(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
12 November 2009 (12.11.2009)

(10) International Publication Number
WO 2009/135526 A1

(51) International Patent Classification:
C07C 323/60 (2006.01) *A61K 31/415* (2006.01)
C07D 231/40 (2006.01) *A61K 31/423* (2006.01)
C07D 241/20 (2006.01) *A61K 31/428* (2006.01)
C07D 263/56 (2006.01) *A61K 31/433* (2006.01)
C07D 277/64 (2006.01) *A61K 31/53* (2006.01)
C07D 285/135 (2006.01) *A61P 3/04* (2006.01)
A61K 31/16 (2006.01) *A61P 3/10* (2006.01)
A61K 31/165 (2006.01)

(21) International Application Number: PCT/EP2008/055594

(22) International Filing Date: 7 May 2008 (07.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: NAPOLETANO, Mauro [IT/IT]; Via Venini, 37, I-20127 Milano (IT). HAACK, Thomas [DE/IT]; Via Bontempelli 15, I-22100 Como (IT). TSCHINKE, Vincenzo [IT/CH]; Kernmattstrasse 24, CH-4102 Binningen (CH). JELAKOVIC, Stjepan [HR/DE]; Merzhauserstrasse 3, 79100 Freiburg (DE). MAH, Robert [CA/CH]; Baselstrasse 40L, CH-4132 Muttenz (CH).

(74) Agent: POMMERENKE, Alexander; Solvias AG, Patents, WRO-1060.P46, Mattenstrasse 22, CH-4002 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

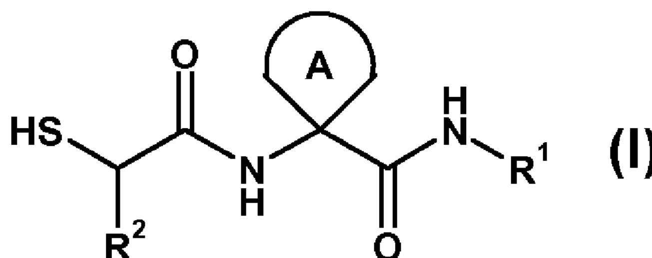
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: ALPHA-MERCAPTO-AMIDES



(57) Abstract: Substituted amides of the general formula (I): with the residues A, R^1 and R^2 as explained in detail in the description are described. The compounds are suitable in particular as neutral endopeptidase inhibitors and are highly potent.

WO 2009/135526 A1

Alpha-mercapto-amides

FIELD OF THE INVENTION

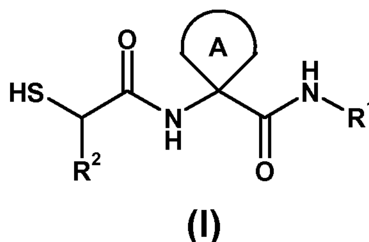
The present invention relates to alpha-mercapto-amides, to processes for their preparation and to the use of the compounds, as neutral endopeptidase (NEP) inhibitors, in particular to medicaments containing such a compound.

BACKGROUND OF THE INVENTION

Various NEP inhibitors and their uses are disclosed, for example, in WO 1997/011717. However, there is still a need for highly potent and selective active compounds. In this context, the improvement of a compound's pharmacokinetic properties, resulting in better oral bioavailability, and/or it's overall safety profile are at the forefront. Properties directed towards better bioavailability are, for example, increased absorption, metabolic stability or solubility, or optimized lipophilicity. Properties directed towards a better safety profile are, for example, increased selectivity against drug metabolizing enzymes such as the cytochrome P450 enzymes or increased selectivity against other vasoactive zinc metalloproteases such as angiotensin converting enzyme (ACE) and aminopeptidase P (APP).

DETAILED DESCRIPTION OF THE INVENTION

The invention therefore provides substituted heterocycles of the general formula (I)



(I) ,

wherein

A is monocyclic C_{3-8}-cycloalkyl or monocyclic, saturated heterocyclyl, each of which are either unsubstituted or substituted by 1-3 C_{1-8}-alkoxy, C_{1-8}-alkyl, halogen, hydroxy or oxo;

R^1 is C_{1-8}-alkyl, aryl-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in C_{1-8}-alkyl, aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo;
R^2 is C_{1-8}-alkoxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkyl, aryl, aryl-C_{1-8}-alkyl, halo-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, carboxy, halogen, hydroxy or oxo;
where the aryl or heterocyclyl moieties are unsubstituted or substituted;
where the thiol group is unprotected or protected with a protecting group R_a, which is hydrolyzed under physiological conditions to give the compound of formula (I);
disulfide derivatives derived from the compound of formula (I) and salts of a compound of formula (I), preferably pharmaceutically acceptable salts thereof.

Thiol protecting groups R_a are for example acyl or sulfonyl groups, which are unsubstituted or substituted with one or more halogen (fluoro or chlorine), hydroxy, N,N-di-C_{1-8}-alkyl-amine, morpholine or C_{1-8}-alkoxy, or N,N-di-C_1-C_4-alkylaminocarbonyl. Acyl radicals are preferably alkanoyl radicals, more preferably C_{1-8}-alkanoyl radicals such as formyl, acetyl, fluoroacetyl, chloroacetyl, dimethylaminoacetyl, or aroyl radicals such as benzoyl. Further suitable thiol protecting groups may be identified using test systems available and known to the person skilled in the art.

Examples of alkyl and alkoxy radicals, which may be linear or branched, are C_{1-8}-alkyl and C_{1-8}-alkoxy radicals such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, pentyl, hexyl, and methoxy, ethoxy, propoxy, i-propoxy, butoxy, i-butoxy, s-butoxy and t-butoxy respectively. C_{1-8}-Alkylenedioxy radicals are preferably methylenedioxy, ethylenedioxy and propylenedioxy. Cycloalkyl is a saturated, cyclic or polycyclic hydrocarbon radical having 3-12 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, cyclooctyl, bicyclo[2.2.2]octyl and adamantyl. C_{1-8}-alkyl radicals in aryl-C_{1-8}-alkyl, heterocyclyl-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl, aryl-C_{1-8}-alkyl and heterocyclyl-C_{1-8}-alkyl and in other substituents, which may be linear or branched, are, for example, methylene, ethylene, 1-methylmethylene, propylene, methyl-

ethylene, 1-ethylmethylene, 1,1-dimethylmethylene, 2-methylpropylene, 2-methylbutylene, 2-methylbutyl-2-ene, butyl-2-ene, butyl-3-ene, propyl-2-ene, tetra-, penta- and hexamethylene.

In case of A, the term cycloalkyl may denote a monocyclic radical having 3-8 and preferably 5 to 7 ring carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Aryl may denote mono- or polycyclic aromatic radicals, which may be mono- or polysubstituted in the aryl moiety, for example phenyl, substituted phenyl, naphthyl or substituted naphthyl. Examples of substituents on such aryl radicals are acetamidinyl-C_{1-8}-alkyl, acyl-C_{1-8}-alkoxy-C_{1-8}-alkyl, (N-acyl)-C_{1-8}-alkoxy-C_{1-8}-alkylamino, C_{2-8}-alkenyl, C_{2-8}-alkenyloxy, C_{1-8}-alkoxy, C_{1-8}-alkoxy-C_{1-8}-alkoxy, C_{1-8}-alkoxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl, (N-C_{1-8}-alkoxy)-C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkoxy, (N-C_{1-8}-alkoxy)-C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl-carbamoyl, C_{1-8}-alkoxy-C_{1-8}-alkyl-carbonyl, C_{1-8}-alkoxy-C_{1-8}-alkyl-carbonylamino, C_{1-8}-alkoxy-C_{1-8}-alkyl-heterocyclyl, 2-C_{1-8}-alkoxy-C_{1-8}-alkyl-4-oxo-imidazol-1-yl, 6-alkoxy-aminocarbonyl-C_{1-8}-alkoxy, C_{1-8}-alkoxy-aminocarbonyl-C_{1-8}-alkyl, C_{1-8}-alkoxycarbonyl, C_{1-8}-alkoxycarbonyl-C_{1-8}-alkoxy, C_{1-8}-alkoxycarbonyl-C_{1-8}-alkyl, C_{1-8}-alkoxycarbonylamino-C_{1-8}-alkoxy, C_{1-8}-alkoxycarbonylamino-C_{1-8}-alkyl, C_{1-8}-alkoxycarbonylphenyl, C_{1-8}-alkyl, (N-C_{1-8}-alkyl)-C_{1-8}-alkoxy-C_{1-8}-alkyl-carbamoyl, (N-C_{1-8}-alkyl)-C_{1-8}-alkoxy-C_{1-8}-alkyl-carbonylamino, (N-C_{1-8}-alkyl)-C_{1-8}-alkoxy-carbonylamino, (N-C_{1-8}-alkyl)-C_{0-8}-alkylcarbonylamino-C_{1-8}-alkoxy, (N-C_{1-8}-alkyl)-C_{0-8}-alkylcarbonylamino-C_{1-8}-alkyl, (N-C_{1-8}-alkyl)-C_{1-8}-alkylsulfonylamino-C_{1-8}-alkoxy, (N-C_{1-8}-alkyl)-C_{1-8}-alkylsulfonylamino-C_{1-8}-alkyl, C_{1-8}-alkylamidinyl, optionally N-mono or N,N-di-C_{1-8}-alkylated amino, C_{1-8}-alkylamino-C_{2-8}-alkoxy, di-C_{1-8}-alkylamino-C_{2-8}-alkoxy, C_{1-8}-alkylamino-C_{1-8}-alkyl, di-C_{1-8}-alkylamino-C_{1-8}-alkyl, C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkoxy, di-C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkoxy, C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkyl, di-C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkyl, C_{1-8}-alkylaminocarbonylamino-C_{1-8}-alkoxy, C_{1-8}-alkylaminocarbonylamino-C_{1-8}-alkyl, C_{1-8}-alkyl-carbamoyl, di-C_{1-8}-alkyl-carbamoyl, C_{0-8}-alkylcarbonylamino, C_{0-8}-alkylcarbonylamino-C_{1-8}-alkoxy, C_{0-8}-alkylcarbonylamino-C_{1-8}-alkyl, C_{1-8}-alkylcarbonyloxy, C_{1-8}-alkylcarbonyloxy-C_{1-8}-alkoxy, C_{1-8}-alkylcarbonyloxy-

C_{1-8}-alkyl, C_{1-8}-alkylenedioxy, C_{1-8}-alkyl-sulfonyl, C_{1-8}-alkylsulfonyl-C_{1-8}-alkoxy, C_{1-8}-alkylsulfonyl-C_{1-8}-alkyl, C_{1-8}-alkylsulfonylamino-C_{1-8}-alkoxy, C_{1-8}-alkylsulfonylamino-C_{1-8}-alkyl, aryl-C_{1-8}-alkanoyl, aryl-C_{0-8}-alkoxy, aryl-C_{0-8}-alkyl, arylamino, aryloxy, arylthio, benzoyloxy-C_{1-8}-alkoxy, benzyloxy, carbamoyl-C_{0-8}-alkoxy, carbamoyl-C_{0-8}-alkyl, carboxy, carboxy-C_{1-8}-alkoxy, carboxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, carboxy-C_{1-8}-alkyl, cyano, cyano-C_{1-8}-alkoxy, cyano-C_{1-8}-alkyl, C_{3-8}-cycloalkyl-C_{1-8}-alkanoyl, C_{3-8}-cycloalkylcarbonylamino-C_{1-8}-alkoxy, C_{3-8}-cycloalkylcarbonylamino-C_{1-8}-alkyl, cyclopropyl-C_{1-8}-alkoxy, cyclopropyl-C_{1-8}-alkyl, O,N-dimethylhydroxylamino-C_{1-8}-alkyl, dioxolanyl-C_{1-8}-alkoxy, halogen, halogen-C_{1-8}-alkoxy, halogen-C_{1-8}-alkyl, heterocyclyl, heterocyclyl-C_{1-8}-alkanoyl, heterocyclyl-C_{1-8}-alkoxy, heterocyclyl-C_{1-8}-alkoxy-C_{1-8}-alkoxy, heterocyclyl-C_{1-8}-alkoxy-C_{1-8}-alkyl, heterocyclyl-C_{1-8}-alkyl, heterocyclylamino, heterocyclyloxy, heterocyclylthio, hydroxy, hydroxy-C_{2-8}-alkoxy, hydroxy-C_{2-8}-alkoxy-C_{1-8}-alkoxy, hydroxy-C_{2-8}-alkoxy-C_{1-8}-alkyl, hydroxy-C_{1-8}-alkyl, (N-hydroxy)-C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkoxy, (N-hydroxy)-C_{1-8}-alkylaminocarbonyl-C_{1-8}-alkyl, hydroxy-C_{1-8}-alkylphenyl, (N-hydroxy)-aminocarbonyl-C_{1-8}-alkoxy, (N-hydroxy)-aminocarbonyl-C_{1-8}-alkyl, hydroxybenzyloxy, methylendioxybenzyloxy, methoxybenyloxy, O-methyloximyl-C_{1-8}-alkyl, nitro, 2-oxo-oxazolidinyl-C_{1-8}-alkoxy, 2-oxo-oxazolidinyl-C_{1-8}-alkyl or pyridylcarbonylamino-C_{1-8}-alkyl.

The term heterocyclyl, except for residue A, denotes mono- or polycyclic, saturated and unsaturated heterocyclic radicals having one or more heteroatoms selected from the group comprising O, S or N, for example from 1 to 4 nitrogen and/or 1 or 2 sulfur and/or 1 or 2 oxygen atoms and which may be mono- or polysubstituted, especially mono- ,di- or trisubstituted. Additionally, the term heterocyclyl may include the above mentioned oxo-substituted radicals. Examples of unsaturated heterocyclyl radicals are benzo[1,3]dioxolyl, benzofuranyl, benzoimidazolyl, benzooxazolyl, benzothiazolyl, benzo[b]thienyl, quinazolinyl, quinolyl, quinoxalinyl, dihydrobenzofuranyl, 1,3-dihydrobenzoimidazol, 3,4-dihydro-2H-benzo[1,4]oxazinyl, dihydro-3H-benzo[1,4]oxazinyl, 1,4-dihydro-benzo[d][1,3]oxazin, dihydro-2H-benzo[1,4]thiazinyl, 3,4-dihydro-1H-quinazolin, 3,4-dihydro-1H-quinolin, 2,3-dihydroindolyl, dihydro-1H-pyrido[2,3-b][1,4]oxazinyl, 1,1-dioxo-dihydro-2H-benzo[1,4]thiazinyl, furyl, imidazolyl, imidazo[1,5-a]pyridinyl, imidazo[1,2-a]pyrimidinyl, indazolyl, indolyl, isobenzofuranyl, isoquinolyl,

[1,5]naphthyridyl, oxazolyl, 1-oxido-pyridyl, 2-oxo-benzoimidazolyl, 3-oxo-4H-benzo[1,4]oxazinyl, 2-oxo-benzooxazolyl, 3-oxo-4H-benzo[1,4]thiazinyl, 2-oxo-dihydro-benzo[e][1,4]diazepinyl, 2-oxo-1,3-dihydro-benzoimidazol, 2-oxo-dihydro-benzo-[d][1,3]oxazinyl, 2-oxo-3,4-dihydro-1H-quinazolin, 2-oxo-3,4-dihydro-1H-quinolin, 4-oxo-dihydro-imidazolyl, 2-oxo-1,3-dihydroindolyl, 1-oxo-3H-isobenzofuranyl, 2-oxo-1H-pyrido[2,3-b][1,4]oxazinyl, 2-oxo-1,3,4,5-tetrahydro-benzo[b]azepin, 2-oxo-tetrahydro-benzo[e][1,4]diazepinyl, 4-oxo-3H-thieno[2,3-d]pyrimidinyl, 5-oxo-4H-[1,2,4]triazinyl, phthalazinyl, pyranyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidinyl, 1H-pyrrolizinyl, pyrrolo[3,2-c]pyridinyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-b]pyridinyl, 1H-pyrrolo[2,3-b]pyridyl, pyrrolyl, 1,3,4,5-tetrahydro-benzo[b]azepin, tetrahydroquinolinyl, tetrahydro-quinoxalinyl, tetrahydroisoquinolinyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazinyl, triazolyl, 1,1,3-trioxo-dihydro-2H-1lambda*6*-benzo[1,4]thiazinyl, [1,2,3]triazolo[1,5-a]pyridinyl or [1,2,4]triazolo[4,3-a]pyridinyl.

The term saturated heterocyclyl, except for residue A, may denote 3-16 membered mono- or bicyclic, saturated heterocyclic radicals having one or more heteroatoms selected from the group comprising O, S, or N, for example from 1 to 4 nitrogen and/or 1 or 2 sulfur or oxygen atoms. Preferred are 3-8 membered, especially preferred 5- or 6-membered monocyclic radicals, which may be condensed to a 3-8 membered, carbocyclic or heterocyclic ring. Another preferred group of saturated heterocyclic radicals are bicyclic radicals possessing a spirocyclic or bridged ring skeleton.

Preferred heterocyclic radicals, except for residue A, are possessing per ring 1 nitrogen, oxygen or sulfur atom, 1-2 nitrogen atoms and 1-2 oxygen atoms or 1-2 nitrogen atoms and 1-2 sulfur atoms, whereby, per ring, at least 1 carbon atom, preferentially 1-7 carbon atoms are present. Heterocyclyl radicals which comprise a nitrogen atom may be linked either via the N atom or via a C atom to the remainder of the molecule.

In case of A, the term monocyclic, saturated heterocyclyl may denote 3-8 membered monocyclic, saturated heterocyclic radicals having one or more heteroatoms selected

from the group comprising O, S or N, for example from 1 to 2 nitrogen and/or 1 or 2 sulfur and/or 1 or 2 oxygen atoms. Prefered are 4-7 membered, especially preferred are 5- or 6-membered monocyclic radicals. Preferred heterocyclic radicals are possessing per ring 1 nitrogen, oxygen or sulfur atom, whereby, per ring, at least 2 carbon atoms, preferentially 2-7 carbon atoms are present.

A heteroatom N in heterocyclyl may comprise NH or N-substituent and additionally –N= in unsaturated heterocyclyl. Substituent may comprise substituents mentioned before, such as C_{1-8}-alkyl, C_{2-8}-alkenyl, C_{2-8}-alkinyl, C_{3-12}-cycloalkyl, C_{3-12}-cycloalkyl-C_{1-8}-alkyl, C_{6-18}-aryl, C_{7-18}-aralkyl, heterocyclyl, heterocyclyl-C_{1-8}-alkyl, heteroaryl-C_{1-8}-alkyl, tri-C_{1-8}-alkyl-silyl, and C_{1-12}-acyl.

Examples for saturated heterocyclyl radicals are azepanyl, azetidinyl, aziridinyl, 3,4-dihydroxypyrrolidinyl, 2,6-dimethylmorpholinyl, 3,5-dimethylmorpholinyl, dioxanyl, [1,4]dioxepanyl, dioxolanyl, 4,4-dioxothiomorpholinyl, dithianyl, dithiolanyl, 2-hydroxy-methylpyrrolidinyl, 4-hydroxypiperidinyl, 3-hydroxypyrrolidinyl, 4-methylpiperazinyl, 1-methylpiperidinyl, 1-methylpyrrolidinyl, morpholinyl, oxathianyl, oxepanyl, 2-oxo-azepanyl, 2-oxo-imidazolidinyl, 2-oxo-oxazolidinyl, 2-oxo-piperidinyl, 4-oxo-piperidinyl, 2-oxo-pyrrolidinyl, 2-oxo-tetrahydro-pyrimidinyl, 4-oxo-thiomorpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, thiepanyl or thiomorpholinyl.

Examples for saturated bicyclic heterocyclyl radicals are 2,5-dioxa-bicyclo[4.1.0]heptanyl, 2-oxa-bicyclo[2.2.1]heptanyl, 2-oxa-bicyclo[4.1.0]heptanyl, 3-oxa-bicyclo[4.1.0]heptanyl, 7-oxa-bicyclo[2.2.1]heptanyl, 2-oxa-bicyclo[3.1.0]hexanyl, 3-oxa-bicyclo[3.1.0]hexanyl, 1-oxa-spiro[2.5]octanyl, 6-oxa-spiro[2.5]octanyl or 3-oxa-bicyclo[3.3.1]nonanyl.

Heterocyclyl radicals may be unsubstituted or mono- or polysubstituted, for example mono- or disubstituted. Examples of substituents on such heterocyclyl radicals are C_{1-6}-alkanoyl, C_{2-6}-alkenyl, C_{2-6}-alkinyl, C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkoxy, C_{1-6}-alkoxy-C_{1-6}-alkyl, C_{1-6}-alkoxycarbonylamino-C_{2-6}-alkoxy, C_{1-6}-alkoxycarbonylamino-

C_{0-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkylcarbonylamino, C_{1-6}-alkylcarbonylamino-C_{2-6}-alkoxy, C_{1-6}-alkylcarbonylamino-C_{1-6}-alkyl, C_{1-6}-alkylcarbonyloxy, C_{1-6}-alkylenedioxy, optionally N-mono or N,N-di-C_{1-6}-alkylated amino, aryl, optionally N-mono or N,N-di-C_{1-6}-alkylated carbamoyl, carbonylamino, carbonylamino-C_{2-6}-alkoxy, carbonylamino-C_{1-6}-alkyl, optionally esterified carboxy, cyano, C_{3-8}-cycloalkoxy, halogen, heteroaryl, heterocyclyl, hydroxy, nitro, oxid, oxo, polyhalogen-C_{1-6}-alkoxy or polyhalogen-C_{1-6}-alkyl.

The term polyhalogen-C_{1-6}-alkyl denotes C_{1-6}-alkyl radicals which may be substituted by 2-8 halogen, for example trifluoromethyl etc.

The term halo-C_{1-8}-alkyl for R^2 may denote mono- or polyhalogenalkyl, such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloroethyl, monofluoroethyl and pentafluoroethyl.

C_{1-8}-alkyl in the residues aryl-C_{1-8}-alkyl and heterocyclyl-C_{1-8}-alkyl may be linear or branched and preferably, the alkyl group is a C_{1-6}-alkyl and more preferably a C_{1-4}-alkyl group, such as methylene, ethylene, 1,2- or 1,3-propylene and 1,2-, 1,3- or 1,4-butylene.

Halogen or halo denotes, for example, fluorine, chlorine or bromine.

Salts are primarily the pharmaceutically acceptable or nontoxic salts of compounds of formula (I). The term “pharmaceutically acceptable salts” encompasses salts with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

Salts of compounds having salt-forming groups are in particular acid addition salts, salts with bases, or, in the presence of a plurality of salt-forming groups, in some cases also mixed salts or internal salts.

Such salts are formed, for example, from compounds of formula (I) with an acidic group, for example a carboxyl or sulfo group, and are, for example, the salts thereof with suitable bases such as non-toxic metal salts derived from metals of group Ia, Ib, IIa and IIb of the Periodic Table of the Elements, for example alkali metal, in particular lithium, sodium, or potassium, salts, alkaline earth metal salts, for example magnesium or calcium salts, and also zinc salts and ammonium salts, including those salts which are formed with organic amines, such as optionally hydroxy-substituted mono-, di- or trialkylamines, in particular mono-, di- or tri(lower alkyl)amines, or with quaternary ammonium bases, e.g. methyl-, ethyl-, diethyl- or triethylamine, mono-, bis- or tris(2-hydroxy(lower alkyl))amines, such as ethanol-, diethanol- or triethanol-amine, tris(hydroxymethyl)methylamine or 2-hydroxy-tert-butylamine, N,N-di(lower alkyl)-N-(hydroxy(lower alkyl))amine, such as N,N-di-N-dimethyl-N-(2-hydroxy-ethyl)amine, or N-methyl-D-glucamine, or quaternary ammonium hydroxides such as tetrabutylammonium hydroxide. The compounds of the formula I having a basic group, for example an amino group, may form acid addition salts, for example with suitable inorganic acids, e.g. hydrohalic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid with replacement of one or both protons, phosphoric acid with replacement of one or more protons, e.g. orthophosphoric acid or metaphosphoric acid, or pyrophosphoric acid with replacement of one or more protons, or with organic carboxylic, sulfonic or phosphonic acids or N-substituted sulfamic acids, e.g. acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid, isonicotinic acid, and also amino acids, for example the alpha-amino acids mentioned above, and also methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, naphthalene-2-sulfonic acid, 2- or 3-phospho-glycerate, glucose 6-phosphate, N-cyclohexylsulfamic acid (with formation of the cyclamates) or with other acidic organic compounds such as ascorbic acid. Compounds of formula (I) having acidic and basic groups may also form internal salts.

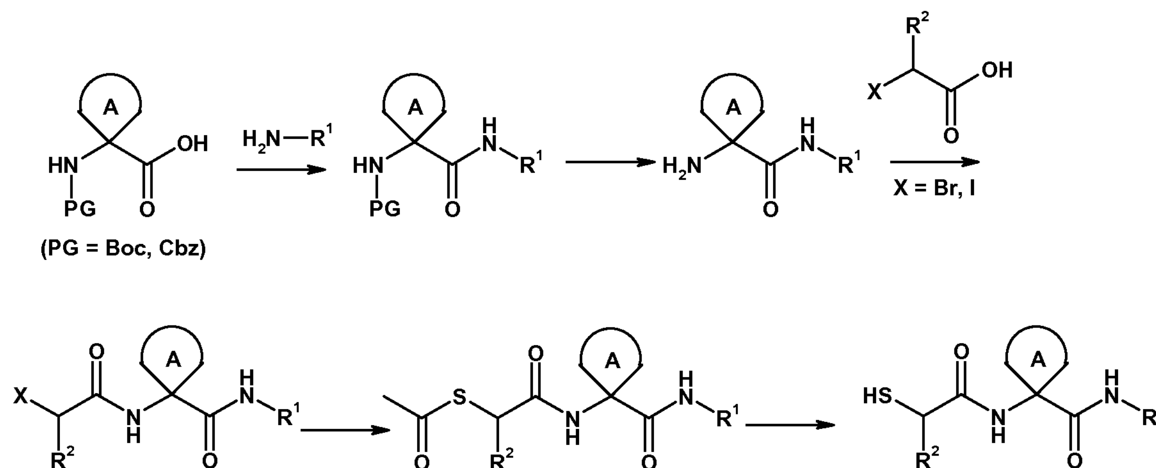
Salts obtained may be converted to other salts in a manner known per se, acid addition salts, for example, by treating with a suitable metal salt such as a sodium, barium or silver salt, of another acid in a suitable solvent in which an inorganic salt which forms is insoluble and thus separates out of the reaction equilibrium, and base salts by release of the free acid and salt reformation.

The compounds of formula (I), including their salts, may also be obtained in the form of hydrates or solvates, incorporating a solvent used in the crystallization process.

For the isolation and purification, pharmaceutically unsuitable salts may also find use.

The compounds of formula (I) also include those compounds in which one or more atoms are replaced by their stable, non-radioactive isotopes; for example a hydrogen atom by deuterium.

The compounds of formula (I) may be prepared in a similar manner to the preparation processses disclosed in the literature (WO 2002/09262) (Scheme 1). Details on the specific preparation variants can be taken from the examples. A further object of the invention is a process for the preparation of compounds of formula (I) according to Scheme 1, and novel intermediates according to general formulae as given in Scheme 1.



Scheme 1

The compounds of formula (I) have at least one asymmetric carbon atom and may therefore be in the form of optically pure enantiomers, mixtures with predominantly one enantiomer or racemates, or --when at least one additional asymmetric carbon atom is present-- be in the form of diastereomers, diastereomeric mixtures, diastereomeric racemates, mixtures of diastereomeric racemates or as meso compounds. The invention encompasses all of these forms. Diastereomeric mixtures, diastereomeric racemates or mixtures of diastereomeric racemates may be separated by customary procedures, for example by column chromatography, thin-layer chromatography, HPLC and the like.

The compounds of formula (I) may also be prepared in optically pure form. The separation into antipodes can be effected by procedures known per se, either preferably at an earlier synthetic stage by salt formation with an optically active acid, for example (+)- or (-)-mandelic acid and separation of the diastereomeric salts by fractional crystallization, or preferably at a relatively late stage by derivatizing with a chiral auxiliary building block, for example (+)- or (-)-camphanoyl chloride, and separation of the diastereomeric products by chromatography and/or crystallization and subsequent cleavage of the bonds to give the chiral auxiliary. The pure diastereomeric salts and derivatives may be analysed to determine the absolute configuration of the piperidine present with common spectroscopic procedures, and X-ray spectroscopy on single crystals constitutes a particularly suitable procedure.

It is possible for the configuration at individual chiral centres in a compound of formula (I) to be inverted selectively. For example, the configuration of asymmetric carbon atoms which bear nucleophilic substituents, such as amino or hydroxyl, may be inverted by second-order nucleophilic substitution, if appropriate after conversion of the bonded nucleophilic substituent to a suitable nucleofugic leaving group and reaction with a reagent which introduces the original substituents, or the configuration at carbon atoms having hydroxyl groups can be inverted by oxidation and reduction, analogously to the process in the European patent application EP-A-0 236 734. Also

advantageous is the reactive functional modification of the hydroxyl group and subsequent replacement thereof by hydroxyl with inversion of configuration.

The compounds of formula (I) also include compounds where one or more atoms are replaced by their stable, non-radioactive isotopes (for example hydrogen by deuterium).

Prodrug derivatives of the compounds described in the present context are derivatives thereof which, on *in vivo* application, release the original compound by a chemical or physiological process. A prodrug may be converted to the original compound, for example, when a physiological pH is attained or by enzymatic conversion. Prodrug derivatives may, for example, be esters of freely available carboxylic acids, S- and O-acyl derivatives of thiols, alcohols or phenols, and the acyl group is as defined in the present context. Preference is given to pharmaceutically useable ester derivatives which are converted by solvolysis in physiological medium to the original carboxylic acid, for example lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or disubstituted lower alkyl esters such as lower ω-(amino, mono- or dialkylamino, carboxyl, lower alkoxycarbonyl)-alkyl esters or such as lower α-(alkanoyloxy, alkoxycarbonyl or dialkylaminocarbonyl)-alkyl esters; as such, pivaloyloxymethyl esters and similar esters are utilized in a conventional manner.

In a preferred embodiment, prodrugs are selected from compounds of formula I, wherein the hydrogen atom of thiol group is substituted by a protective group R_a, which is split off in a physiological environment, such as C_1-C_8-acyl (the term acyl may include residues from carboxylic and sulfonic acids), N,N-di-C_1-C_4-alkylamino-carbonyl (dimethylaminocarbonyl) and C_1-C_6-alkoxycarbonyl (methoxy-, ethoxy- or t-butoxycarbonyl).

Owing to the close relationship between a free compound, a prodrug derivative and a salt compound, a certain compound in this invention also encompasses its prodrug derivative and salt form, where these are possible and appropriate.

The compounds of the formula (I) also include compounds that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in WO 2004/098538 A2.

The compounds of the formula (I) also include compounds that have been converted at one or more sites such that a nitrate-ester-containing linker is attached to an existing oxygen and/or nitrogen. Such “nitroderivatives” of the compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for converting compounds into their nitroderivatives are described in WO 2007/045551 A2.

Neutral endopeptidase 3.4.24.11 (NEP), also called neprilysin, enkephalinase, common acute lymphoblastic leukemia antigen or CD10 is a zinc-containing metallo-protease that cleaves specific biologically active peptides. NEP is widely distributed in the body and has been purified from kidney, brain and intestinal tissues. Several peptides have been identified as substrates for NEP *in vitro*; however, the distribution of this peptidase and that of its potential substrates is likely to impart functional selectivity to NEP *in vivo*. Pharmacological inhibition of NEP affects the metabolism of the peptides and thus enhances their biologic function.

In the central nervous system, NEP participates in the hydrolysis of Met- and Leu-enkephalin. These peptides have the ability to mediate analgesia. Hence, inhibition of NEP has been demonstrated to yield an anti-nociceptive activity (Chipkin et al., J. Pharmacol. Exp. Ther. 1988; 245:829-838).

In the heart, kidney and vasculature, NEP participates in the degradation of natriuretic peptides and bradykinin. The natriuretic peptides ANP, atrial natriuretic peptide, BNP, brain natriuretic peptide, CNP, C-type natriuretic peptide and urodilatin mediate diuretic, natriuretic, anti-inflammatory, antifibrotic and anti-mitogenic actions. Bradykinin regulates the tonus of vascular smooth muscle tissues. Hence, inhibition of NEP

has been demonstrated to lower blood pressure, to improve peripheral arterial disease, to increase diuresis, to be cardioprotective and anti-atherosclerotic as well as protective against ischemic infarcts and endothelial dysfunction (Mukassam-Daher, Expert Opinion Therapeutic Targets 2006; 10:239-252).

In sensory nerves, NEP participates in the degradation of CGRP, calcitonin gene-related peptide, a potent vasodilator that plays an important role in the initiation, progression and maintenance of hypertension via interactions with pro-hypertensive systems, including renin-angiotensin-aldosterone system, sympathetic nervous system and endothelin system; and via anti-hypertrophy and anti-proliferation of vascular smooth muscle cells. The decrease in CGRP synthesis and release contributes to the elevated blood pressure. Hence, inhibition of NEP may potentiate the effects of CGRP and its compensatory depressor role in the development of hypertension (Deng and Li, Peptides 2005; 26:1676-1685).

In addition, NEP participates in the catabolism of vasoactive intestinal peptide. Vasoactive intestinal peptide increases genital blood flow resulting in increased vaginal, labial and clitoral blood flow. Hence, inhibition of NEP potentiates the activity of vasoactive intestinal peptide and is useful for the treatment of female sexual arousal disorder (FSAD) (Pryde et al., Journal of Medicinal Chemistry 2006; 49:4409-4424).

NEP participates also in the degradation of incretin glucagon-like peptide-1. Glucagon-like peptide 1 has insulinotropic activity in the pancreas and may also regulate food consumption. Hence, inhibition of NEP enhances glucose-dependent insulin release, reduces food consumption and is useful for the treatment of diabetes, insulin resistance and obesity. These potential therapeutic applications for NEP inhibitors have led to intensive drug discovery efforts. Several selective NEP inhibitors of various chemical classes have been discovered and some have been tested clinically.

The ability of the herein described compounds of formula (I) to inhibit NEP activity can be shown for example by an *in vitro* assay that determines the hydrolysis of a fluorogenic substrate by NEP derived from rat kidney cortex membranes using a

modified procedure of Orlowski and Wilk (Biochemistry, 1981; 20:4942-50). The incubation mixture of 100 µl contains:

TRIS/HCl	50 mM, pH 7.6
Membrane from rat kidney cortex	2.5 µg/ml
Aminopeptidase M	20 IU (ng/ml)
Succ-Ala-Ala-Phe-AMC (SAAP)	50 µM
Test compound	1 nM - 10 µM

The test compound is dissolved in DMSO at a concentration of 1 mM prior to serial dilution with assay buffer. The final compound concentrations in the incubation mixture range between 10 µM and 1 nM. The incubation mixture is incubated for 45 min at 30°C. The hydrolysis product, 7-amido-4-methylcoumarin, is quantified by fluorescence ($\lambda_{ecc.}$:355 nm; $\lambda_{em.}$:460 nm) using Victor V^2 detector (Perkin Elmer).

Examples of *in vitro* NEP inhibition:

Compound of Example	**IC_{50} value [nM]***
1	8.06
5	3.86

* A higher inhibiting activity corresponds to a lower IC_{50} value.

The NEP inhibitory activity of herein disclosed compounds of formula (I) can also be shown for example by an ex vivo assay that determines the hydrolysis of a fluoro-genic substrate by NEP derived from rat kidney homogenate using a modified procedure of Orlowski and Wilk (Biochemistry, 1981; 20:4942-50). Male spontaneous hypertensive rats (SHR) of 11-14 weeks of age are subjected in groups of 3 to i.v. administration of test compound or vehicle. The test compound is applied in a volume of 1.0 ml at a concentration ranging between 2 to 20 µmol/kg body weight. Five to fifteen minutes after the tail vein injection the animals are sacrified and their kidneys are removed for homogenization in a TRIS-buffered Triton-X100 solution. The NEP activity in the homogenate is measured in a mixture of 100 µl containing

TRIS/HCl	50 mM, pH 7.6
SHR kidney homogenate	200 µg/ml
Aminopeptidase M	20 IU (ng/ml)
Succ-Ala-Ala-Phe-AMC (SAAP)	50 µM

that is incubated for 45 minutes at 30°C. Subsequently, the hydrolysis product, 7-amido-4-methylcoumarin, is quantified by fluorescence ($\lambda_{ecc.}$:355 nm; $\lambda_{em.}$:460 nm) using Victor V^2 detector (Perkin Elmer).

The percentage of inhibited NEP activity by compounds of formula (I) is calculated as follows:

$$\%Inhib = \frac{Spl - B}{Cont - B} \times 100$$

where:

- **Spl** is fluorescence measured in the well
- **B** is fluorescence measured in blank wells
- **Cont** is fluorescence measured in the control wells

IC_{50} values are calculated by fitting a 4-parameter logistic curve to the recorded %Inhib at specific test article concentrations according to following nonlinear equation:

$$Y = \frac{a - d}{1 + \left(\frac{X}{c}\right)^b} + d$$

The equation is fit to sigmoidal concentration-repsonse curves where

- ***Y*** is the observed response as dependent variable
- ***X*** is the test compound concentration as independent variable
- ***c*** is the inflection point (EC50 or IC50) for the curve respectively the negative log of the compound concentration giving a half-maximal effect ie. if **Y** is halfway between the lower and upper asymptotes **X** equals *c*.
- ***a*** is the limiting response as **X** approaches zero.

- ***d*** is the background effect or effect at infinite X concentration.
- ***b*** is the slope-factor in the region of the IC50 or Hill coefficient. The sign of *b* is positive when the response increases with increasing dose and is negative when the response decreases with increasing dose (inhibition).

Examples of NEP inhibitory activity:

Compound of Example	Dose [µmol/kg]	%Inhib*
1	2	41.2
	20	69.6
5	2	49.5
	20	87.9

* A higher inhibiting activity corresponds to higher % Inhib value.

The bioavailability of the compounds described herein can be tested *in vivo* using the following protocol:

The investigations take place in pre-catheterized (carotid artery) male rats (300 g ± 20%) that can move freely throughout the study. The compound is administered intravenously and orally (gavage) in separate sets of animals. The applied doses for oral administration may range from 0.5 to 50 mg/kg body weight; the doses for intravenous administration may range from 0.5 to 20 mg/kg body weight. Blood samples are collected through the catheter before compound administration and over the subsequent 24-hour period using an automated sampling device (AccuSampler, DiLab Europe, Lund, Sweden). Plasma levels of the compound are determined using a validated LC-MS analytical method. The pharmacokinetic analysis is performed on the plasma concentration-time curves after averaging all plasma concentrations across time points for each route of administration. Typical pharmacokinetics parameters to be calculated include: maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the curve from 0 hours to the time point of the last quantifiable concentration (AUC_{0-t}), area under the curve from time 0 to infinity (AUC_{0-inf}), elimination rate constant

(K), terminal half-life ($t_{½}$), absolute oral bioavailability or fraction absorbed (F), clearance (CL), and Volume of distribution during the terminal phase (Vd).

Five major metabolizing CYP450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are responsible for more than 95% of the drug metabolizing activity in humans.
The goals in evaluating in vitro drug metabolism are:
(1) to identify all of the major metabolic pathways that affect the test compound and its metabolites, including the identification of the specific enzymes responsible for metabolism and elucidation of the intermediates formed; and
(2) to explore and anticipate the effects of the test drug on the metabolism of other drugs and the effects of other drugs on its metabolism.
The most complete picture for hepatic metabolism can be obtained with intact liver systems (e.g. hepatocytes, microsomes), in which the cofactors are self-sufficient and the natural orientation and location for linked enzymes is preserved.
However, when many compounds have to be tested simultaneously, a simpler screening tool is advantageous. The cDNAs for the common CYP450s have been cloned and the recombinant human enzymatic proteins have been expressed in a variety of cells. Use of these recombinant enzymes provides an excellent way to quickly assess specific enzyme inhibition activities and/or confirm results identified in microsomes.

The metabolic properties (inhibition constants on human cytochrome P450 isoforms) of the compounds described herein can be tested *in vivo* using the following protocol:

To assess the inhibitory activity towards CYP450 enzymes, the enzymatic reaction is monitored in the presence of different concentrations of test compound (serial dilution) and compared to maximal enzyme activity (control : no test compound). In principle, inhibition can occur by three different mechanisms: (1) competitive inhibition, (2) non-competitive inhibition, and (3) mechanism-based inhibition.
In any case, the inhibition strength is dependent on the concentration of test compound. Testing the CYP450 enzyme activity over a test compound concentration

range identifies the test compound concentration at which half maximal enzyme inhibition is observed (IC_{50} concentration).
For screening purposes, the inhibitory potential of a test compound can be tested with ready to use kits (CYP450 High Throughput Inhibitor Screening kit, e.g. CYP1A2/CEC, #459500, BD Biosciences, Franklin Lakes, NJ USA), which are available for all of the five above-mentioned major CYP isoforms. In such kits, recombinant human CYP450 isoforms expressed in insect cells are incubated with isoform specific, fluorogenic substrates in the presence of different test compound concentrations. Enzymatic activity converts the fluorogenic substrate into a fluorochrome product, the concentration of which is measured with a fluoro-spectrophotometer. Fluorescence is directly proportional to enzyme activity.
In a typical standard assay using the CYP450 High Throughput Inhibitor Screening kit, a compound is tested at 2 nM to 33 µM concentration range in a phosphate buffer (50 mM, pH 7.4) containing a glucose 6-phosphate dehydrogenase/NADP/NADPH regeneration system and a suitable fluorogenic substrate: e.g. 3-cyano-7-ethoxy-coumarin (CYP1A2). As control inhibitors, the following substances can be used: furafylline (CYP1A2), sulfaphenazole (CYP2C9), tranylcypromine (CYP2C19), quinidine (CYP2D6) and ketoconazole (CYP3A4).
The reaction is started by the addition of 2.5 nM (final concentration) CYP450 isozyme, incubated at 37°C for 15 to 45 minutes, and then terminated by the addition of 187.5 mM tris-hydroxy-aminomethane base/acetonitrile (20/80, v/v).
The amount of generated fluorochrome is then determined by fluorescence spectroscopy with suitable exitation and emission wavelength settings: e.g. 410 nm excitation and 460 nm emission wavelength (CYP1A2).
Alternatively and/or complimentary, assays using human liver microsomes (e.g. BD Biosciences, #452161) in combination with a CYP isoform-specific standard substrate (e.g. midazolam for CYP3A4/5) as described by R. L. Walsky and R. S. Obach in *Validated assay for human cytochrome p450 activities*; Pharmacokinetics, Pharmacodynamics, and Drug Metabolism, Pfizer, Groton, Connecticut; Drug Metabolism and Disposition: (2004)32, 647-660, can be used. To determine whether a test compound inhibits CYP3A enzyme activity, for example, hydroxylation of midazolam by human liver microsomes at varying test compound

concentrations is monitored. Hydroxy-midazolam production is directly proportional to enzyme activity and can be determined by liquid chromatography-tandem mass spectrometry. Additionally, the microsomal assay can be run without and with a 15 min pre-incubation of microsomes with test compound prior to the addition of standard substrate. Test compounds or their metabolite(s) that have the potential to irreversibly modify the P450 enzyme will have a stronger inhibitory effect after pre-incubation.

In a typical standard assay using the human liver microsome assay, compounds are tested at 10 nM to 50 µM concentration range in a phosphate buffer (100 mM potassium phosphate, 3.3 mM $MgCl_2$, pH 7.4) containing a NADPH regeneration system (glucose 6-phosphate dehydrogenase, NADP, NADPH) and 10 µM substrate (e.g. midazolam for CYP3A4/5) and 0.1 mg/mL microsomal protein. As control inhibitors, the same substances as described above can be used (e.g. ketoconazole (CYP3A4/5)). If pre-incubation of the compound is desired, all assay components except substrate are mixed and incubated for 15 minutes at 37°C. After that period, substrate is added to the assay mix and then incubation at 37°C is continued for 15 minutes. Without pre-incubation, all assay components are mixed simultaneously and then incubated at 37°C for 15 minutes. Termination of the enzymatic reaction is achieved by the addition of a HCOOH/acetonitrile/H_2O (4/30/66, v/v/v) solution. Samples are then incubated in the refrigerator (4 ± 2°C) for 1 h ± 10 min to increase protein precipitation. Directly before analysis by LC/MSMS, the samples are centrifuged at 3,500 g for 60 min at 4°C to separate precipitated protein. The supernatant is mixed with acetonitrile/water (50/50, v/v), and then directly analyzed for compound content with LC/MSMS.

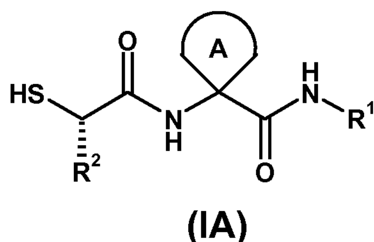
Evaluation of the data from either experimental setup is then done as follows: the fraction of remaining activity at a specific compound concentration versus the activity in the control as a function of compound concentration is used to compute IC_{50} values. This is done by fitting a 4-parameter logistic function to the experimental data set.

Metabolic stability of herein disclosed compounds of formula (I) can be a factor influencing their bioavailability. Metabolic stability can be tested for example by

determination of the hepatic intrinsic microsomal clearance using the procedure of Obach (Drug Metabolism and Disposition, 1999; 27(11):1350-1359).

The definitions of the substituents of the preferred compounds mentioned below are not to be regarded as closed, but rather parts of these definitions may be exchanged with one another or with the definitions given above in a sensible manner, for example to replace general by more specific definitions. The definitions are valid in accordance with general chemical principles, such as, for example, the common valences for atoms.

Preferred inventive compounds are those of the general formula (IA)



(IA)

where A, R^1 and R^2 are each as defined above for the compounds of the formula (I).

A further, preferred group of compounds of formula (I), or more preferably of formula (IA) and the salts thereof, preferably the pharmaceutically acceptable salts thereof, are compounds in which

A is monocyclic C_{3-8}-cycloalkyl which is either unsubstituted or substituted by 1-3 C_{1-8}-alkoxy, C_{1-8}-alkyl, halogen, hydroxy or oxo;

R^1 is C_{1-8}-alkyl, aryl-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in C_{1-8}-alkyl, aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo; and

R^2 is C_{1-8}-alkoxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkyl, aryl, aryl-C_{1-8}-alkyl, halo-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, carboxy, halogen, hydroxy or oxo.

A further, preferred group of compounds of formula (I), or more preferably of formula (IA) and the salts thereof, preferably the pharmaceutically acceptable salts thereof, are compounds in which

A is monocyclic, saturated heterocyclyl which is either unsubstituted or substituted by 1-3 C_{1-8}-alkoxy, C_{1-8}-alkyl, halogen, hydroxy or oxo;

R^1 is C_{1-8}-alkyl, aryl-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in C_{1-8}-alkyl, aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo: and

R^2 is C_{1-8}-alkoxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkyl, aryl, aryl-C_{1-8}-alkyl, halo-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, carboxy, halogen, hydroxy or oxo.

A further, preferred group of compounds of formula (I), or more preferably of formula (IA) and the salts thereof, preferably the pharmaceutically acceptable salts thereof, are compounds in which

A is monocyclic C_{5-7}-cycloalkyl or monocyclic, saturated heterocyclyl having one heteroatom selected from the group comprising O, S or N; each of which are either unsubstituted or substituted by 1-3 C_{1-8}-alkoxy, C_{1-8}-alkyl, halogen, hydroxy or oxo. Particularly preferred groups A are cyclohexyl, cyclopentyl or tetrahydropyran-4-yl.

A further, preferred group of compounds of formula (I), or more preferably of formula (IA) and the salts thereof, preferably the pharmaceutically acceptable salts thereof, are compounds in which

R^1 is C_{1-8}-alkyl, aryl-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in C_{1-8}-alkyl, aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo; R^1 is particularly preferred aryl-C_{2-4}-alkyl, heterocyclyl or heterocyclyl-C_{2-4}-alkyl wherein C_{2-4}-alkyl in aryl-C_{2-4}-alkyl or in heterocyclyl-C_{2-4}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo.

A further, preferred group of compounds of formula (I), or more preferably of formula (IA) and the salts thereof, preferably the pharmaceutically acceptable salts thereof, are compounds in which

R^2 is C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkyl, aryl or aryl-C_{1-8}-alkyl wherein C_{1-8}-alkyl in aryl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, carboxy, halogen, hydroxy or oxo; In particular, R^2 is benzyl, isopropyl, 2-methoxyethyl, methyl or propyl.

The compounds of formula (I), or preferably of formula (IA), and their pharmaceutically useable salts may find use as medicaments, for example in the form of pharmaceutical preparations. Accordingly, this invention is also directed to a pharmaceutical composition comprising a compound of formula (I), or preferably of formula (IA), and a pharmaceutically acceptable carrier or diluents.

The pharmaceutical preparations may be administered enterally, such as orally, for example in the form of tablets, coated tablets, sugar-coated tablets, hard and soft gelatine capsules, solutions, emulsions or suspensions, nasally, for example in the form of nasal sprays, rectally, for example in the form of suppositories, or transdermally, for example in the form of ointments or patches. The administration may also be parenteral, such as intramuscular or intravenous, for example in the form of injection solutions.

To prepare tablets, coated tablets, sugar-coated tablets and hard gelatine capsules, the compounds of formula (I), or preferably of formula (IA), and pharmaceutically useable salts thereof, may be processed with pharmaceutically inert, inorganic or organic excipients. Such excipients used, for example for tablets, coated tablets and hard gelatine capsules, may be lactose, corn starch, or derivatives thereof, talc, stearic acid or salts thereof etc.

Suitable excipients for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semisolid and liquid polyols, etc.

Suitable excipients for preparing solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose, etc.

Suitable excipients for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, bile acids, lecithin, etc.
Suitable excipients for suppositories are, for example, natural or hardened oils, waxes, fats, semisolid or liquid polyols, etc.
The pharmaceutical preparations may additionally also comprise preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavourings, salts for altering the osmotic pressure, buffers, coatings or antioxidants. They may also comprise other therapeutically valuable substances.

Thus, the herein disclosed compounds of formula (I), or preferably of formula (IA), and pharmaceutically useable salts thereof, by inhibiting the neutral endopeptidase EC.3.4.24.11, can have beneficial effects in the treatment of a number of disorders, including hypertension (including malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary types of hypertension), primary and secondary pulmonary hypertension, primary and secondary aldosteronism, oedema, salt retention, ascites, peripheral vascular resistance, arterial hypertrophy, vascular disorders including peripheral vascular disease, peripheral occlusive disease, intermittent claudication, migraine and Raynaud's disease, luminal hyperplasia, restenosis after coronary or peripheral angioplasty, heart failure including acute or chronic diastolic and congestive heart failure, left ventricular dysfunction, endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, myocarditits, pericarditis, endocarditis, supraventricular and ventricular arrhythmias, atrial fibrillation, cardiac fibrosis, atrial flutter, detrimental vascular remodeling, plaque stabilization, atherosclerosis including coronary arterial disease, myocardial infarction and its sequelae, cerebrovascular disease including embolic and thrombotic stroke, angina pectoris including unstable and stable forms, acute and chronic renal disease including diabetic and non-diabetic forms, renal fibrosis, polycystic kidney disease, chronic kidney disease, renal failure conditions such as nephrotic syndrome, diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease and end-stage renal disease (ESRD), kidney transplants, urinary tract disorders, lupus nephritis, insulin

resistance, type 2 diabetes, diabetic complications, obesity, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, metabolic syndrome, obesity, cyclical oedema, Menières disease and hypercalciuria.

In addition, the compounds of the invention may have activity in other therapeutic areas including for example the treatment of glaucoma, cataracts, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders (especially male and female infertility, polycystic ovarian syndrome, implantation failure), erectile dysfunction, female sexual dysfunction, male sexual dysfunction, sexual desire and arousal disorders, genital sensation and sensitivity disorders, orgasmic disorders, vaginal and clitoric blood flow disorders, sexual pain disorders, endometriosis, pelvic inflammatory disease,

Also, the compounds of the invention should treat asthma, inflammation, leukemia, pain, epilepsy, pain, depression, psychotic conditions, affective disorders, cognitive disorders such as Alzheimer’s disease and dementia and geriatric confusion, premenstrual syndrome, cerebral ischemia, stroke, subarachnoid hemorraghe, traumatic brain injury, cerebral vasospasm, cerebral ischemias, stroke, subarachnoid haemorrhage, migraine, traumatic brain injury, cerebral vasculitis, inflammatory neuropathies and gastrointestinal disorders (especially diarrhoea and irritable bowel syndrome), liver disease, cirrhosis, hepato-renal syndrome, Crohn’s disease, wound healing (especially diabetic and venous ulcers and pressure sores), septic shock, the modulation of gastric acid secretion and cystic fibrosis. In a preferred embodiment, the compounds of the invention are useful in the treatment of hypertension and hypertension-derived pathologies of the cardiovascular and renal system.

The compounds described herein and their pharmaceutically usable salts can be used in combination with

(i) one or more blood pressure-lowering active ingredients, as such for example:

- renin inhibitors such as aliskiren, or compounds disclosed in WO 2005/090305, WO 2006/005741, WO 2006/095020, WO 2006/103275, WO 2006/103277 and WO 2007/031558, etc.;

- angiotensin II receptor blockers such as candesartan, irbesartan, olmesartan, losartan, valsartan, telmisartan, etc.;
- ACE inhibitors such as quinapril, ramipril, trandolapril, lisinopril, captopril, enalapril etc.;
- calcium antagonists such as nifedipine, nicardipine, verapamil, isradipine, nimodipine, amlodipine, felodipine, nisoldipine, diltiazem, fendiline, flunarizine, perhexiline, gallopamil etc.;
- diuretics such as hydrochlorthiazide, chlorothiazide, acetazolamide, amiloride, bumetanide, benzthiazide, etacrynic acid, furosemide, indacrinone, metolazone, triamterene, chlortalidone, etc.;
- aldosterone receptor blockers such as spironolactone, eplerenone;
- aldosterone synthesis inhibitors such as fadrozole, FAD286 etc.;
- endothelin receptor blockers such as bosentan, avosentan, darusentan, ambrisentan, atrasentan, enrasentan, tezosentan, sitaxentan, clazosentan etc.;
- phosphodiesterase inhibitors such as amrinone, iodenafil, sildenafil, vardenavil, tadalafil;
- direct vasodilators such as dihydralazine, minoxidil, pinacidil, diazoxide, nitroprusside, flosequinan etc.;
- guanylcyclase activators such as BAY 41-2272, BAY 63-2521, BAY 58-2667, HMR 1776,
- α- and β-receptor blockers such as phentolamine, phenoxybenzamine, prazosin, doxazosin, terazosin, carvedilol, atenolol, metoprolol, nadolol, propranolol, timolol, carteolol etc.;
- sympatholytics such as methyldopa, clonidine, guanabenz, reserpine

(ii) one or more agents having inotropic activity, as such for example:

- cardiac glycosides such as digoxin;
- β-receptor stimulators such as dobutamine
- thyroid hormone such as thyroxine

(iii) one or more agents having antidiabetic activity, as such for example:

- insulins such as insulin aspart, insulin human, insulin lispro, insulin glargine and further fast-, medium- and long-acting insulin derivatives and combinations
- insulin sensitizers such as rosiglitazone, pioglitazone;

- sulphonylureas such as glimepiride, chlorpropamide, glipizide, glyburide etc.;
- biguanides such as metformin;
- glucosidase inhibitors such as acarbose, miglitol;
- meglitinides such as repaglinide, nateglinide;
- dipeptidyl protease IV inhibitors such as sitagliptin, vildagliptin, denagliptin etc.;

(iv) one or more obesity-reducing ingredients, as such for example:

- lipase inhibitors such as orlistat;
- appetite suppressants such as sibutramine, phentermine;

(v) one or more lipid-lowering active ingredients, such as, for example,

- HMG-CoA reductase inhibitors such as lovastatin, fluvastatin, pravastatin, atorvastatin, simvastatin, rosuvastatin etc.;
- fibrate derivatives such as fenofibrate, gemfibrozil etc.;
- bile acid-binding active ingredients such as colestipol, colestyramine, colesevelam
- cholesterol absorption inhibitors such as ezetimibe
- nicotinic acid such as niacin

(vi) one or more anti-inflammatory agents, such as, for example,

- non-selective cyclooxygnease-1/2 inhibitors such as acetyl salicylic acid, ibuproven, diclofenac, paracetamol, mefenamic acid, indometacin, naproxen etc.;
- selective cyclooxygenase-2 inhibitors such as celcoxib, rofecoxib, lumiracoxib, etoricoxib etc.;
- glucocorticoids such as cortisone, hydrocortisone, prednisolone, betamethasone, triamcinolone, dexamethasone etc.;

and other agents which are suitable for the treatment of high blood pressure, heart failure or vascular disorders associated with diabetes and renal disorders, such as acute or chronic renal failure, in humans and animals. Such combinations can be used separately or in products which comprise a plurality of components.

The dose may vary within wide limits and has of course to be adapted to the individual circumstances in each individual case. In general, for oral administration, a daily dose of about 3 mg to about 3 g, preferably about 10 mg to about 1 g, for example

about 300 mg, per adult (70 kg), divided into preferably 1-3 individual doses which may, for example, be of equal size, may be appropriate, although the upper limit specified may also be exceeded if this should be found to be appropriate; typically, children receive a lower dose according to their age and body weight.

Another object of the invention is a method of delivering a compound of formula (I), or preferably of formula (IA), to a host, comprising administering to a host an effective amount of a compound of formula (I), or preferably of formula (IA).

A further object of the invention is the use of the a compound of formula (I), or preferably of formula (IA), for the manufacture of a medicament useful in the of inhibition of the neutral endopeptidase EC.3.4.24.11.

EXAMPLES

The examples which follow illustrate the present invention. All temperatures are reported in degrees Celsius, pressures in mbar. Unless stated otherwise, the reactions take place at room temperature. The abbreviation “Rf = xx (A)” means, for example, that the Rf value xx is obtained in the solvent system A. The ratio of the solvents relative to one another is always reported in parts by volume. Chemical names of end products and intermediates were obtained with the aid of the program AutoNom 2000 (Automatic Nomenclature).

HPLC gradient on X-Terra RP18 (5 μm); column: 4.6 x 50 mm; T = 50°C;
Detection: UV @ 220nm:
95% H_2O*/15% CH_3CN* to 5% H_2O*/95% CH_3CN* in 0.8 minutes + 8.7 minutes (1.2 ml/min); *: containing 0.1% formic acid

The following abbreviations are used:

AcOH	acetic acid
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
CH_3CN	acetonitrile

Cy	cyclohexane
DCC	dicyclohexylcarbodiimide
DIBAL	diisobutylaluminium hydride
DMF	N,N-dimethylformamide
EDC•HCl	N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride [25952-53-8]
Et_3N	triethylamine
Et_2O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HBr	hydrobromic acid
HCl	hydrochloric acid
H_2O	water
K_2CO_3	potassium carbonate
MeI	methyl iodide
MeOH	methanol
min	minute(s)
m.p.	melting point (temperature)
N_2	nitrogen
Na_2CO_3	sodium carbonate
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulphate
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4Br	ammonium bromide
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium [51364-51-3]
$Pd(OAc)_2$	palladium acetate
$P(tert\text{-}Bu)_3$	tri-tert-butyl phosphine
$P(o\text{-}tolyl)_3$	tri-o-tolyl-phosphine
Ra/Ni	Raney-nickel

Rf	ratio of distance which a substance travels to distance of the eluent front from the start point in thin layer chromatography
Rt	retention time of a substance in HPLC (in minutes)
RT	room temperature (23°C)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
WSC•HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride [25952-53-8]

Example 1

1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid (3-phenyl-propyl)-amide

1.0 mmol of thioacetic acid S-{(S)-2-methyl-1-[1-(3-phenyl-propylcarbamoyl)-cyclopentylcarbamoyl]-propyl} ester is dissolved under N_2 atmosphere in 15 ml of EtOH, with gentle heating. The mixture is cooled to 0°C and 3 ml of 1N NaOH is added. The reaction is stirred under N_2 for 4 h at RT. After this time the pH is taken to 2-3 with 10% HCl. The solvent is concentrated by evaporation and the residue partitioned between H_2O (5 ml) and CH_2Cl_2 (5 ml). The organic layer is collected, dried with Na_2SO_4 and the solvent is evaporated under reduced pressure. The obtained solid is triturated with petroleum ether to afford the title compound as a white solid. Rf = 0.30 (Cy-EtOAc 7:3); Rt = 6.22.

The starting material(s) is(are) prepared as follows :

a) Thioacetic acid S-{(S)-2-methyl-1-[1-(3-phenyl-propylcarbamoyl)-cyclopentyl-carbamoyl]-propyl} ester

A suspension of 1.0 mmol of 1-((R)-2-bromo-3-methyl-butyrylamino)-cyclopentane-carboxylic acid (3-phenyl-propyl)-amide and 1.5 mmol of potassium thioacetate in 7 ml of DMF is stirred at room temperature for 48 h. The solvent is concentrated by evaporation and the residue is dissolved in 15 ml of H_2O and extracted first with ether (10 ml) and then with EtOAc (10 ml). The combined organic layers are dried with Na_2SO_4 and the solvent is evaporated under reduced pressure. The residue is purified by Varian Mega Bond Elut (SI), eluting with Cy-EtOAc 9:1 → 7:3 to afford the

title compound as a white solid (after triturating with ether). Rf = 0.33 (Cy-EtOAc 1:1); Rt = 6.29.

b) 1-((R)-2-Bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid (3-phenyl-propyl)-amide

A solution of 1.0 mmol of 1-amino-cyclopentanecarboxylic acid (3-phenyl-propyl)-amide, 1.0 mmol of (R)-2-bromo-3-methyl-butyric acid [76792-22-8] and 1.1 mmol of DMAP in 5 ml of CH_2Cl_2 is cooled to 0°C. 1.1 mmol of WSC•HCl is added and the reaction mixture is stirred at RT for 24 h. After this time, the mixture is partitioned between H_2O (2 x 10 ml) and CH_2Cl_2. The organic layer is dried with Na_2SO_4 and the solvent is evaporated under reduced pressure. The residue is purified by Varian Mega Bond Elut (SI) eluting with Cy-EtOAc 95:5 to afford the title compound as a white solid. Rf = 0.40 (Cy-EtOAc 1:1); Rt = 6.27.

c) 1-Amino-cyclopentanecarboxylic acid (3-phenyl-propyl)-amide

1.0 mmol of [1-(3-phenyl-propylcarbamoyl)-cyclopentyl]-carbamic acid tert-butyl ester is dissolved in 6 ml of a solution of CH_2Cl_2/TFA 1:1. The reaction mixture is stirred at RT for 15 h. The solvent is evaporated under reduced pressure to afford the title compound as a yellow oil. Rf = 0.30 (CH_2Cl_2-MeOH 1:1); Rt = 2.82.

d) [1-(3-Phenyl-propylcarbamoyl)-cyclopentyl]-carbamic acid tert-butyl ester

A solution of 1.0 mmol of 3-phenyl-1-propylamine [2038-57-5], 1..0 mmol of 1-tert-butoxycarbonylamino-cyclopentanecarboxylic acid [35264-09-6] and 1.1 mmol of DMAP in 5 ml of CH_2Cl_2 is cooled to 0°C. 1.1 mmol of WSC•HCl is added and the reaction mixture is stirred at RT for 48 h. After this time, the mixture is partitioned between H_2O (2 x 10 ml) and CH_2Cl_2. The organic layer is dried with Na_2SO_4 and the solvent is evaporated under reduced pressure. The residue is purified by Biotage Flash Chromatography (SI, 40+M) eluting with Cy-EtOAc 8:2 to afford the title compound as a white solid. Rf = 0.42 (Cy-EtOAc 1:1); Rt = 6.52.

The following compounds are prepared in an analogous manner to the process described in Example 1:

2 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(4-methoxy-phenyl)-propyl]-amide

using 3-(4-methoxy-phenyl)-propylamine [36397-23-6] instead of 3-phenyl-1-propylamine in step d. Off-white solid; Rf = 0.38 (Cy-EtOAc 1:1); Rt = 6.13.

11 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(4-fluoro-phenyl)-propyl]-amide

using 3-(4-fluoro-phenyl)-propylamine [101488-65-7] instead of 3-phenyl-1-propylamine in step d. The title compound is identified based on the Rf value.

12 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(4-chloro-phenyl)-propyl]-amide

using 3-(4-chloro-phenyl)-propylamine [18655-50-0] instead of 3-phenyl-1-propylamine in step d. The title compound is identified based on the Rf value.

5 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [2-methoxy-3-(4-methoxy-phenyl)-propyl]-amide

using 1-amino-3-(4-methoxy-phenyl)-propan-2-ol hydrochloride instead of 3-phenyl-1-propylamine in step d. White solid; Rf = 0.29 (Cy-EtOAc 1:1); Rt = 5.95.

The starting material(s) is(are) prepared as follows :

a) 1-Amino-3-(4-methoxy-phenyl)-propan-2-ol hydrochloride

A mixture of 1.0 mmol of 1-(3-azido-2-methoxy-propyl)-4-methoxy-benzene and 18 mg of Pd/C in 5 ml of MeOH is hydrogenated at 30 psi for 4 h. The catalyst is filtered off and the filtrate is evaporated. The residue is dissolved in EtOAc and HCl/EtOAc is added. The solvent is evaporated under reduced pressure and the residue is tritured with Et_2O and filtred. The title compound is obtained as white solid. Rf = 0.52 (BuOH-AcOH-H_2O = 3:1:1); Rt = 1.94.

b) 1-(3-Azido-2-methoxy-propyl)-4-methoxy-benzene

2.1 mol of NaH (60% dispersion in oil) is added portionwise to a solution of 1.0 mol of 1-azido-3-(4-methoxy-phenyl)-propan-2-ol [845910-13-6] in 7 ml of dry DMF.The mixture is stirred at RT for 2 h. 2.1 mol of MeI in 2 ml of dry DMF is added dropwise.

The reaction is stirred at RT overnight. The solvent is evaporated; brine is added and the mixture is extracted with EtOAc (3X). The combined organic layers are dried with Na_2SO_4 and the solvent is evaporated under reduced pressure. The residue is purified by by flash chromatography (SiO_2 60F) to afford the title compound as a yellow oil. Rf = 0.50 (EtOAc-petroleum ether = 20:80); Rt = 5.93.

6 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid heptylamide

using heptylamine [111-68-2] instead of 3-phenyl-1-propylamine in step d. White solid; Rf = 0.22 (Cy-EtOAc 7:3); Rt = 6.74.

Example 3

1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(2-methyl-benzooxazol-6-yl)-propyl]-amide

1.0 mmol of thioacetic acid S-((S)-2-methyl-1-{1-[3-(2-methyl-benzooxazol-6-yl)-propylcarbamoyl]-cyclopentylcarbamoyl}-propyl) ester is dissolved under N_2 atmosphere in 10 ml of degassed ethanol. The mixture is treated with 3.0 ml of 1N NaOH. The reaction is stirred under N_2 at RT for 3 h. The mixture is cooled to 0°C and the pH is taken to 5-6 with 10% HCl. The solvent is evaporated under reduced pressure and the residue is partitioned between H_2O and CH_2Cl_2. The organic layer is collected,dried with Na_2SO_4 and the solvent evaporated under reduced pressure. The obtained solid is triturated with petroleum ether to afford the title compound as a white solid. Rt = 5.56.

The starting material(s) is(are) prepared as follows :

a) Thioacetic acid S-((S)-2-methyl-1-{1-[3-(2-methyl-benzooxazol-6-yl)-propylcarbamoyl]-cyclopentylcarbamoyl}-propyl) ester

150 mmol of potassium salt of thioacetic acid is added to a supension of 1.0 mmol of 1-((S)-2-bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(2-methyl-benzooxazol-6-yl)-propyl]-amide in 10 ml DMF under nitrogen at 0°C. The reaction mixture is stirred for 30 min after which it is brought up to RT and stirred again for 48 h. The reaction solution is concentrated in under reduced pressure, partitioned

between Et_2O and water and extracted with EtOAc (3X). The combined organic layers are washed with $NaHCO_3$ and brine, dried with Na_2SO_4 and evaporated under reduced pressure. The crude product is purified by Varian Mega Bond Elut (Si) eluting with petroleum ether/EtOAc from initial 2:8 to a mixture of 8:2 to afford the title compound as colorless oil. Rf = 0.53 (EtOAc); Rt = 5.60.

b) 1-((S)-2-Bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(2-methyl-benzooxazol-6-yl)-propyl]-amide

A solution of 0.66 mmol of 1-((S)-2-bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid methyl ester [248263-14-1], 1.0 mmol of 3-(2-methyl-benzooxazol-6-yl)-propylamine hydrochloride and 1.3 mmol of triethylamine in 5 ml of toluene under nitrogen at 0°C is treated with 1.3 mmol of trimethylaluminum (2M in toluene). The mixture is stirred for 1 h ar RT, the for 2 h at 60°C. The reaction mixture is poured onto a mixture of 1N NaOH and ice and extracted with EtOAc (1X) and CH_2Cl_2 (4X). The combined organic layers are dried with Na_2SO_4 and evaporated under reduced pressure. The title compound is obtained from the residue by flash chromatography (SiO_2 60F) as a white solid. Rf = 0.47 (EtOAc); Rt = 5.69.

c) 3-(2-Methyl-benzooxazol-6-yl)-propylamine hydrochloride

1.0 mmol of 3-(2-methyl-benzooxazol-6-yl)-acrylonitrile is taken up in 45 ml of EtOH and 5 ml of 30% NH_3 solution and subjected to hydrogenation at 35 psi for 2 h using 35 mg of 30%w/w Ra/Ni. The mixture is filtered through a short plug of Hyflow and the filtrate is evaporated. The residue is treated repeatedly with a mixture of CH_2Cl_2 and EtOH and evaporated to remove residual water. The crude compound is dissolved in a small amount of EtOAc and HCl/EtOAc is added. The solvent is removed by evaporation and the residue is tritured with Et_2O and filtred. The resulting white solid is washed with CH_2Cl_2 and diethyl ether and dried in vacuo. Rf = 0.43 (CH_2Cl_2-MeOH-25%NH_3 80:20:2); Rt = 1.08.

d) 3-(2-Methyl-benzooxazol-6-yl)-acrylonitrile

A mixture of 1.0 mmol of 6-bromo-2-methyl-benzooxazole [151230-42-1], 2 mmol of acrylonitrile, 1.0 mmol of sodium acetate, 0.1 mmol of $Pd(OAc)_2$ and 0.2 mmol of $P(o\text{-}tolyl)_3$ in 3 ml of DMF under N_2 atmosphere is treated at 150°C for 1h in the

microwave. The reaction is filtered through a short plug of Hyflow. The solvent of the filtarate is concentrated by evaporation. The title compound is obtained from the residue by chromatography on Varian Mega Bond Elut (Si) eluting with EtOAc to a mixture of petroleum ether/EtOAc 10:1 to afford the title compound as a mixture of cis and trans geometric isomers. Rf = 0.15 (CH_2Cl_2-MeOH 100:2); Rt = 4.48.

The following compounds are prepared in an analogous manner to the process described in Example 3:

7 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid (5-ethyl-[1,3,4]thiadiazol-2-yl)-amide

using 5-ethyl-[1,3,4]thiadiazol-2-ylamine [14068-53-2] instead of 3-(2-methyl-benzo-oxazol-6-yl)-propylamine in step b. White solid; Rf = 0.53 (petroleum ether-EtOAc 60:40); Rt = 3.24.

8 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [4-(3-methoxy-benzyl)-[1,3,5]triazin-2-yl]-amide

using 4-(3-methoxy-benzyl)-[1,3,5]triazin-2-ylamine instead of 3-phenyl-1-propyl-amine in step b. The title compound is identified based on the Rf value.

The starting material(s) is(are) prepared as follows :

a) 4-(3-Methoxy-benzyl)-[1,3,5]triazin-2-ylamine

A mixture of 1.0 mmol of N-formylguanidine [4471-51-6] and 2 mmol of (3-methoxy-phenyl)-acetonitrile [104-47-2] is heated to 200°C for 6 h. The reaction mixture is cooled to RT, poured in H_2O and extracted with EtOAc. The organic layer is dried with Na_2SO_4 and the solvent is concentrated by evaporation. The residue is purified by by flash chromatography (SiO_2 60F) to afford the title compound as a brown solid. Rf = 0.57 (CH_2Cl_2-MeOH-25%NH_3 = 90:10:1).

9 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid (1H-pyrazol-4-yl)-amide

using 1H-pyrazol-4-ylamine [28466-26-4] instead of 3-phenyl-1-propylamine in step b. The title compound is identified based on the Rf value.

10 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid (1-ethyl-1H-pyrazol-4-yl)-amide

using 1-ethyl-1H-pyrazol-4-ylamine [876343-24-7] instead of 3-phenyl-1-propylamine in step b. The title compound is identified based on the Rf value.

13 1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(2-methyl-benzothiazol-5-yl)-propyl]-amide

using (E)-3-(2-methyl-benzothiazol-5-yl)-acrylonitrile [03983-98-8] instead of 3-(2-methyl-benzooxazol-6-yl)-acrylonitrile in step c. The title compound is identified based on the Rf value.

Example 4

1-((S)-2-Mercapto-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [2-hydroxy-3-(4-methoxy-phenyl)-propyl]-amide

The title compound is prepared in an analogous manner to the process described in Example 3 using thioacetic acid S-((S)-1-{1-[2-hydroxy-3-(4-methoxy-phenyl)-propyl-carbamoyl]-cyclopentylcarbamoyl}-2-methyl-propyl) ester instead of thioacetic acid S-((S)-2-methyl-1-{1-[3-(2-methyl-benzooxazol-6-yl)-propylcarbamoyl]-cyclopentyl-carbamoyl}-propyl) ester. White solid. Rf = 0.19 (petroleum ether-EtOAc 50:50).

The starting material(s) is(are) prepared as follows :

a) Thioacetic acid S-((S)-1-{1-[2-hydroxy-3-(4-methoxy-phenyl)-propylcarbamoyl]-cyclopentylcarbamoyl}-2-methyl-propyl) ester

The title compound is prepared in an analogous manner to the process described in Example 3a using 1-((S)-2-bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [2-hydroxy-3-(4-methoxy-phenyl)-propyl]-amide instead of 1-((S)-2-bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [3-(2-methyl-benzooxazol-6-yl)-propyl]-amide. The title compound is obtained from the residue by flash chromatography (SiO_2 60F) as a white solid. Rf = 0.23 (petroleum ether-EtOAc 40:60); Rt = 5.38.

b) 1-((S)-2-Bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [2-hydroxy-3-(4-methoxy-phenyl)-propyl]-amide

A solution of 1.0 mmol of 1-((S)-2-bromo-3-methyl-butyrylamino)-cyclopentane-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-3-(4-methoxy-phenyl)-propyl]-amide in 5 ml of THF is mixed with 2.0 mmol of tetrabutylammonium fluoride (1M solution in THF), and the solution is stirred at RT for 10 h. The reaction solution is then diluted with water and extracted with CH_2Cl_2 (2X). The combined organic phases are dried with Na_2SO_4 and evaporated under reduced pressure. The title compound is obtained from the residue by flash chromatography (SiO_2 60F) as a white solid. Rf = 0.23 (petroleum ether-EtOAc 40:60); Rt = 5.37.

c) 1-((S)-2-Bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-3-(4-methoxy-phenyl)-propyl]-amide

The title compound is prepared in an analogous manner to the process described in Example 1b using 2-(tert-butyl-dimethyl-silanyloxy)-3-(4-methoxy-phenyl)-propyl-amine instead of 1-amino-cyclopentanecarboxylic acid (3-phenyl-propyl)-amide and 1-((S)-2-bromo-3-methyl-butyrylamino)-cyclopentanecarboxylic acid. [248262-45-5] instead of (R)-2-bromo-3-methyl-butyric acid [76792-22-8]. The crude compound is triturated with hexanes to afford the title compound as a white solid. Rf = 0.80 (hexanes-EtOAc 50:50); Rt = 7.88.

d) 2-(tert-Butyl-dimethyl-silanyloxy)-3-(4-methoxy-phenyl)-propylamine

A mixture of 1.0 mmol of [2-azido-1-(4-methoxy-benzyl)-ethoxy]-tert-butyl-dimethyl-silane and 150 mg of Pd/C 10% in 5 ml of MeOH is hydrogenated at 30 psi for 1 h. The catalyst is filtered off and the filtrate is evaporated. The crude title compound is obtained from the residue as a coulorless oil. Rf = 0.25 (petroleum ether-EtOAc 70:30).

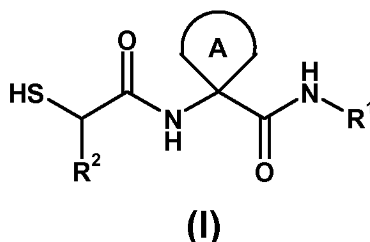
e) [2-Azido-1-(4-methoxy-benzyl)-ethoxy]-tert-butyl-dimethyl-silane

A solution of 1.0 mmol of 1-azido-3-(4-methoxy-phenyl)-propan-2-ol [845910-13-6] and 1.03 mmol of imidazole in 5 ml of DMF at 0°C is treated with 1.2 mmol of tert-butyl-dimethyl-silyl chloride, and the solution is stirred at RT for 10 h. The reaction solution is then poured on water and extracted with EtOAc (2X). The combined

organic phases are dried with Na_2SO_4 and evaporated under reduced pressure. The title compound is obtained from the residue by flash chromatography (SiO_2 60F) as a coulorless oil. Rf = 0.83 (petroleum ether-EtOAc 10:90).

Claims

1. Compound of the formula (I)



(I)

,

wherein

A is monocyclic C_{3-8}-cycloalkyl or monocyclic, saturated heterocyclyl, each of which are either unsubstituted or substituted by 1-3 C_{1-8}-alkoxy, C_{1-8}-alkyl, halogen, hydroxy or oxo;

R^1 is C_{1-8}-alkyl, aryl-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in C_{1-8}-alkyl, aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo;

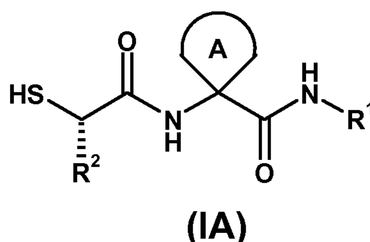
R^2 is C_{1-8}-alkoxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkyl, aryl, aryl-C_{1-8}-alkyl, halo-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, carboxy, halogen, hydroxy or oxo;

where the aryl or heterocyclyl moieties are unsubstituted or substituted;

where the thiol group is unprotected or protected with a protecting group R_a, which is hydrolyzed under physiological conditions to give the compound of formula (I);

a disulfide derivative derived from the compound of formula (I) or a salt of a compound of formula (I), preferably a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 corresponding to formula (IA)



(IA)

,

wherein A, R^1 and R^2 are each defined according to claim 1.

3. A compound according to claims 1 or 2, wherein the group R_a is an acyl or sulfonyl group, which is unsubstituted or substituted with one or more halogen, hydroxy, N,N-di-C_{1-8}-alkyl-amine, morpholine or C_{1-8}-alkoxy, or is N,N-di-C_1-C_4-alkylaminocarbonyl.

4. A compound according to claims 1 or 2, wherein heterocyclyl A denotes a 3-8 membered heterocyclic radical having one or more heteroatoms selected from the group comprising O, S or N.

5. A compound according to claims 1 or 2, wherein A is monocyclic C_{5-7}-cycloalkyl or monocyclic, saturated heterocyclyl having one heteroatom selected from the group comprising O, S or N; each of which are either unsubstituted or substituted by 1-3 C_{1-8}-alkoxy, C_{1-8}-alkyl, halogen, hydroxy or oxo.

6. A compound according to claim 5, wherein A is cyclohexyl, cyclopentyl or tetra-hydropyran-4-yl.

7. A compound according to claims 1 or 2, wherein R^1 is C_{1-8}-alkyl, aryl-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in C_{1-8}-alkyl, aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo.

8. A compound according to claim 7, wherein R^1 is aryl-C_{2-4}-alkyl, heterocyclyl or heterocyclyl-C_{2-4}-alkyl, wherein C_{2-4}-alkyl in aryl-C_{2-4}-alkyl or in heterocyclyl-C_{2-4}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo.

9. A compound according to claims 1 or 2, wherein R^2 is C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkyl, aryl or aryl-C_{1-8}-alkyl wherein C_{1-8}-alkyl in aryl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, carboxy, halogen, hydroxy or oxo.

10. A compound according to claim 9, wherein R^2 is benzyl, isopropyl, 2-methoxyethyl, methyl or propyl.

11. A compound according to claims 1 or 2, wherein
A is monocyclic, saturated heterocyclyl which is either unsubstituted or substituted by 1-3 C_{1-8}-alkoxy, C_{1-8}-alkyl, halogen, hydroxy or oxo;
R^1 is C_{1-8}-alkyl, aryl-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in C_{1-8}-alkyl, aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, halogen, hydroxy or oxo: and
R^2 is C_{1-8}-alkoxy-C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkoxy-C_{1-8}-alkyl, C_{1-8}-alkyl, aryl, aryl-C_{1-8}-alkyl, halo-C_{1-8}-alkyl, heterocyclyl or heterocyclyl-C_{1-8}-alkyl, wherein C_{1-8}-alkyl in aryl-C_{1-8}-alkyl or in heterocyclyl-C_{1-8}-alkyl is unsubstituted or substituted with 1-3 C_{1-8}-alkoxy, carboxy, halogen, hydroxy or oxo.

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, or a compound of formula (IA) or a pharmaceutically acceptable salt thereof according to claim 2, and a pharmaceutically acceptable carrier or diluents.

13. A method of delivering a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, or a compound of formula (IA) or a pharmaceutically acceptable salt thereof according to claim 2 to a host, comprising administering to a host an effective amount of a compound of formula (I), or preferably of formula (IA).

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, or a compound of formula (IA) or a pharmaceutically acceptable salt thereof according to claim 2 for the manufacture of a medicament useful in the inhibition of the neutral endopeptidase EC.3.4.24.11.

15. A compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 1, or a compound of formula (IA) or a pharmaceutically acceptable

salt thereof according to claim 2 useful in the inhibition of the neutral endopeptidase EC.3.4.24.11.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/055594

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C323/60 C07D231/40 C07D241/20 C07D263/56 C07D277/64
C07D285/135 A61K31/16 A61K31/165 A61K31/415 A61K31/423
A61K31/428 A61K31/433 A61K31/53 A61P3/04 A61P3/10

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)
C07C C07D 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, BEILSTEIN Data, WPI Data, 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.
A	US 5 432 186 A (C.A. FINK) 11 July 1995 (1995-07-11) column 1; claim 1 -----	1-15
A	US 6 660 756 B2 (S. CHALLENGER, ET AL.) 9 December 2003 (2003-12-09) columns 1-2 -----	1-15
	-/--	

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

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

"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	Date of mailing of the international search report
28 January 2009	03/02/2009
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer English, Russell

Form PCT/ISA/210 (second sheet) (April 2005)

International application No
PCT/EP2008/055594

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D.C. PRYDE, ET AL.: "Novel selective inhibitors of neutral endopeptidase for the treatment of female sexual arousal disorder. Synthesis and activity of functionalised glutaramides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 14, 15 June 2006 (2006-06-15), pages 4409-4424, XP002465622 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US ISSN: 0022-2623 table 3	1-15
A	D.C. PRYDE, ET AL.: "Novel selective inhibitors of neutral endopeptidase for the treatment of female sexual arousal disorder" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 15, no. 1, 6 October 2006 (2006-10-06), pages 142-159, XP002465623 ELSEVIER SCIENCE, OXFORD, GB ISSN: 0968-0896 table 4	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/055594

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5432186	A	11-07-1995	US	5506244 A	09-04-1996
			ZA	9409050 A	11-08-1995
US 6660756	B2	09-12-2003	US	2003105132 A1	05-06-2003
			US	2004106611 A1	03-06-2004