl)-acrylamide	
VI-16	N-(α-phenylethyl)-acrylamide	
VI-17	N-(2-dimethylamino-ethyl)-acrylamide	

Example S3: Preparation of N,N-dipropyl-isophthalamic acid chloride

[0050] A solution of 1.30 g ofN,N-dipropyl-isophthalamic acid and 1.9 ml of $SOCl_2$ in 5 ml of benzene was heated to reflux temperature until gas evolution ceased (30 min). The solution was evaporated and the residue co-distilled with toluene to give 1.41 g of the N,N-dipropyl-isophthalamic acid chloride.

Example S4: Preparation of a compound of formula XI, i.e. 3-{[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy-phosphinoyl}-2-methyl-propionic acid

(a) Preparation of 3-[((R)-1-tert-butoxycarbonylamino-2-phenyl-ethyl)-hydroxy-phosphinoyl] -2-methyl-propionic acid methyl ester

[0051] A mixture of 5.00 g of ((R)-1-tert-butoxycarbonylamino-2-phenyl-ethyl)-phosphinic acid and 18.3 ml of HN

$(TMS)_2$ was heated to 110°C for 1 h. To the solution was added 2.5 ml of methyl methacrylate and heating was continued at 110°C for 2 h. The solution was cooled to 70° slowly diluted with 10 ml of EtOH and evaporated. The residue was chromatographed on silica using a gradient of CH_2Cl_2/MeOH (9:1) → CH_2Cl_2/MeOH/AcOH (10:1:0.3) to give 4.10 g of the title compound. MS: 386.5 (M+

(b) Preparation of 3-[((R)-1-amino-2-phenyl-ethyl)-hydroxy-phosphinoyl]-2-methyl-propionic acid methyl ester; salt with trifluoro-acetic acid

[0052] A solution of 1.75 g of 3-[((R)-1-tert-butoxycarbonylamino-2-phenyl-ethyl)-hydroxyphosphinoyl]-2-methyl-propionic acid methyl ester and 3.40 ml of CF_3COOH in 20 ml of CH_2Cl_2 was stirred at 20°C for 16 h and evaporated to give 2.23 g of the crude title compound.

(c) Preparation of 3-{[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy-phosphinoyl}-2-methyl-propionic acid methyl ester

[0053] To a solution of 2.23 g of the crude amine as TFA salt (a compound of formula XIV) in 15 ml of dioxane, 1.9 ml of NEt_3 and a solution of 1.47 g of N,N-dipropyl-isophthalamic acid chloride in 2 ml of dioxane were subsequently added at 0°C and stirring was continued at 20°C for 3 h. The mixture was partitioned between AcOEt and brine and the pH adjusted to 2 using hydrochloric acid. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed on silica using a gradient of CH_2Cl_2 → CH_2Cl_2/MeOH/AcOH (10:1:0.5) to give 2.15 g of the title compound. MS: 515.3 (M-H)-.

(d) Preparation of 3-{[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy-phosphinoyl}-2-methyl-propionic acid

[0054] A solution of 2.11 g of 3-{[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy-phosphinoyl}-2-methyl-propionic acid methyl ester in 8 ml of MeOH was treated with a solution of 865 mg of $LiOH \cdot H_2O$ in 2 ml of H_2O and the turbid solution was stirred at 20°C for 1.5 h. The mixture was evaporated and the residue partitioned between aqueous HCl (pH = 2) and AcOEt. The organic layer was washed with brine, dried and evaporated to give 1.54 g of the title compound. MS: 501.4 $(M-H)^-$.

Example 1: Preparation of compounds of formula I starting from a compound of formula II and a compound of formula III

[0055]

(a) A mixture of 0.4 mmol of the appropriate compound of formula V and 0.6 ml of $HN(TMS)_2$ was heated to 110°C for 1 h. To the solution 0.6 mmol of the appropriate compound of formula VI was added and heating was continued at 110°C for 1-4 h. The solution was cooled to 20°, diluted with 1 ml of EtOH and evaporated. The residue was chromatographed on silica using a gradient of CH_2Cl_2/MeOH (9:1) → CH_2Cl_2/MeOH/-AcOH (10:1:0.5) to give the desired compound of formula IV in 30 to 70 % yield.

No.	compound of formula IV	MS
IV-1	(1-tert-butoxycarbonylamino-3-methyl-butyl)-(2-phenylcarb-amoyl-propyl)-phosphinic acid	411.5 (M-H)-
IV-2	(1-tert-butoxycarbonylamino-3-methylsulfanyl-butyl)-(2- phenylcarbamoyl-propyl)-phosphinic acid	443.4 $(M-H)^-$
IV-3	(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-(2-p-tolylcarb- amoyl-propyl)-phosphinic acid	459.1 $(M-H)^-$
IV-4	((R)-1-tert-butoxycarbonylamino-2-phenyl-ethyl)-(2-p-tolyl- carbamoyl-propyl)-phosphinic acid	459.1 $(M-H)^-$
IV-5	(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-(2-p-tolylcarb- amoyl-butyl)-phosphinic acid	475.3 $(M+H)^+$
IV-6	(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-(3-methyl-2-p- tolylcarbamoyl-butyl)-phosphinic acid	489.1 $(M+H)^+$
IV-7[1)]	(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-(2-phenyl-2-p- tolylcarbamoyl-ethyl)-phosphinic acid	522.3 $(M)^+$

(continued)

No.	compound of formula IV	MS
IV-8	(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-(3-phenyl-2-p- tolylcarbamoyl-propyl)-phosphinic acid	537.4 $(M+H)^+$
IV-9	3-[(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-hydroxy- phosphinoylmethyl]-N-phenyl-succinamic acid methyl ester	505.3 $(M+H)^+$
IV-10	[1-tert-butoxycarbonylamino-2-(3,5-difluoro-phenyl)-ethyl]- (2-phenylcarbamoyl-propyl)-phosphinic acid	481.8 $(M-H)^-$

1) Compound IV-7 was prepared by an inverse sequence of reactions, i.e., the corresponding compound of formula V was reacted with 2-phenylacrylic acid to give 3-[(1-tert-butoxycarbonylamino-2-phenyl-ethyl)-hydroxy-phosphinoyl]-2-phenylpropionic acid (MS: 432.4 $(M-H)^-$), which was reacted with p-toluidine to give (1-tert-butoxycarbonylamino-2-phenyl-ethyl)-(2-phenyl-2-p-tolylcarbamoyl-ethyl)-phosphinic acid.

(b) A solution of 0.20 mmol of the appropriate compound of formula IV and 0.23 ml of CF_3COOH in 2.0 ml of CH_2Cl_2 was stirred at 20°C for 1.5 h and evaporated. The resulting crude compound of formula II (as TFA salt) was dissolved in 1 ml of tetrahydrofurane and subsequently treated with 0.22 mmol of the appropriate compound of formula III, 0.70 mmol of NEt_3, 0.24 mmol of 1-hydroxybenzotriazole and 0.26 mmol of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride and the suspension was stirred at 20°C for 1.5 h. The mixture was partitioned between aqueous sat. NH_4Cl and AcOEt, the organic layer was washed with brine, dried and evaporated. The crude material was purified by HPLC (RP-18 column) using a gradient of $CH_3CN:H_2O$ (20:80) → $CH_3CN:H_2O$ (95:5) to give the desired compound of formula I in 30 to 40 % yield.

[0056] The following compounds were prepared according to the above Example:

No.	compound of formula I	MS
I-1	{(R)-1-[3-(methyl-propyl-carbamoyl)-benzoylamino]-2-phenyl-ethyl}- (2-phenylcarbamoyl-propyl)-phosphinic acid	550.3 $(M+H)^+$
I-2	{(R)-1-[3-(methyl-pentyl-carbamoyl)-benzoylamino]-2-phenyl-ethyl}- (2-phenylcarbamoyl-propyl)-phosphinic acid	578.3 $(M+H)^+$
I-3	[(R)-1-(3-dipentylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phen- ylcarbamoyl-propyl)-phosphinic acid	634.3 $(M+H)^+$
I-4	[(R)-1-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-phenyl-ethyl]- (2-phenylcarbamoyl-propyl)-phosphinic acid	592.0 $(M+H)^+$
I-5	{(R)-1-[3-(2-oxo-pyrrolidin-1-yl)-5-propoxy-benzoylamino]-2-phenyl- ethyl}-(2-phenylcarbamoyl-propyl)-phosphinic acid	592.0 $(M+H)^+$
I-6	{(R)-1-[(1-butyl-1H-indole-6-carbonyl)-amino]-2-phenyl-ethyl}-(2- phenylcarbamoyl-propyl)-phosphinic acid	546.2 $(M+H)^+$
I-7	(2-phenylcarbamoyl-propyl)-{(R)-2-phenyl-1-[(quinoline-2-carbonyl)-amino]-ethyl}-phosphinic acid	502.0 $(M+H)^+$
I-8	[(R)-1-(3-hydroxy-2-methyl-benzoylamino)-2-phenyl-ethyl]-(2-phen- ylcarbamoyl-propyl)-phosphinic acid	481.0 $(M+H)^+$
I-9	[1-(3-dipropylcarbamoyl-benzoylamino)-3-methyl-butyl]-(2-phenyl- carbamoyl-propyl)-phosphinic acid	542.5 $(M-H)^-$
I-10	[1-(3-dipropylcarbamoyl-benzoylamino)-3-methylsulfanyl-butyl]-(2-phenylcarbamoyl-propyl)-phosphinic acid	574.8 $(M-H)^-$
I-11	[2-(3,5-difluoro-phenyl)-1-(3-dipropylcarbamoyl-benzoylamino)- ethyl]-(2-phenylcarbamoyl-propyl)-phosphinic acid	612.5 $(M-H)^-$
I-12	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-p-tolyl- carbamoyl-ethyl)-phosphinic acid	578.4 $(M+H)^+$
I-13	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-p-tolyl- carbamoyl-butyl)-phosphinic acid	606.1 $(M+H)^+$
I-14	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(3-methyl-2- p-tolylcarbamoyl-butyl)-phosphinic acid	620.2 $(M+H)^+$
I-15	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenyl-2- -tolylcarbamoyl-ethyl)-phosphinic acid	652.5 $(M-H)^-$

(continued)

No.	compound of formula I	MS
I-16	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(3-phenyl-2- p-tolylcarbamoyl-propyl)-phosphinic acid	668.2 $(M+H)^+$
I-17	3-{[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy- phosphinoylmethyl}-N-phenyl-succinamic acid methyl ester	636.1 $(M+H)^+$

Example 2: Preparation of compounds of formula I starting from a compound of formula XI and a compound of formula XII

[0057] The crude 3-{[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy-phosphinoyl}-2-methyl-propionic acid (0.10 mmol) was dissolved in 0.7 ml of tetrahydrofurane and subsequently treated with 0.16 mmol of the appropriate compound of formula XII, 0.40 mmol of NEt_3, 0.16 mmol of 1-hydroxybenzotriazole and 0.26 mmol of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride and the suspension was stirred at 45°C for 3 h. The mixture was partitioned between aqueous sat. NH_4Cl and AcOEt, the organic layer was washed with brine, dried and evaporated. The crude material was purified by HPLC (RP-18 column) using a gradient of CH_3CN:H_2O (20:80) → CH_3CN:H_2O (95:5) to give the desired compound of formula I in 10-60% yield as a mixture of isomers. Separation of the isomeric mixture was accomplished by thick layer chromatography on silica using CH_2Cl_2/MeOH/AcOH 9:1:0.25. The lower running spot represents the 1(R),2(S)-stereo isomer.

[0058] The following compounds were prepared according to the above Example:

No.	compound of formula I	MS
I-18	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenylcarbamoyl-propyl)-phosphinic acid	576.6 $(M-H)^-$
I-19	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S)-2- phenylcarbamoyl-propyl)-phosphinic acid	576.6 (M-H)-
I-20	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-p- tolylcarbamoyl-propyl)-phosphinic acid	592.2 (M-H)-
I-21	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S)-2-p- tolylcarbamoyl-propyl)-phosphinic acid	590.8 $(M-H)^-$
I-22	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((R)-2-p- tolylcarbamoyl-propyl)-phosphinic acid	590.5 $(M-H)^-$
I-23	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3-ethoxy-phenylcarbamoyl)-ethyl]-phosphinic acid	608.2 $(M+H)^+$
I-24	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3-tri- fluoromethyl-phenylcarbamoyl)-ethyl]-phosphinic acid	632.3 $(M+H)^+$
I-25	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(5-methyl- pyridin-2-ylcarbamoyl)-ethyl]-phosphinic acid	579.2 $(M+H)^+$
I-26	[2-(4-tert-butyl-phenylcarbamoyl)-ethyl]-[1-(3-dipropylcarbamoyl- benzoylamino)-2-phenyl-ethyl]-phosphinic acid	618.6 $(M-H)^-$
I-27	[2-(4-dimethylamino-phenylcarbamoyl)-ethyl]-[1-(3-dipropylcarb- amoyl-benzoylamino)-2-phenyl-ethyl]-phosphinic acid	607.2 $(M+H)^+$
I-28	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4- hydroxy-phenylcarbamoyl)-ethyl]-phosphinic acid	580.2 $(M+H)^+$
I-29	4-(3-{[1-(3-dipropylcarbanioyl-benzoylamino)-2-phenyl-ethyl]- hydroxy-phosphinoyl}-propionylamino)-benzoic acid methyl ester	622.3 $(M+H)^+$
I-30	[2-(3,4-dimethoxy-phenylcarbamoyl)-ethyl]-[1-(3-dipropylcarbamoyl- benzoylamino)-2-phenyl-ethyl]-phosphinic acid	624.2 $(M+H)^+$
I-31	[2-(3,5-dimethoxy-phenylcarbamoyl)-ethyl]-[1-(3-dipropylcarbamoyl- benzoylamino)-2-phenyl-ethyl]-phosphinic acid	622.8 $(M-H)^-$
I-32	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3,4,5-tri- methoxy-phenylcarbamoyl)-ethyl]-phosphinic acid	654.2 $(M+H)^+$
I-33	[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(1(S)- phenyl-ethylcarbamoyl)-ethyl]-phosphinic acid	590.4 $(M-H)^-$

(continued)

No.	compound of formula I	MS
I-34	[2-(2-dimethylamino-ethylcarbamoyl)-ethyl]-[1-(3-dipropylcarbamoyl- benzoylamino) -2-phenyl-ethyl] -phosphinic acid	559.2 $(M+H)^+$
I-35	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-iso- propylcarbamoyl-propyl)-phosphinic acid	542.5 $(M-H)^-$
I-36	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-iso-butylcarbamoyl-propyl)-phosphinic acid	556.5 $(M-H)^-$
I-37	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3- methyl-butylcarbamoyl)-propyl]-phosphinic acid	570.5 $(M-H)^-$
I-38	[2-(3,3-dimethyl-butylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarb- amoyl-benzoylamino)-2-phenyl-ethyl]-phosphinic acid	584.5 $(M-H)^-$
I-39	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4,4,4- trifluoro-butylcarbamoyl)-propyl]-phosphinic acid	610.4 $(M-H)^-$
I-40	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2- (3,3,4,4-tetrafluoro-butylcarbamoyl)-propyl]-phosphinic acid	628.5 $(M-H)^-$
I-41	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2- (2,2,3,3,4,4,4-heptafluoro-butylcarbamoyl)-propyl]-phosphinic acid	682.2 $(M-H)^-$
I-42	(2-cyclohexylcarbamoyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzo- ylamino)-2-phenyl-ethyl]-phosphinic acid	582.5 $(M-H)^-$
I-43	[2-(2-cyclohexyl-ethylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarb- amoyl-benzoylamino)-2-phenyl-ethyl]-phosphinic acid	610.4 (M-H)-
I-44	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4- hydroxy-phenylcarbamoyl)-propyl]-phosphinic acid	592.5 $(M-H)^-$
I-45	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4- methoxy-phenylcarbamoyl) -propyl] -phosphinic acid	606.5 $(M-H)^-$
1-46	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(pyridin-2-ylcarbamoyl)-propyl]-phosphinic acid	577.6 $(M-H)^-$
I-47	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(5- methyl-pyridin-2-ylcarbamoyl)-propyl]-phosphinic acid	591.5 $(M-H)^-$
I-48	(2-benzylcarbamoyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzoyl- amino)-2-phenyl-ethyl]-phosphinic acid	590.5 $(M-H)^-$
I-49	{2-[(3,5-dimethyl-isoxazol-4-ylmethyl)-carbamoyl]-propyl}-[(R)-1-(3- dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-phosphinic acid	609.5 $(M-H)^-$
I-50	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phen- ethylcarbamoyl-propyl)-phosphinic acid	604.7 $(M-H)^-$
I-51	[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(1- methyl-2-phenyl-ethylcarbamoyl)-propyl]-phosphinic acid	618.6 $(M-H)^-$
1-52	{2-[2-(2,4-dimethyl-phenyl)-1-methyl-ethylcarbamoyl]-propyl}-[(R)-1- (3-dipropylcarbamoyl-benzoylamino) -2-phenyl-ethyl] -phosphinic acid	646.5 $(M-H)^-$

[0059] Byway of example NMR data [1H-NMR (300 MHz, internal standard TMS, *J* values in Hz, CD_3OD)] are given for two compounds, i.e. compounds I-18 and I-37: Compound I-18: 7.77 (m, 1H), 7.67-7.47 (m, 5H), 7.40-7.07 (m, 8H), 4.80 (m, 1H), 3.60-2.95 (m, 7H), 2.55-2.27 (m, 1H), 2.05-1.80 (m, 1H), 1.80-1.45 (m, 4H), 1.42 and 1.39 (d each, J = 6 each, ratio 3:2, 3H together), 1.04 (m, 3H), 0.70 (m, 3H). Compound I-37:7.74 (m, 1H), 7.60 (s, 1H), 7.50 (m, 2H), 7.30-7.10 (m, 5H), 4.72 (m, 1H), 3.50-2.75 (m, 9H), 2.35-2.10 (m 1H),1.90-1.30 (m 8H), 1.26 and 1.24 (d each, J = 6 each, ratio 3:2, 3H together), 1.00 (m, 3H), 0.91 and 0.89 (d each, J = 6 each, ratio 2:3, 6H together), 0.70 (m, 3H).

Example 3: Preparation of a compound of formula I starting from another compound of formula I

[0060] A solution of 14 mg of 3-{[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy-phosphinoylmethyl}-N-phenyl-succinamic acid methyl ester (compound I-17) in 1 ml of MeOH and 3 mg of NaOH was warmed to 45° for 3 h. The solution was evaporated, the residue partitioned between 1N aqueous hydrochloric acid and CH_2Cl_2, the organic layer was washed with water, dried and evaporated to give 11 mg of 3-{[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-hydroxy-phosphinoylmethyl}-N-phenyl-succinamic acid (compound I-53).

No.	compound of formula I	MS
1-53	3-{[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]- hydroxy-phosphinoylmethyl}-N-phenyl-succinamic acid	620.3 $(M-H)^-$

[0061] The compounds of the invention and pharmaceutically suitable salts thereof (hereinafter: Pharmaceutical Compounds) have pharmacological activity and are useful as pharmaceuticals. In particular, Pharmaceutical Compounds exhibit β-secretase inhibitory activity.

[0062] Cellular screening methods for inhibitors of A-beta production, testing methods for the *in vivo* suppression of A-beta production, and assays with membranes or cellular extracts for the detection of secretase activity are known in the art and have been disclosed in numerous publications, including WO 98/22493, US 5,703,129, US 5,593,846 and GB 2,395,124. Beta-secretase has been descibed in several publications including EP 855,444, WO 00/17,369, WO 00/58,479, WO 00/47,618, WO 01/00,663 and WO 01/00,665.

[0063] For example, inhibition of β-secretase of the Pharmaceutical Compounds may be demonstrated by their ability, e.g., to inhibit the cleavage of a fluorescent peptide substrate (e.g. in an assay like e.g. the FRET Assay as described *inter alia* by Grueninger-Leitch et al.) or to displace, e.g., a peptidic β-secretase inhibitor at the active binding site of β-secretase, e.g. as demonstrated in accordance with the following test method.

Competitive Radioligand Binding Assay (RLBA)

[0064] 96 well microplates (Optiplate Packard) are coated with purified BACE protein (see e.g. GB 2,385,124: Examples 1 and 2) using a concentration of 1 μg/ml in 30 mM sodium citrate buffer adjusted to pH 5.5. The coating is achieved by incubation of 100 μl/well for 1-3 days at 4°C. The plate is then washed with 2 x 300 μl/well of 10 mM citrate pH 4.1. To each well 100 μl binding buffer (30 mM citrate, 100 mM NaCl, 0.1% BSA, pH 4.1) is dispensed. The test compound is added in 5 μl from a DMSO stock solution or appropriate dilutions. To this the tracer (tritiated Compound A, see e.g. GB 2,385,124: Example 4) is added in 10 μl/well from a 10 μCi/ml stock solution in binding buffer. After incubation for 1.5-2 hours in a humid chamber at ambient temperature the plate is washed with 2 x 300μl/well water and flipped on a dry towel. Following the addition of 50μl/well Micro-Scint20 (Packard) the plate is sealed and vibrated for 5 seconds. The bound radioactivity is counted on a Topcount (Packard). Total binding is typically between 2000 and 10000 cpm/well depending mainly on the purity and concentration of the BACE protein. Nonspecific binding as assessed by competition with >1 μM peptidic inhibitor (Bachem # H-4848) is typically between 30 and 300 cpm/well. The IC-50 values are calculated by Microsoft Excel FIT.

[0065] The preferred compounds show an IC_{50}<1.0 μM. In the list below some examplary data for the β-secretase inhibition are given:

Example No.	IC_{50} in vitro [μM]	Example No.	IC_{50} in vitro [μM]
I-5	0.05	I-37	0.04
I-14	0.20	I-42	0.02
I-18	0.01		

[0066] Pharmaceutical Compounds are accordingly useful as β-secretase inhibitors, e.g. in the treatment of diseases and conditions in which β-secretase activity plays a role or is implicated. Such conditions include in particular Alzheimer's disease and Cerebral Amyloid Angiopathy.

[0067] Beta-secretase inhibitors can be further optimized for their ability to inhibit the secretion of A-beta in cell culture systems which are well known in the art. For example, the production of A-beta can be measured by immunoassay in cell culture supernatant of HEK293 cells which overexpress by transfection the amyloid precursor protein (APP). The A-beta production can also be measured in supernatant human neuroblastoma cell lines which express the endogenous APP. In addition, beta-secretase inhibitors can be optimized for efficacy in transgenic mouse models of Alzheimer's disease which generate A-beta containing Alzheimer-like plaques in the CNS of the affected mice. Finally, beta-secretase inhibitors are expected to reduce the A-beta concentration in the brain and in cerebrospinal fluid of patients suffering from Alzheimer's disease and also in healthy individuals which have not yet developed A-beta plaques.

[0068] Biochemical and immunological studies revealed that the dominant proteinaceous component of the amyloid plaque occurring in the cerebral cortex of individuals effected by Alzheimer's disease (AD) is an approximately 4.2 kilodalton (kD) protein of about 39 to 43 amino acids. This protein was designated A-beta-amyloid peptide, and sometimes beta/A4; referred to herein as A-beta. In addition to deposition of A-beta in amyloid plaques, A-beta is also found in the

walls of meningeal and parenchymal arterioles, small arteries, capillaries, and sometimes, venules. Since there are strong indications that A-beta depositions are causally related to AD, it would be desirable to inhibit the formation of A-beta *in vivo* thus preventing and reducing neurological degeneration, by controlling the formation of amyloid plaques, reducing neurotoxicity and, generally, mediating the pathology associated with A-beta production -

[0069] A-beta appears to be an internal polypeptide derived from a type 1 integral membrane protein, termed beta amyloid precursor protein (APP). APP is normally produced by many cells both *in vivo* and in cultured cells, derived from various animals and humans. A-beta is derived from cleavage of APP by an enzyme (protease) system(s), collectively termed secretases, including beta-secretase(s), generating the N-terminus of A-beta.

[0070] In another embodiment, the present invention provides the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to the β-secretase inhibition. In still another embodiment the present invention provides the use of compounds of formula I and their pharmaceutically acceptable salts in the manufacture of medicaments for the prevention or treatment of Alzheimer's disease.

[0071] Pharmaceutical Compounds can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

[0072] Pharmaceutical Compounds can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, e.g., as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, e.g., vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, e.g., water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, e.g., natural or hardened oils, waxes, fats, semiliquid or liquid polyols and the like.

[0073] The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

[0074] Medicaments containing Pharmaceutical Compound and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more Pharmaceutical Compound and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

[0075] The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a Pharmaceutical Compound. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

[0076]

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Mix items 1, 2, 3 and 4 and granulate with purified water. Dry the granules at 50°C. Pass the granules through suitable milling equipment. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

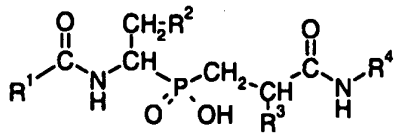
[0077]

Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

[0078] Mix items 1, 2 and 3 in a suitable mixer for 30 minutes. Add items 4 and 5 and mix for 3 minutes. Fill into a suitable capsule.

Claims

1. A compound of formula I



(I)

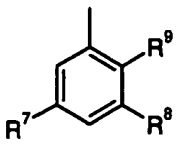
wherein

R^1 is aryl or heteroaryl;
R^2 is $(C_1\text{-}C_5)$-alkyl or phenyl;
R^3 is hydrogen, $(C_1\text{-}C_5)$-alkyl, O-$(C_1\text{-}C_5)$-alkyl or phenyl;
R^4 is $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, phenyl, pyridyl, or indolyl;

"aryl" is phenyl which is unsubstituted or substituted by a substituent selected from OH, halogen, $(C_1\text{-}C_5)$-alkyl, O-$(C_1\text{-}C_5)$-alkyl, pyrrolidonyl and $C(O)NR^5R^6$, wherein R^5 is hydrogen or $(C_1\text{-}C_5)$-alkyl and R^6 is unsubstituted $(C_1\text{-}C_5)$-alkyl or $(C_1\text{-}C_5)$-alkyl substituted by phenyl;
"heteroaryl" is unsubstituted or substituted by $(C_1\text{-}C_5)$-alkyl;
"$(C_1\text{-}C_5)$-alkyl" or $(C_1\text{-}C_6)$-alkyl is unsubstituted or substituted by a substituent selected from phenyl, COOH, $COOCH_3$ and S-$(C_1\text{-}C_5)$-alkyl;
and pharmaceutically acceptable salts thereof.

2. The compound of formula I according to claim 1 wherein

R^1 is a group of formula (a)



(a)

wherein

R^7 is hydrogen, $(C_1\text{-}C_5)$-alkyl or O-$(C_1\text{-}C_4)$-alkyl;

R^8 is OH, pyrrolidonyl or $-C(O)NR^5R^6$ wherein R^5 is hydrogen or (C_1-C_5)-alkyl and R^6 is (C_1-C_5)-alkyl or (C_1-C_5)-alkyl substituted by phenyl, and
R^9 is hydrogen or (C_1-C_5)-alkyl; or
R^1 is indolyl substituted by (C_1-C_5)-alkyl, or quinolinyl.

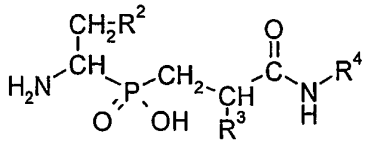
3. The compound of formula I according to claim 1 wherein R^2 is phenyl which is unsubstituted or substituted with fluorine.

4. The compound of formula I according to claim 1 wherein R^3 is hydrogen, (C_1-C_5)-alkyl or phenyl.

5. The compound of formula I according to claim 1 wherein R^4 is unsubstituted (C_1-C_6)-alkyl; (C_1-C_6)-alkyl substituted by one or more substituents selected from halogen, $N[(C_1-C_6)\text{-alkyl}]_2$, (C_3-C_6)-cycloalkyl, unsubstituted phenyl, phenyl substituted by one or more (C_1-C_5)-alkyl, and isoxazolyl substituted by one or more (C_1-C_5)-alkyl; or cyclohexyl; or unsubstituted phenyl or phenyl substituted by OH, $N[(C_1-C_6)\text{-alkyl}]_2$, unsubstituted (C_1-C_6)-alkyl, (C_1-C_6)-akyl substituted by halogen; $O\text{-}(C_1-C_4)$-alkyl or $COO(C_1-C_5)$-alkyl; or unsubstituted pyridyl or pyridyl substituted by methyl.

6. The compound of formula I according to claim 1 selected from
{(R)-1-[3-(methyl-propyl-carbamoyl)-benzoylamino] -2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinic acid,
{(R)-1-[3-(methyl-pentyl-carbamoyl)-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinic acid,
[(R)-1-(3-dipentylcarbamoyl-benzoylamino)-2-phenyl-ethyl] -(2-phenylcarbamoyl-propyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-5-methyl-benzoylamino)-2-phenyl-ethyl]-(2-phenylcarbamoyl-propyl)-phosphinic acid,
{(R)-1-[3-(2-oxo-pyrrolidin-1-yl)-5-propoxy-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinic acid,
{(R)-1-[(1-butyl-1H-indole-6-carbonyl)-amino]-2-phenyl-ethyl}-(2-phenylcarbamoylpropyl)-phosphinic acid,
[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-p-tolylcarbamoyl-butyl)-phosphinic acid,
[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(3-methyl-2-p-tolylcarbamoyl-butyl)-phosphinic acid,
[1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenyl-2-p-tolylcarbamoyl-ethyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S)-2-phenylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-p-tolylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S) -2-p-tolylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((R)-2-p-tolylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-isobutylcarbamoylpropyl)-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3-methyl-butylcarbamoyl)-propyl]-phosphinic acid,
[2-(3,3-dimethyl-butylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl] -phosphinic acid,
[(R)- 1- (3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl] - [2-(4,4,4-trifluoro-butylcarbamoyl)-propyl] -phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3,3,4,4-tetrafluorobutylcarbamoyl)-propyl]-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl] - [2-(2,2,3,3,4,4,4-heptafluoro-butylcarbamoyl)-propyl]-phosphinic acid,
(2-cyclohexylcarbamoyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl] -phosphinic acid,
[2-(2-cyclohexyl-ethylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phenyl-ethyl] -phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]- [2-(4-hydroxyphenylcarbamoyl)-propyl] -phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4-methoxy-phenylcarbamoyl)-propyl]-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(pyridin-2-ylcarbamoyl)-propyl]-phosphinic acid,
[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(5-methyl-pyridin-2-ylcarbamoyl)-propyl]-phosphinic acid and
(2-benzylcarbamoyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenylethyl]-phosphinic acid.

7. A process for the preparation of a compound of formula I according to claim 1 comprising reacting a compound of formula II



(II)

wherein

R^2 is $(C_1\text{-}C_5)$-alkyl or phenyl;
R^3 is hydrogen, $(C_1\text{-}C_5)$-alkyl, O-$(C_1\text{-}C_5)$-alkyl or phenyl; and
R^4 is $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, phenyl, pyridyl, or indolyl;

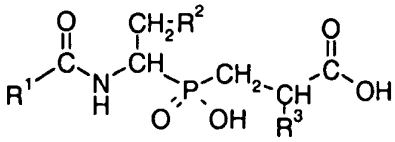
with a compound of formula III

$$R^1\text{-}COR^{10} \qquad \text{(III)}$$

wherein

R^1 is aryl or heteroaryl; and
R^{10} is halogen or OH;

and, if desired, converting the resulting compound into a pharmaceutically acceptable salt; or comprising reacting a compound of formula XI



(XI)

wherein

R^1 is aryl or heteroaryl;
R^2 is $(C_1\text{-}C_5)$-alkyl or phenyl;
R^3 is hydrogen, $(C_1\text{-}C_5)$-alkyl, O-$(C_1\text{-}C_5)$-alkoxy or phenyl;

with a compound of formula XII

$$H_2N\text{-}R^4 \qquad \text{(XII)}$$

wherein

R^4 is $(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, phenyl, pyridyl or indolyl,

and, if desired, converting the resulting compound into a pharmaceutically acceptable salt.

8. A compound of formula I or a pharmaceutically acceptable salt thereof according to claim 1, whenever prepared by a process according to claim 7.

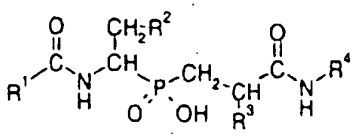
9. Use of a compound of formula I or a pharmaceutically acceptable salt thereof according to claim 1 for the manufacture of a medicament for the treatment of a disease related to the inhibition of β-secretase.

10. A pharmaceutical composition containing a compound of formula I or a pharmaceutically acceptable salt thereof according to claim 1 and pharmaceutically acceptable excipients.

11. A pharmaceutical composition according to claim 10 for the treatment of Alzheimer's disease.

Patentansprüche

1. Verbindung der Formel I



(I)

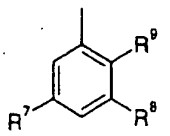
worin

R^1 Aryl oder Heteroaryl ist;
R^2 (C_1-C_5)-Alkyl oder Phenyl ist;
R^3 Wasserstoff, (C_1-C_5)-Alkyl, O-(C_1-C_5)-Alkyl oder Phenyl ist;
R^4 (C_1-C_6)-Alkyl, (C_3-C_6)-Cycloalkyl, Phenyl, Pyridyl oder Indolyl ist;

"Aryl" Phenyl ist, das unsubstituiert oder durch einen Substituenten, ausgewählt aus OH, Halogen, (C_1-C_5)-Alkyl, O-(C_1-C_5)-Alkyl, Pyrrolidonyl und C(O)NR^5R^6, substituiert ist, worin R^5 Wasserstoff oder (C_1-C_5)-Alkyl ist und R^6 unsubstituiertes (C_1-C_5)-Alkyl oder durch Phenyl substituiertes (C_1-C_5)-Alkyl ist;
"Heteroaryl" unsubstituiert oder durch (C_1-C_5)-Alkyl substituiert ist;
"(C_1-C_5)-Alkyl" oder (C_1-C_6)-Alkyl unsubstituiert oder durch einen Substituenten, ausgewählt aus Phenyl, COOH, $COOCH_3$ und S-(C_1-C_5)-Alkyl, substituiert ist;
und pharmazeutisch akzeptable Salze davon.

2. Verbindung der Formel I nach Anspruch 1, worin

R^1 eine Gruppe der Formel (a)



(a)

ist, worin
R^7 Wasserstoff, (C_1-C_5)-Alkyl oder O-(C_1-C_4)-Alkyl ist;
R^8 OH, Pyrrolidonyl oder -C(O)NR^5R^6 ist, worin R^5 Wasserstoff oder (C_1-C_5)-Alkyl ist und R^6 (C_1-C_5)-Alkyl oder durch Phenyl substituiertes (C_1-C_5)-Alkyl ist, und
R^9 Wasserstoff oder (C_1-C_5)-Alkyl ist oder
R^1 Indolyl, substituiert durch (C_1-C_5)-Alkyl oder Chinolinyl, ist.

3. Verbindung der Formel I nach Anspruch 1, worin R^2 Phenyl ist, das unsubstituiert oder mit Fluor substituiert ist.

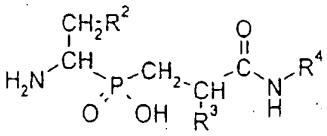
4. Verbindung der Formel I nach Anspruch 1, worin R^3 Wasserstoff, (C_1-C_5)-Alkyl oder Phenyl ist.

5. Verbindung der Formel I nach Anspruch 1, worin R^4 unsubstituiertes (C_1-C_6)-Alkyl; (C_1-C_6)-Alkyl, substituiert durch einen oder mehrere Substituenten, ausgewählt aus Halogen, N[(C_1-C_6)-Alkyl]$_2$, (C_3-C_6)-Cycloalkyl, unsubstituiertem Phenyl, Phenyl, substituiert durch ein oder mehrere (C_1-C_5)-Alkyl, und Isoxazolyl, substituiert durch ein oder mehrere (C_1-C_5)-Alkyl; oder Cyclohexyl oder unsubstituiertes Phenyl oder Phenyl, substituiert durch OH, N[(C_1-C_6)-Alkyl]$_2$, unsubstituiertes (C_1-C_6)-Alkyl, (C_1-C_6)-Alkyl, substituiert durch Halogen; O-(C_1-C_4)-Alkyl oder COO(C_1-C_5)-Alkyl oder unsubstituiertes Pyridyl oder Pyridyl, substituiert durch Methyl, ist.

6. Verbindung der Formel I nach Anspruch 1, ausgewählt aus
{(R)-1-[3-(Methyl-propyl-carbamoyl)-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinsäure,

{(R)-1-[3-(Methyl-pentyl-carbamoyl)-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinsäure,
[(R)-1-(3-Dipentylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenylcarbamoyl-propyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-5-methyl-benzoylamino)-2-phenyl-ethyl]-(2-phenylcarbamoyl-propyl)-phosphinsäure,
{(R)-1-[3-(2-oxo-Pyrrolidin-1-yl)-5-propoxy-benzoylamino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinsäure,
{(R)-1-[(1-Butyl-1H-indol-6-carbonyl)-amino]-2-phenyl-ethyl}-(2-phenylcarbamoyl-propyl)-phosphinsäure,
[1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-p-tolylcarbamoyl-butyl)-phosphinsäure,
[1-(3-Dipropytcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(3-methyl-2-p-tolylcarbamoylbutyl)-phosphinsäure,
[1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenyl-2-p-tolylcarbamoylethyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-phenylcarbamoyl-propyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S)-2-phenylcarbamoylpropyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylainino)-2-phenyl-ethyl]-(2-p-tolylcarbamoyl-propyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((S)-2-p-tolylcarbamoylpropyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-((R)-2-p-tolylcarbamoylpropyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-(2-isobutylcarbamoyl-propyl)-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3-methyl-butylcarbamoyl)-propyl]-phosphinsäure,
[2-(3,3-Dimethyl-butylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4,4,4-trifluor-butyl-carbamoyl)-propyl]-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(3,3,4,4-tetrafluor-butyl-carbamoyl)-propyl]-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(2,2,3,3,4,4,4-hepta-fluorbutylcarbamoyl)-propyl]-phosphinsäure,
(2-Cyclohexylcarbalnoyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenylethyl]-phosphinsäure,
[2-(2-Cyclohexyl-ethylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4-hydroxy-phenylcarbamoyl)-propyl]-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(4-methoxy-phenylcarbamoyl)-propyl]-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(pyridin-2-ylcarbamoyl)-propyl]-phosphinsäure,
[(R)-1-(3-Dipropylcarbamoyl-benzoylamino)-2-phenyl-ethyl]-[2-(5-methyl-pyridin-2-yl-carbamoyl)-propyl]-phosphinsäure und
(2-Benzylcarbanioyl-propyl)-[(R)-1-(3-dipropylcarbamoyl-benzoylamino)-2-phenylethyl]-phosphinsäure.

7. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1, umfassend das Umsetzen einer Verbindung der Formel II



(II)

,

worin R^2 (C_1-C_5)-Alkyl oder Phenyl ist;

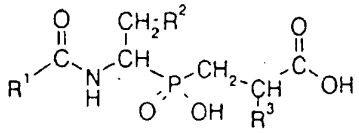
R^3 Wasserstoff, (C_1-C_5)-Alkyl, O-(C_1-C_5)-Alkyl oder Phenyl ist und
R^4 (C_1-C_6)-Alkyl, (C_3-C_6)-Cycloalkyl, Phenyl, Pyridyl oder Indolyl ist;
mit einer Verbindung der Formel III

$$R^1\text{-}COR^{10} \qquad \text{(III)},$$

worin

R^1 Aryl oder Heteroaryl ist und
R^{10} Halogen oder OH ist,

und, wenn erwünscht, Umwandeln der resultierenden Verbindung in ein pharmazeutisch akzeptables Salz oder umfassend das Umsetzen einer Verbindung der Formel XI



(XI)

worin

R^1 Aryl oder Heteroaryl ist;
R^2(C_1-C_5)-Alkyl oder Phenyl ist;
R^3 Wasserstoff, (C_1-C_5)-Alkyl, O-(C_1-C_5)-Alkoxy oder Phenyl ist,

mit einer Verbindung der Formel XII

$$H_2N\text{-}R^4 \qquad \text{(XII)},$$

worin
R^4 (C_1-C_6)-Alkyl, (C_3-C_6)-Cycloalkyl, Phenyl, Pyridyl oder Indolyl ist,
und, wenn gewünscht, das Umwandeln der resultierenden Verbindung in ein pharmazeutisch akzeptables Salz.

8. Verbindung der Formel I oder ein pharmazeutisch akzeptables Salz davon nach Anspruch 1, hergestellt durch ein Verfahren nach Anspruch 7.

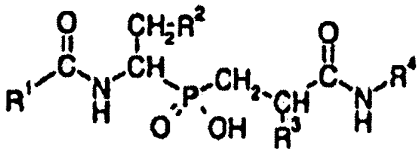
9. Verwendung einer Verbindung der Formel I oder eines pharmazeutisch akzeptablen Salzes davon nach Anspruch 1 zur Herstellung eines Medikaments für die Behandlung einer Krankheit, die mit der Inhibierung von β-Sekretase in Verbindung steht.

10. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel I oder ein pharmazeutisch akzeptables Salz davon nach Anspruch 1 und pharmazeutisch akzeptable Hilfsmittel.

11. Pharmazeutische Zusammensetzung nach Anspruch 10 zur Behandlung von Alzheimer-Krankheit.

Revendications

1. Composé de formule I



(I)

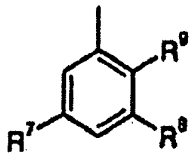
dans lequel

R^1 est aryle ou hétéroaryle;
R^2 est alkyle en C_1-C_5 ou phényle;
R^3 est hydrogène, alkyle en C_1-C_5, O-(alkyle en (C_1-C_5)) ou phényle;
R^4 est alkyle en C_1-C_6, cycloalkyle en C_3-C_6, phényle, pyridyle ou indolyle;
"aryle" est un groupement phényle qui n'est pas substitué ou substitué par un substituant choisi parmi OH, halogène, alkyle en C_1-C_5, un O-(alkyle en (C_1-C_5)), pyrrolidonyle et C(O)NR^5R^6, dans lequel R^5 est hydrogène ou alkyle en C_1-C_5 et R^6 est alkyle en C_1-C_5 non substitué ou alkyle en C_1-C_5 substitué par phényle;

"hétéroaryle" n'est pas substitué ou substitué par un alkyle en C_1-C_5;
l'"alkyle en C_1-C_5" ou l'alkyle en C_1-C_6 n'est pas substitué ou substitué par un substituent choisi parmi phényle, COOH, $COOCH_3$ et S-(alkyle en (C_1-C_5));

et leurs sels pharmaceutiquement acceptables.

2. Composé de formule I selon la revendication 1 dans lequel R^1 est un groupement de formule (a)



(a)

dans lequel
R^7 est hydrogène, alkyle en C_1-C_5, O-(alkyle en (C_1-C_4));
R^8 est OH, pyrrolidonyle ou -C(O)NR^5R^6 dans lequel R^5 est hydrogène ou alkyle en C_1-C_5 et R^6 est alkyle en C_1-C_5 ou alkyle en C_1-C_5 substitué par phényle, et
R^9 est hydrogène ou alkyle en C_1-C_5; ou
R^1 est un indolyle substitué par alkyle en C_1-C_5, ou quinoléinyle.

3. Composé de formule I selon la revendication 1 dans lequel R^2 est un phényle qui n'est pas substitué ou substitué par un atome de fluor.

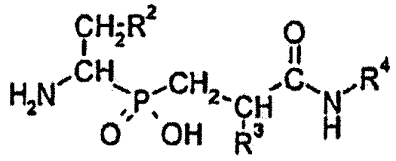
4. Composé de formule 1 selon la revendication 1 dans lequel R^3 est un hydrogène, un alkyle en C_1-C_5 ou un phényle.

5. Composé de formule 1 selon la revendication 1 dans lequel R^4 est un alkyle en C_1-C_6 non substitué, un alkyle en C_1-C_5 substitué par un ou plusieurs substituants choisis parmi halogène, N[alkyle en C_1-C_6]$_2$, cycloalkyle en C_3-C_6, phényle non substitué, phényle substitué par un ou plusieurs alkyles en C_1-C_5, et isoxazolyle substitué par un ou plusieurs alkyle en C_1-C_5; ou cyclohexyle; ou phényle non substitué ou phényle substitué par OH, N[alkyle en C_1-C_6]$_2$, alkyle en C_1-C_6 non substitué, alkyle en C_1-C_6 substitué par halogène ; O-(alkyle en (C_1-C_4)) ou COO-(alkyle en (C_1-C_5)); ou pyridyle non substitué ou pyridyle substitué par méthyle.

6. Composé de formule I selon la revendication 1 choisi parmi
Acide {(R)-1-[3-(méthylpropylcarbamoyl)-benzoylamino]-2-phényléthyl}-(2-phénylcarbamoylpropyl) phosphinique,
Acide {(R)-1-[3-(méthylpentylcarbamoyl)-benzoylamino]-2-phényléthyl}-(2-phénylcarbamoylpropyl) phosphinique,
Acide [(R)-1-(3-dipentylcarbamoylbenzoylamino)-2-phényléthyl]-(2-phénylcarbamoylpropyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoyl-5-méthylbenzoylamino)-2-phényléthyl]-(2-phénylcarbamoylpropyl) phosphinique,
Acide {(R)-1-[3-(2-oxopyrrolidin-1-yl)-5-propoxybenzoylamino]-2-phényléthyl}-(2-phénylcarbamoylpropyl) phosphinique,
Acide {(R)-1-[(1-butyl-1H-indole-6-carbonyl)-amino]-2-phényléthyl}-(2-phénylcarbamoylpropyl) phosphinique,
Acide [1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-(2-p-tolylcarbamoylbutyl) phosphinique,
Acide [1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-(3-méthyl-2-p-tolylcarbamoylbutyl) phosphinique,
Acide [1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-(2-phényl-2-p-tolylcarbamoyléthyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-(2-phénylcarbamoylpropyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-((S)-2-phénylcarbamoyl propyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-(2-p-tolylcarbamoylpropyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-((S)-2-p-tolylcarbamoylpropyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-((R)-2-p-tolylcarbamoylpropyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-(2-isobutylcarbamoylpropyl) phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-[2-(3-méthylbutylcarbamoyl)-propyl] phosphinique,
Acide [2-(3,3-diméthylbutylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl] phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényléthyl]-[2-(4,4,4-trifluorobutylcarbamoyl)-propyl] phosphi-

nique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl]-[2-(3,3,4,4-tétrafluorobutylcarbamoyl)-propyl] phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl]-[2-(2,2,3,3,4,4,4-heptafluorobutylcarbamoyl)-propyl] phosphinique,
Acide (2-cyclohexylcarbamoylpropyl)-[(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl] phosphinique,
Acide [2-(2-cyclohexylethylcarbamoyl)-propyl]-[(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl] phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl]-[2-(4-hydroxyphénylcarbamoyl)-propyl] phosphinique,
Acide [(R)-1 -(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl]-[2-(4-méthoxyphényle carbamoyl) -propyl] phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl]-[2-(pyridin-2-ylcarbamoyl) -propyl] phosphinique,
Acide [(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phénylethyl]-[2-(5-méthylpyridin-2-ylcarbamoyl) -propyl] phosphinique et
Acide (2-benzylcarbamoylpropyl)-[(R)-1-(3-dipropylcarbamoylbenzoylamino)-2-phényl-éthyl] phosphinique.

7. Procédé de préparation d'un composé de formule I selon la revendication 1, comprenant la réaction d'un composé de formule II



(II)

dans lequel

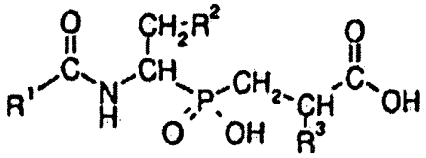
R^2 est alkyle en C_1-C_5 ou phényle;
R^3 est hydrogène, alkyle en C_1-C_5, O-(alkyle en (C_1-C_5)) ou phényle; et
R^4 est alkyle en C_1-C_6, cycloalkyle en C_3-C_6, phényle, pyridyle ou indolyle; avec un composé de formule III

$$R_1\ COR^{10} \qquad (III)$$

dans lequel

R^1 est aryle ou hétéroaryle; et
R^{10} est halogène ou OH;

et, si on le désire, la conversion du composé obtenu en un sel pharmaceutiquement acceptable; ou comprenant la réaction d'un composé de formule XI



(XI)

dans lequel

R^1 est aryle ou hétéroaryle;
R^2 est alkyle en C_1-C_5 ou phényle;
R^3 est hydrogène, alkyle en C_1-C_5, O-(alcoxy en (C_1-C_5)) ou phényle; avec un composé de formule XII

H_2N-R^4 (XII)

dans lequel

R^4 est alkyle en C_1-C_6, cycloalkyle en C_3-C_6, phényle, pyridyle ou indolyle et, si on le désire, la conversion du composé obtenu en un sel pharmaceutiquement acceptable.

8. Composé de formule I ou d'un de ses sels pharmaceutiquement acceptables selon la revendication 1, qui est préparé par un procédé selon la revendication 7.

9. Utilisation d'un composé de formule 1 ou d'un de ses sels pharmaceutiquement acceptables selon la revendication 1 pour la fabrication d'un médicament destiné au traitement de la maladie associée à l'inhibition de la β-secrétase.

10. Composition pharmaceutique contenant un composé de formule I ou d'un de ses sels pharmaceutiquement acceptables selon la revendication 1 et des excipients pharmaceutiquement acceptables.

11. Composition pharmaceutique selon la revendication 10 pour le traitement de la maladie d'Alzheimer.

REFERENCES CITED IN THE DESCRIPTION

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