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Sulfonylaminocarboxylic acids

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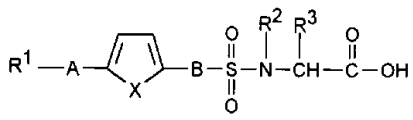
Abstract

Sulfonylaminocarboxylic acids

Compounds of the formula I



(I)

are suitable for the production of pharmaceuticals for the prophylaxis and therapy of disorders in the course of which an increased activity of matrix-degrading metalloproteinases is involved.

P/00/011 28/5/91
Regulation 3.2(2)

AUSTRALIA

Patents Act 1990

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title: SULFONYLAMINOCARBOXYLIC ACIDS

The following statement is a full description of this invention, including the best method of performing it known to us :-

Hoechst Aktiengesellschaft HOE 97/F 130 Dr.TH/St

Description

Sulfonylaminocarboxylic acids

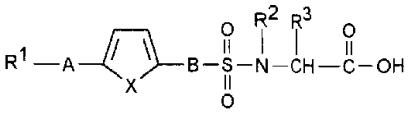
The invention relates to novel sulfonylaminocarboxylic acids, processes for their preparation and use thereof as pharmaceuticals.

The Applications EP 0 606 046, WO 95/35276 and WO 96/27583 describe arylsulfonamidohydroxamic acids and their action as matrix metalloproteinase inhibitors. Specific arylsulfonamidocarboxylic acids are used as intermediates for the preparation of thrombin inhibitors (EP 0 468 231) and aldose reductase inhibitors (EP 0 305 947). The Application EP 0 757 037 also describes the action of sulfonylaminocarboxylic acid derivatives as metalloproteinase inhibitors.

The arylsulfonyl group has furthermore proven useful as an effective protective group of the amino function of α-aminocarboxylic acids (R. Roemmele, H. Rapoport, J. Org. Chem. 53 (1988) 2367-2371).

In the attempt to find efficacious compounds for the treatment of connective tissue disorders, it has now been found that the sulfonylaminocarboxylic acids according to the invention are strong inhibitors of the matrix metalloproteinases. Particular value is placed here on the inhibition of stromelysin (matrix metalloproteinase 3) and of neutrophil collagenase (MMP-8), since both enzymes are substantially involved, as important constituents of the cartilaginous tissue, in the degradation of the proteoglycans (A. J. Fosang et al. J. Clin. Invest. 98 (1996) 2292-2299).

The invention therefore relates to the compound of the formula I



(I)

and/or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerable salt of the compound of the formula I, where

R^1 is 1. phenyl,

2. phenyl, which is mono- or disubstituted by

2.1. (C_1 -C_6)-alkyl, which is linear, cyclic or branched,

2.2. hydroxyl,

2.3. (C_1-C_6)-alkyl-C(O)-O-,

2.4. (C_1 -C_6)-alkyl-O-,

2.5. (C_1 -C_6)-alkyl-O-(C_1 -C_4)-alkyl-O-,

2.6. halogen,

2.7. -CF_3,

2.8. -CN,

2.9. -NO_2,

2.10. HO-C(O)-,

2.11. (C_1-C_6)-alkyl-O-C(O)-,

2.12. methylenedioxo,

2.13. R^4-(R^5)N-C(O)-,

2.14. R^4-(R^5)N-, or

3. a heteroaromatic from the following group 3.1. to 3.15., which is unsubstituted or substituted as described under 2.1 to 2.14,

3.1. pyrrole,

3.2. pyrazole,

3.3. imidazole,

3.4. triazole,

3.5. thiophene,

3.6. thiazole,

3.7. oxazole,

3.8. isoxazole,

3.9. pyridine,

3.10. pyrimidine,

3.11. indole,

3.12 benzothiophene,

3.13. benzimidazole,

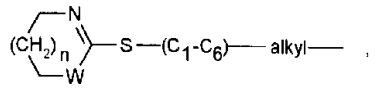
3.14. benzoxazole or

3.15. benzothiazole

R^2, R^4 and R^5 are identical or different and are

1. a hydrogen atom,
2. $(C_1\text{-}C_6)$-alkyl-,
3. HO-C(O)-$(C_1\text{-}C_6)$-alkyl-,
4. phenyl-$(CH_2)_n$-, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. or is substituted by -NH-C(O)-$(C_1\text{-}C_3)$-alkyl and n is the integer zero, 1 or 2, or
5. picolyl or
6. R^4 and R^5 together with the ring amino group form a 4- to 7-membered ring, in which one of the carbon atoms is optionally replaced by -O-, -S- or -NH- or two adjacent carbon atoms of the 4- to 7-membered ring are part of a benzyl radical,

R^3 is

1. a hydrogen atom,
2. $(C_1\text{-}C_{10})$-alkyl, in which alkyl is unsubstituted, and/or a hydrogen atom of the alkyl radical is replaced by -OH,
3. $(C_2\text{-}C_{10})$-alkenyl-, in which alkenyl is linear or branched,
4. R^2-O-$(C_1\text{-}C_6)$-alkyl-,
5. R^2-S(O)$_n$-$(C_1\text{-}C_6)$-alkyl-, where n has the abovementioned meaning,
6. R^2-S(O)(=NH)-$(C_1\text{-}C_6)$-alkyl-,
7. 

in which n is the integer zero, 1 or 2 and
W is a nitrogen, oxygen or sulfur atom,

8. phenyl-$(CH_2)_m$-, in which m is the integer zero, 1, 2, 3, 4, 5 or 6 and/or a hydrogen atom of the -$(CH_2)_m$- chain is replaced by -OH and phenyl is unsubstituted or mono- or disubstituted by

8.1 as described under 2.1.to 2.14.,

8.2 -O-$(CH_2)_m$-phenyl, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and m is the integer zero, 1, 2, 3, 4, 5 or 6,

8.3 -C(O)-$(CH_2)_m$-phenyl, in which phenyl is as defined under 8.2,

9. heteroaryl-$(CH_2)_m$-, in which heteroaryl is as defined under 3.1. to 3.15., m is as defined above and/or a hydrogen atom of the -$(CH_2)_m$-chain is replaced by -OH and heteroaryl is unsubstituted or mono- or disubstituted by

9.1 as described under 2.1 to 2.14 or

9.2 -CH(O),

9.3 -SO_2-phenyl, in which phenyl is unsubstituted or is as defined under 8.2 or 8.3,

9.4 -O-$(CH_2)_m$-phenyl,

10. -$(CH_2)_m$-P(O)(OH)-$(C_1$-$C_3)$-alkyl, in which m is as defined above, or

11. R^6-C(O)-$(C_1$-$C_6)$-alkyl-, in which

R^6 is 1. a hydrogen atom,

2. $(C_1$-$C_6)$-alkyl-, in which alkyl is linear, branched or cyclic,

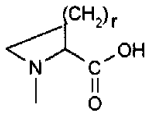
3. phenyl, in which phenyl is unsubstituted or substituted as described under 2.1 to 2.14,

4. heteroaryl, in which heteroaryl is as defined under 3.1. to 3.15. and/or is substituted as

described under 2.1 to 2.14 or is substituted by -(C_1-C_4)-alkyl-COOH,

5. HO-,
6. R^2O-, in which R^2 has the abovementioned meaning,
7. is R^4-(R^5)N-, in which R^4 and R^5 are as defined above,
8. heteroaryl-$(CH_2)_m$-NH-, in which heteroaryl is as defined under 3.1 to 3.15.and/or as described under 2.1. to 2.14 and m is as defined above,
9. R^4-(R^5)N-NH-, in which R^4 and R^5 are as defined above, or
10. HO-C(O)-CH(R^3)-NH-, in which R^3 is as defined above, or

R^2 and R^3 together form a ring having a ring carboxyl group, of the subformula II,



(II)

in which r is the integer zero, 1, 2 or 3 and/or one of the carbon atoms in the ring is replaced by -O-, -S- or -(R^7)N-, in which

R^7 is
1. a hydrogen atom,
2. (C_1-C_6)-alkyl,
3. phenyl, in which phenyl is unsubstituted or is substituted as described under 2.1 to 2.14,
4. benzyl, in which benzyl is unsubstituted or substituted as described under 2.1 to 2.14, or

5. $R^2N-C(=NH)-$, where R^2 has the abovementioned meaning,

and/or the carbon atoms in the ring of the subformula II are mono- or polysubstituted by (C_1-C_6)-alkyl-, phenyl-, phenyl-$(CH_2)_m$- or HO-,

A is a) a covalent bond,
b) -O-,
c) -CH=CH- or
d) -C≡C-,

B is a) $-(CH_2)_m-$, in which m has the abovementioned meaning,
b) $-O-(CH_2)_p$, in which p is an integer from 1 to 5, or
c) -CH=CH-, and

X is -CH=CH-, an oxygen atom or a sulfur atom.

A compound of the formula I is preferred where

R^1 is 1. phenyl or
2. phenyl which is monosubstituted by
2.1. (C_1-C_6)-alkyl-, in which alkyl is linear, cyclic or branched,
2.2. -OH,
2.3. (C_1-C_6)-alkyl-C(O)-O-,
2.4. (C_1-C_6)-alkyl-O-,
2.5. (C_1-C_6)-alkyl-O-(C_1-C_4)-alkyl-O-,
2.6. halogen,
2.7. $-CF_3$ or
2.8. $R^4-(R^5)N-$,

R^2, R^4 and R^5 are identical or different and are
1. a hydrogen atom or
2. (C_1-C_6)-alkyl-,

R^3 is 1. $(C_1\text{-}C_{10})$-alkyl-, in which alkyl is linear, branched or cyclic, and/or in which a hydrogen atom of the alkyl radical is replaced by -OH,

2. $R^{2'}$-$S(O)_n$-$(C_1\text{-}C_6)$-alkyl-, in which $R^{2'}$ is $(C_1\text{-}C_6)$-alkyl- or phenyl-$(CH_2)_n$- and n is the integer zero or 1,

3. phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and/or a hydrogen atom of the -$(CH_2)_m$- chain is replaced by -OH and m is the integer 1, 2, 3, 4 or 5,

4. heteroaryl-$(CH_2)_m$-, in which heteroaryl has the meaning mentioned under 3.3, 3.5, 3.6, 3.9 or 3.11 and/or is substituted as described under 2.1. to 2.14. and/or a hydrogen atom of the -$(CH_2)_m$-chain is replaced by -OH and m is the integer 1, 2, 3 or 4, or

5. R^6-C(O)-$(C_1\text{-}C_6)$-alkyl-, in which

R^6 is 1. -OH,

2. R^2O-, in which R^2 is defined as above,

3. R^4-(R^5)N-, in which R^4 and R^5 are as defined above, or

4. R^4 and R^5 together with the ring amino group form a 5- to 6-membered ring in which one of the carbon atoms is optionally replaced by -O-, -S- or -NH- or two adjacent carbon atoms of the 5- to 6-membered ring are part of a benzyl radical,

6. R^2 and R^3 together form a ring having a ring carboxyl group, of the subformula II, in which n is the integer 1 or 2 and/or one of the carbon atoms in the ring is replaced by -O- or -(R^7)N-, and

R^7 is 1. a hydrogen atom,

2. $(C_1$-$C_6)$-alkyl,

3. phenyl, in which phenyl is unsubstituted or substituted as described under 2.1 to 2.14,

4. benzyl, in which benzyl is unsubstituted or substituted as described under 2.1 to 2.14., or

5. R^2N-C(=NH)-, in which R^2 is as defined above,

and/or the carbon atoms in the ring of the subformula II are monosubstituted by phenyl or -OH,

A is a) a covalent bond or

b) -O-,

B is a) $-(CH_2)_m$-, in which m is the integer zero, 1 or 2, or

b) $-O-(CH_2)_p$, in which p is an integer 1 or 2, and

X is -CH=CH-.

A compound of the formula I is particularly preferred where

R^1 is 1. phenyl or

2. phenyl which is monosubstituted by

2.1. halogen, in particular chlorine or fluorine or

2.2. R^4-(R^5)N-, where R^4 and R^5 are identical or different and are

2.2.1. $(C_1$ -$C_3)$-alkyl or

2.2.2. R^4 and R^5 together with the ring amino group form a 5- to 6-membered ring, one of the carbon atoms optionally being replaced by -O- or -N-,

R^2 is a hydrogen atom,

R^3 is 1. heteroaryl-$(CH_2)_m$ -, in which heteroaryl is as defined under 3.5, 3.11 or 3.13 and the heteroaryl is unsubstituted or monosubstituted as described under 2.1 to 2.14 and m is the integer 1 or 2, or

2. R^6-C(O)-(C_2-C_3)-alkyl, in which

R^6 is 1. -OH,

2. R^2-O-, in which R^2 is as defined above or

3. R^4-(R^5)N-, in which R^4 and R^5 are identical or different and are

3.1. a hydrogen atom,

3.2. (C_1 -C_3)-alkyl-,

3.3. phenyl-(CH_2)-, where phenyl is unsubstituted or mono- or disubstituted as described under 2.1 to 2.14 and n is the integer zero, 1 or 2,

3.4. R^4 and R^5 together with the ring amino group form a 5- to 6-membered ring, where one of the carbon atoms is optionally replaced by -O- or -NH-, or form an indoline radical, or

3.5. HO-C(O)-CH(R^3)-NH-, in which R^3 is as defined above,

A is a covalent bond,

B is -(CH_2)$_o$-, in which o is zero and

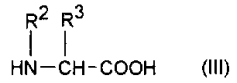
X is -CH=CH-.

The expression "R^4 and R^5 together with the ring amino group form a 4- to 7-membered ring and/or one of the carbon atoms is replaced by -O-, -S- or -NH-" is understood as meaning radicals which are derived, for example, from azetidine, pyrrole, pyrroline, pyridine, azepine, piperidine, oxazole, isoxazole, imidazole, indoline, pyrazole, thiazole, isothiazole, diazepine, thiomorpholine, pyrimidine or pyrazine. The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine. The term "alkyl" or "alkenyl" is understood as meaning hydrocarbon radicals whose carbon chains are straight-chain or branched. Cyclic alkyl radicals are, for example, 3- to 6-membered monocyclic systems such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Furthermore, the alkenyl radicals can also contain several double bonds.

The starting substances of the chemical reactions are known or can easily be prepared by methods known from the literature.

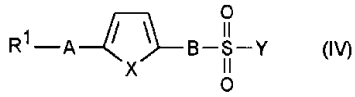
The invention further relates to a process for the preparation of the compound of the formula I and/or a stereoisomeric form of the compound of the formula I and/or of a physiologically tolerable salt of the compound of the formula I, which comprises

a) reacting an aminocarboxylic acid of the formula III,



(III)

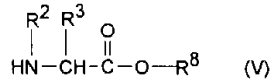
in which R^2 and R^3 are as defined in formula I, with a sulfonic acid derivative of the formula IV,



(IV)

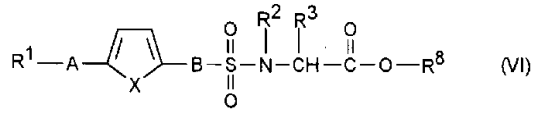
in which R^1, A and B are as defined in formula I and Y is a halogen atom, imidazolyl or $-OR^8$, in which R^8 is a hydrogen atom, (C_1-C_6)-alkyl, phenyl or benzyl, if appropriate substituted,
in the presence of a base or optionally of a dehydrating agent to give a compound of the formula I, or

b) reacting an aminocarboxylic acid ester of the formula V,



(V)

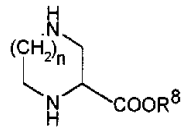
in which R^2, R^3 and R^8 have the abovementioned meaning,
with a sulfonic acid derivative of the formula IV under the abovementioned conditions to give a compound of the formula VI



(VI)

and converting the compound of the formula VI into a compound of the formula I with removal of the radical R^8, preferably in the presence of a base or acid, or

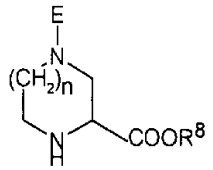
c) reacting the compound of the formula VII,



(VII)

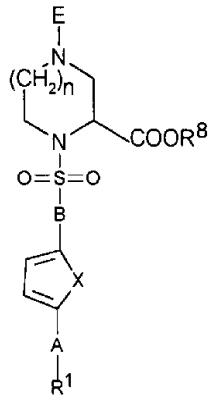
where n is the integer zero, 1 or 2,

with the aid of a protective group E to give a compound of the formula VIII,



(VIII)

converting the compound of the formula VIII with a sulfonic acid derivative of the formula IV under the abovementioned conditions into a compound of the formula IX



(IX)

and then converting the compound of the formula IX into the compound of the formula I with removal of the protective group E and of the radical R^8 with the aid of suitable cleavage reagents.

d) resolving a compound of the formula I, which on account of its chemical structure occurs in enantiomeric forms, prepared by process a), b) or c) into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups, or

e) isolating the compound of the formula I prepared by process a), b), c) or d) either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts.

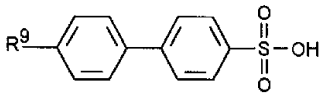
Suitable protective groups E used for this purpose are preferably the N-protective groups customary in peptide chemistry, for example protective groups of the urethane type, benzyloxycarbonyl (Z), t-butoxycarbonyl (Boc), 9-fluorenyloxycarbonyl (Fmoc), allyloxycarbonyl (Aloc) or of the acid amide type, in particular formyl, acetyl or trifluoroacetyl, and of the alkyl type, for example benzyl.

Compounds of the formula III employed in which R^2 is a hydrogen atom and R^3 is the characteristic radical of a natural α-amino acid are preferably glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid and aspartic acid. In the case of natural, but also unnatural, α-amino acids which have a functional group such as amino, hydroxyl, carboxyl, mercapto, guanidyl, imidazolyl or indolyl in the side chain R^3, this group can also be protected.

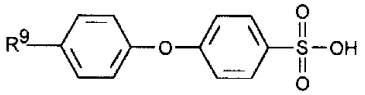
In the case of an imidazole radical in R^3 the sulfonic acid derivative of the formula IV employed for the sulfonamide formation serves, for example, as a protective group of the imidazole nitrogen, which can be removed again, in particular in the presence of bases such as sodium hydroxide solution.

To prepare compounds of the formula I in which R^2 and R^3 together form a ring of the substructure II, starting substances of the formula III used are, for example, proline, 3- or 4-hydroxyproline, piperidine-2-carboxylic acid, piperazine-2-carboxylic acid and hexahydropyridazine-3-carboxylic acid, it being possible, in particular, for the nitrogen in the 4-position of the piperazine-2-carboxylic acid to be substituted by a protective group Z, for example benzyloxycarbonyl or tert-butyloxycarbonyl as described in process variant c) or by a radical R^7.

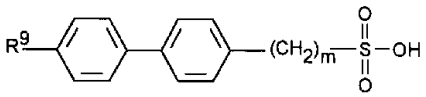
Starting materials used for the preparation of the sulfonic acid derivatives of the formula IV are preferably sulfonic acids or their salts of the formula X, for example



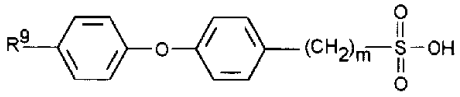
Xa



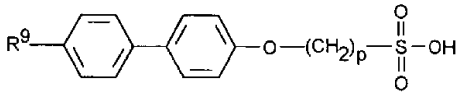
Xb



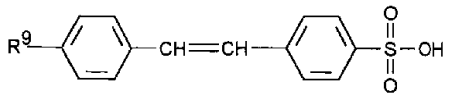
Xc



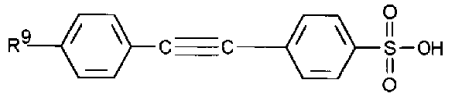
Xd



Xe



Xf



Xg

where R^9 is a radical described under 2.1. to 2.14.

To prepare the arylsulfonic acids of the formulae Xa and b, the sulfonation process using concentrated sulfuric acid, optionally in the presence of a catalyst, sulfur trioxide and its addition compounds or halosulfonic acids, such as chlorosulfonic acid, described in Houben-Weyl „Methoden der Organischen Chemie" [Methods of Organic Chemistry], Volume 9, pp. 450-546 is preferably used. Particularly in the case of the diphenyl ethers of the formula Xb, the use of concentrated sufluric acid and acetic anhydride as solvents (cf. C.M. Suter, J. Am. Chem. Soc. 53 (1931) 1114), or the reaction with excess chlorosulfonic acid (J.P. Bassin, R. Cremlyn and F. Swinbourne; Phosphorus, Sulfur and Silicon 72 (1992) 157) has proven suitable. Sulfonic acids according to the formula Xc, Xd or Xe can be prepaed in a known manner by reacting the appropriate arylalkyl halide with sulfites such as sodium sulfite or ammonium sulfite in aqueous or aqueous/alcoholic solution, it being possible to accelerate the reaction in the presence of tetraorganoammonium salts such as tetrabutylammonium chloride.

Sulfonic acid derivatives according to formula IV used are in particular the sulfonyl chlorides. For their preparation, the corresponding sulfonic acids, also in the form of their salts such as sodium, ammonium or pyridinium salts, are reacted in a known manner with phosphorus pentachloride or thionyl chloride without or in the presence of a solvnet such as phosphorus oxychloride or of an inert solvent such as methylene chloride, cyclohexane or chloroform, in general at reaction temperatures from 20°C up to the boiling point of the reaction medium used.

The reaction of the sulfonic acid derivatives of the formula IV with the amino acids of the formulae III, V or VII according to process variants a), b) or c) advantageously proceeds in the manner of the Schotten-Baumann reaction. Suitable bases for this purpose are particularly alkali metal hydroxides such as sodium hydroxide, but also alkali metal acetates, hydrogencarbonates, carbonates and amines. The reaction takes place in water or in a water-miscible or immiscible solvent such as tetrahydrofuran (THF), acetone, dioxane or acetonitrile, the reaction temperature in general being kept at from -10°C to 50°C. In the case in which the reaction is carried out in anhydrous medium, tetrahydrofuran or methylene chloride, acetonitrile or dioxane in the presence of a base, such as triethylamine, N-methylmorpholine, N-ethyl or diisopropylethylamine is particularly used, possibly in the presence of N,N-dimethylaminopyridine as a catalyst.

In another variant, the aminocarboxylic acids of the formula III, IV or VII can first be converted into their silylated form with the aid of a silylating agent such as bis-trimethylsilyltrifluoroacetamide (BSTFA) and they can then be reacted with sulfonic acid derivatives to give compounds of the formula I.

The physiologically tolerable salts of the compounds of the formula I capable of salt formation, including their stereoisomeric forms, are prepared in a manner known per se. With basic reagents such as hydroxides, carbonates, hydrogencarbonates, alcoholates and also ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine or triethanolamine or alternatively basic amino acids, for example lysine, ornithine or arginine, the carboxylic acids form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts. If the compounds of the formula I have basic groups, stable acid addition salts can also be prepared with strong acids. Those suitable for this purpose are both inorganic and organic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, benzenesulfonic, p-toluenesulfonic, 4-bromobenzenesulfonic, cyclohexylamidosulfonic, trifluormethylsulfonic, acetic, oxalic, tartaric, succinic or trifluoroacetic acid.

The invention also relates to pharmaceuticals comprising an efficacious amount of at least one compound of the formula I and/or of a physiologically tolerable salt of the compound of the formula I and/or an optionally stereoisomeric form of the compound of the formula I, together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

On account of the pharmacological properties, the compounds according to the invention are suitable for the prophylaxis and therapy of all those disorders in the course of which an increased activity of matrix-degrading metalloproteinases is involved. These include degenerative joint disorders such as osteoarthroses, spondyloses, chondrolysis after joint trauma or relatively long immobilization of the joint after meniscus or patella injuries or tears of the ligaments. Furthermore, these also include disorders of the connective tissue such as collagenoses, periodontal disorders, wound healing disorders and chronic disorders of the locomotory apparatus such as inflammatory, immunologically or metabolically related acute and chronic arthritides, arthropathies, myalgias and disorders of the bone metabolism. The compounds of the formula I are furthermore suitable for the treatment of ulceration, atherosclerosis and stenoses. The compounds of the formula I are furthermore suitable for the treatment of inflammations, carcinomatous disorders, formation of tumor metastases, cachexia, anorexia and septic shock. The pharmaceuticals according to the invention are in general administered orally or parenterally. Rectal or transdermal administration is also possible.

The invention also relates to a process for the production of a pharmaceutical, which comprises bringing at least one compound of the formula I into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, other suitable active compounds, additives or auxiliaries.

Suitable solid or pharmaceutical preparation forms are, for example, granules, powders, coated tablets, tablets, (micro)capsules, suppositories, syrups,

juices, suspensions, emulsions, drops or injectable solutions and also preparations with protracted release of active compound, in whose preparation customary auxiliaries, such as excipients, disintegrants, binders, coating agents, swelling agents, glidants or lubricants, flavorings, sweeteners and solubilizers are used. Frequently used auxiliaries which may be mentioned are magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, lactoprotein, gelatin, starch, cellulose and its derivatives, animal and vegetable oils such as fish liver oil, sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol.

The pharmaceutical preparations are preferably prepared and administered in dose units, each unit as active constituent containing a specific dose of the compound of the formula I according to the invention. In solid dose units such as tablets, capsules, coated tablets or suppositories, this dose can be up to approximately 1000 mg, but preferably approximately 50 to 300 mg, and in injection solutions in ampoule form up to approximately 300 mg, but preferably approximately 10 to 100 mg.

For the treatment of an adult patient weighing approximately 70 kg - depending on the efficacy of the compounds according to formula I, daily doses of approximately 20 mg to 1000 mg, preferably approximately 100 mg to 500 mg, of active compound are indicated. Under certain circumstances, however, higher or lower daily doses may be appropriate. The daily dose can be administered both by single administration in the form of an individual dose unit or else of several smaller dose units and by multiple administration of subdivided doses at specific intervals.

^{1}H-NMR spectra have been recorded on a 200 MHz apparatus from Varian, as a rule using tetramethylsilane (TMS) as an internal standard and at room temperature (RT). The solvents used are in each case indicated. As a rule, final products are determined by mass-spectroscopic methods (FAB-, ESI-MS). Temperature data in degrees Celsius, RT means room temperature (22-26°C). Abbreviations used are either explained or correspond to the customary conventions.

Example 1: N-(Phenoxybenzenesulfonyl)homoserine
(prepared accoding to process variant a)

10 g (54.9 mmol) of D,L-homoserine lactone are treated with ice-cooling with 50 ml of 1N NaOH and 50 ml of tetrahydrofuran (THF). 16.0 g (59.5 mmol) of phenoxybenzenesulfonyl chloride in 50 ml of THF are added dropwise at 5°C with stirring, after half of the addition the reaction mixture being treated with 7.1 g (54.9 mmol) of diisopropylethylamine. After stirring overnight, the mixture is adjusted to pH = 5.5 using 2N HCl and extracted several times with ethyl acetate. The combined organic phases are filtered, after drying over sodium sulfate, and evaporated under reduced pressure. Recrystallization from glacial acetic acid/petroleum ether affords the abovementioned compound.

Yield: 18.3 g (73% of theory) Melting point: 134°C

^{1}H-NMR (DMSO- d6): 1.6 - 1.85 (m, 2H); 3.2 - 3.45 (m, 3H); 3.75 - 3.95 (m, 1H); 7.0 - 8.1 (m, 9H)

Example 2: (2R)-1-(4-Chlorobiphenylsulfonyl)-4-cis-hydroxyproline
(prepared according to process variant a)

2 g (15.2 mmol) of D-cis-hydroxyproline are dissolved in dry acetonitrile and heated under reflux for 2 hours together with 12.1 ml (46.7 mmol, 3.1 equivalents) of BSTFA (bis-trimethylsilyltrifluoroacetamide). The mixture is then treated with 4.4 g (15.2 mmol) of 4-chlorobiphenylsulfonyl chloride in 15 ml of acetonitrile and is left under reflux for a further 4 hours. A thick, white precipitate of the O-silylated-N-sulfonated compound is formed. After cooling of the suspension and completion of the precipitation, this is separated off and well dried under reduced pressure. The yield of the reaction is quantitative.

For desilylation, 100 mg of the O-silylated compound are taken up in 10 ml of methanol (MeOH) and stirred at room temperature (RT) for 2 hours with 10 ml of 1N HCl with addition of 100 mg of KF. Filtration of the precipitate with

suction and drying under reduced pressure affords the abovementioned product.

Yield: 61 mg (84% of theory)

^{1}H-NMR (DMSO- d6): 1.8 - 2.2 (m, 2H); 3.15 (m, 1H); 3.3 (dd, 2H); 4.0 (m, 1H); 4.3 (dd, 1H); 7.6; 7.8 (2d, 4H); 7.9 (s, 4H)

Example 29: (R)-N-(4-Chlorobiphenylsulfonyl)tryptophan
(prepared according to process variant b)

29a) (R)-N-(4-Chlorobiphenylsulfonyl)tryptophan methyl ester

5.1 g (20 mmol) of D-tryptophan methyl ester hydrochloride are suspended in 50 ml of dry acetonitrile, treated with 2.0 g (20 mmol) of triethylamine and stirred at RT. After addition of 6.2 ml (24 mmol) of BSTFA, the mixture is stirred at 80°C for 2 hours, then 5.75 g (20 mmol) of 4-chlorobiphenylsulfonyl chloride in 50 ml of acetonitrile and a further 2.0 g of TEA are added dropwise and the mixture is kept at 80°C for 2 hours. After cooling to RT, 100 ml of 1N HCl are added to the reaction mixture with stirring, a crystalline precipitate being deposited. Recrystallization from methanol/water affords the abovementioned methyl ester.

Yield: 6.8 g (92% of theory) Melting point: 189°C

29 b) (R)-N-(4-Chlorobiphenylsulfonyl)tryptophan

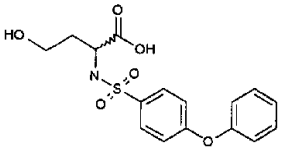
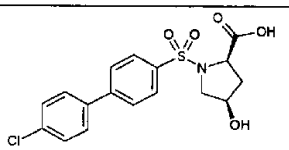
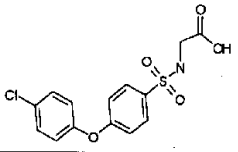
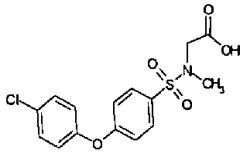
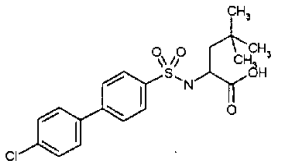
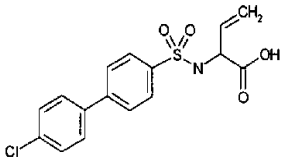
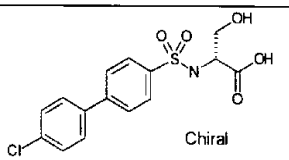
2.34 g (5 mmol) of the above methyl ester are dissolved in 30 ml of methanol and, after addition of 10 ml of 1N NaOH, stirred at 40°C for 6 hours. Adjustment of the solution to pH = 6 using 1N HCl affords the abovementioned carboxylic acid in crystalline form.

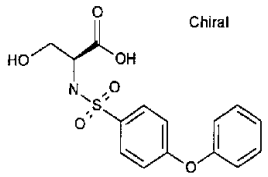
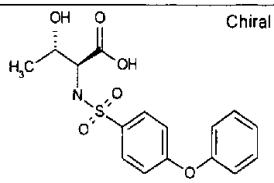
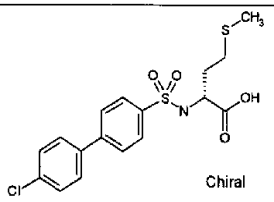
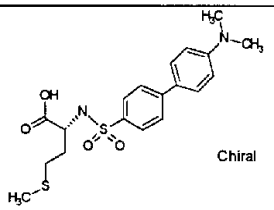
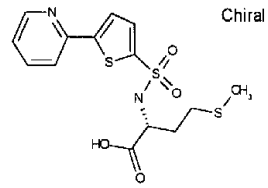
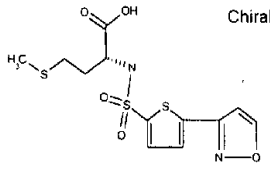
Yield: 1.8 g (81% of theory) Melting point: 138 °C to 140 °C

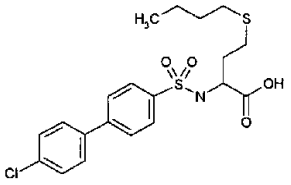
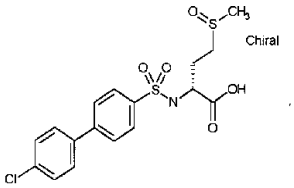
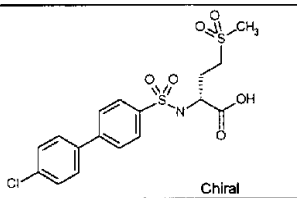
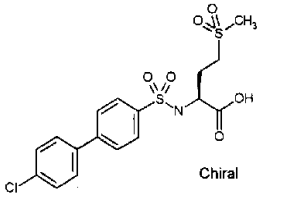
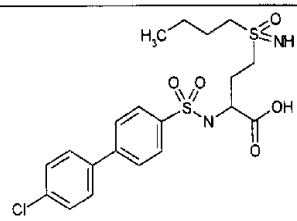
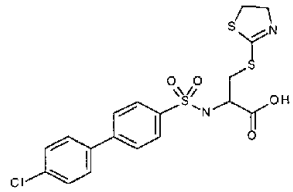
^{1}H-NMR (DMSO- d6): 2.8-2.92 (m,1H), 3.0-3.12 (m, 1H), 3.83-3.97 (m, 1H), 6.85- 7.8 (m, 13 H), 8.3 (d, 1H), 10.75 (s,1H), 12.4 (s, 1H)

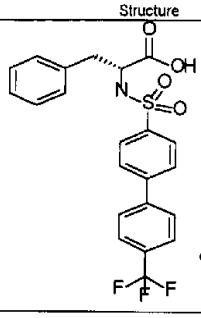
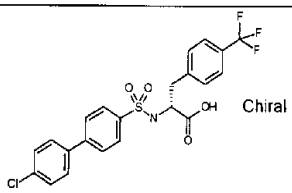
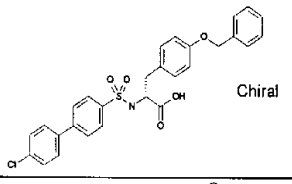
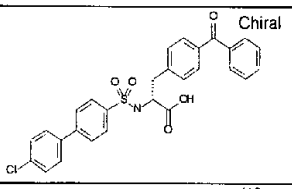
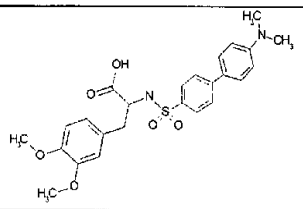
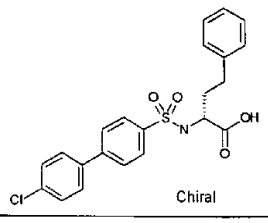
The examples mentioned in Table 1 which follows have been prepared analogously to Examples 1, 2 and 29.

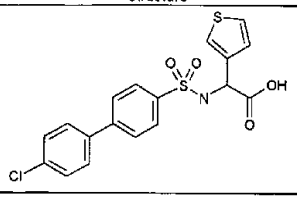
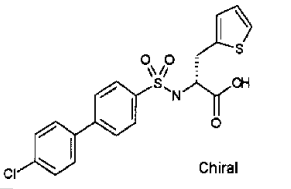
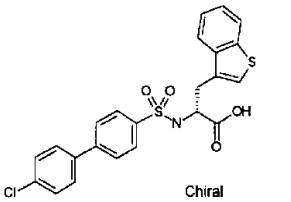
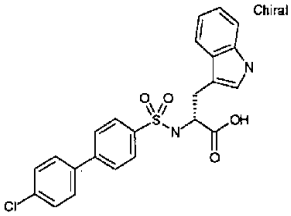
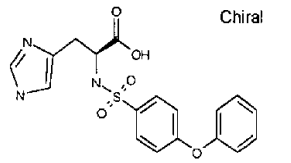
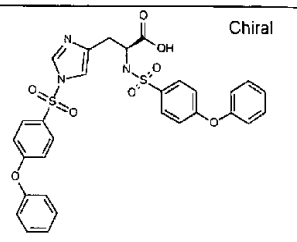
Table 1:

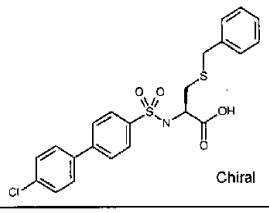
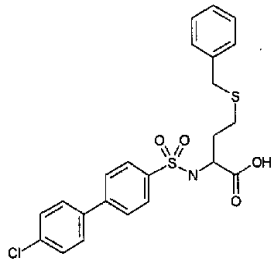
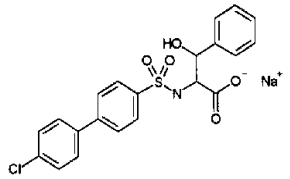
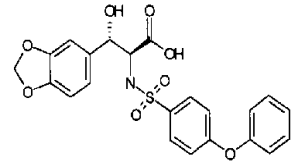
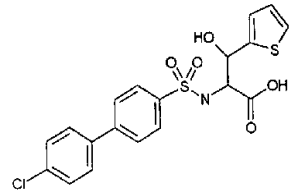
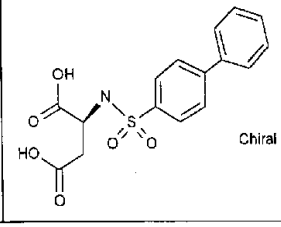
Example	Structure	Note	M.p. (°C)	MS (M+ H)
1		racemate	134	
2				382.1 (M-1)
3			162-164	
4			128-130	
5		racemate		396.1
6		racemate		352.1 (M-1)
7	 Chiral			356.1

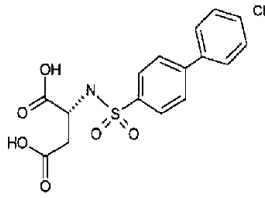
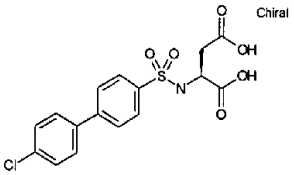
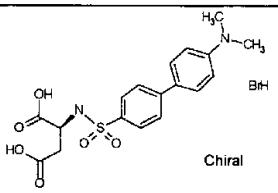
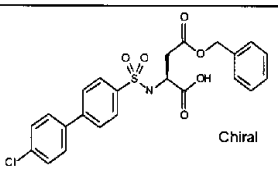
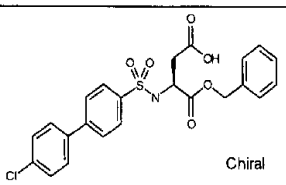
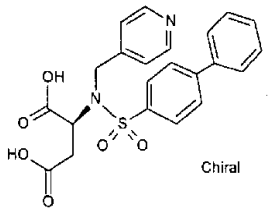
Example	Structure	Note	M.p. (°C)	MS (M+ H)
8	 Chiral		202-203	
9	 Chiral		96-98	
10	 Chiral			400.1(M-1)
11	 Chiral		180-186 (amorphous)	409.2
12	 Chiral		115-125 (amorphous)	373.1
13	 Chiral		70-76 (amorphous)	363.0

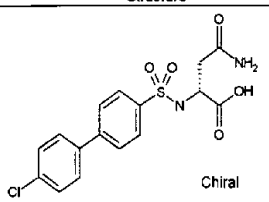
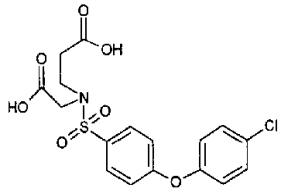
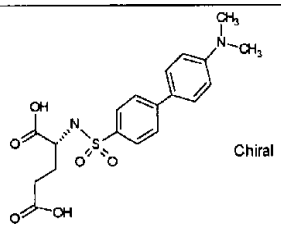
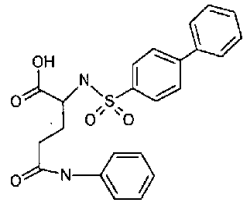
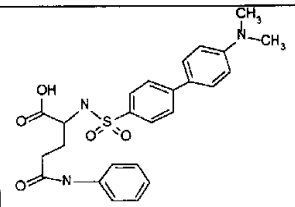
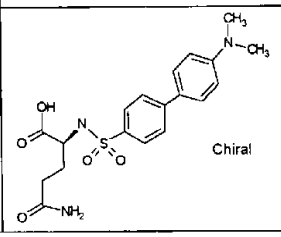
Example	Structure	Note	M.p. (°C)	MS (M+ H)
14		racemate		442.1
15		Chiral		416.1 (M-1)
16		Chiral		432.0 (M-1)
17		Chiral		432.0 (M-1)
18		racemate		473.1
19		racemate		457.0

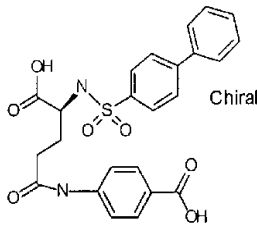
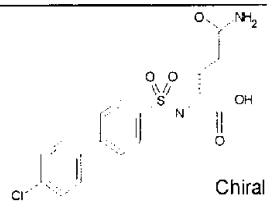
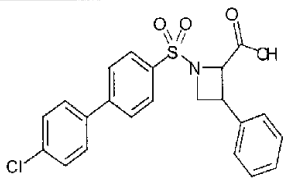
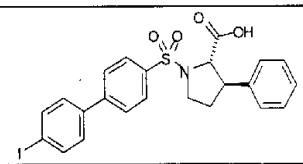
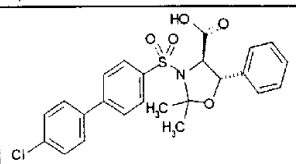
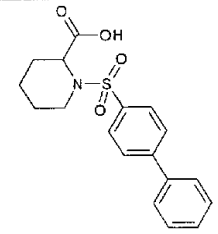
Example	Structure	Note	M.p. (°C)	MS (M+ H)
20	 Chiral		159-162	449.1
21	 Chiral			482.0 (M-1)
22	 Chiral			520.1 (M-1)
23	 Chiral			520.1
24		racemate	230.0 (amorphous)	485.3
25	 Chiral			430.1

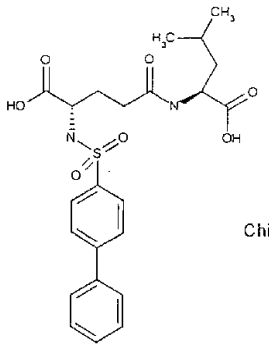
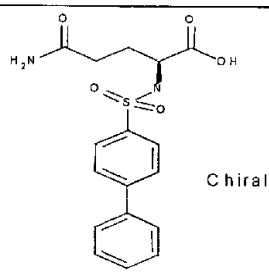
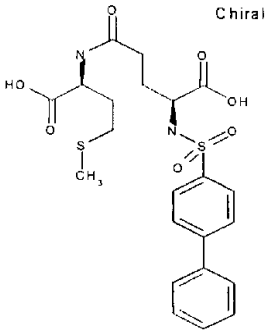
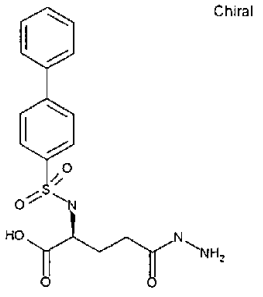
Example	Structure	Note	M.p. (°C)	MS (M+ H)
26		racemate		408.0
27	 Chiral		>200 (dec.)	
28	 Chiral			472.1
29	 Chiral			455.1(M-1)
30	 Chiral		183-185	
31	 Chiral		120-122	

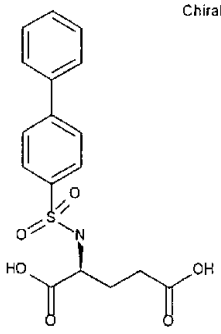
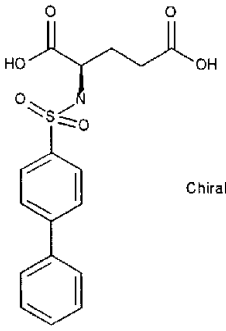
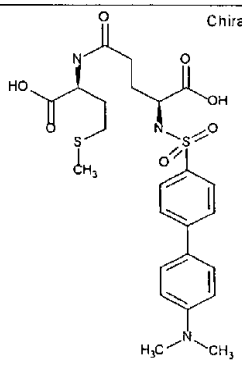
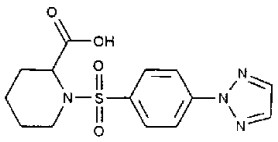
Example	Structure	Note	M.p. (°C)	MS (M+ H)
32	 Chiral			462.1 (M-1)
33		racemate		476.1
34		DL-threo-diastereomer mixture		454.1(M-1)
35		racemate	176	
36		diastereomer mixture		436.0 (M-1)
37	 Chiral	S isomer	186.7	348.1 (M-1)

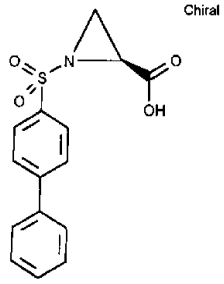
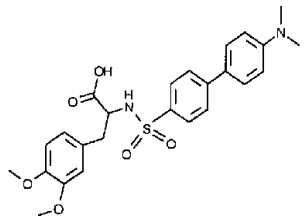
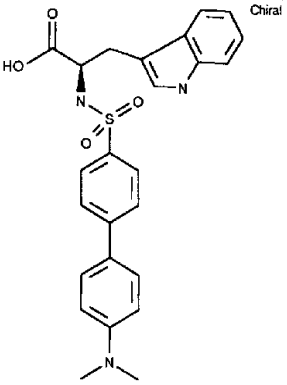
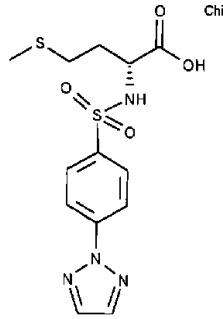
Example	Structure	Note	M.p. (°C)	MS (M+ H)
38	 Chiral	R isomer	>55 (amorphous)	350.1
39	 Chiral			384.0 (M-1)
40	 Chiral		121-127 (amorphous)	393.2
41	 Chiral			472.1
42	 Chiral			474.1
43	 Chiral		105	439.1 (M-1)

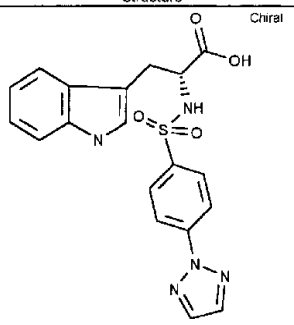
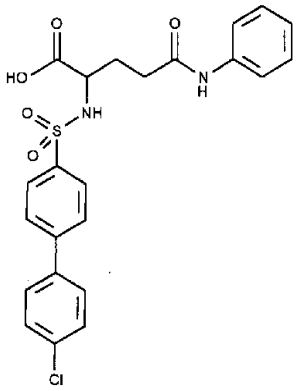
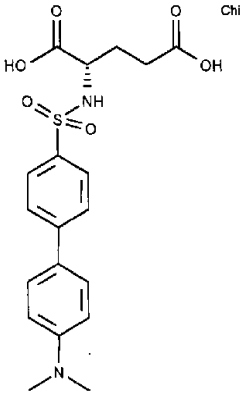
Example	Structure	Note	M.p. (°C)	MS (M+ H)
44	 Chiral			383.1
45			169-171	
46	 Chiral		165.0 (amorphous)	407.2 (M-1)
47		racemate	227-230	439.2
48		racemate	212-214	
49	 Chiral		213-215	406.2

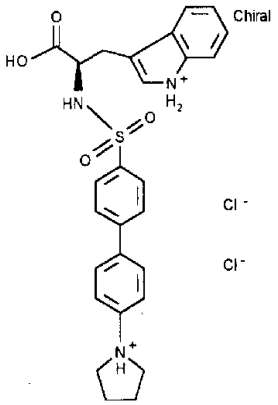
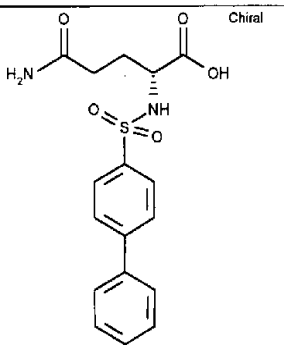
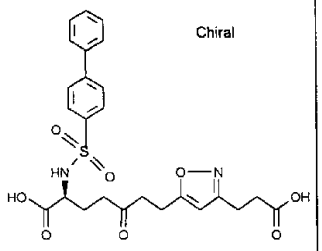
Example	Structure	Note	M.p. (°C)	MS (M+ H)
50	 Chiral		266.0	483.2
51	 Chiral			395.1 (M-1)
52		trans-diastereomer pair		428.1 (M-1)
53		(2S,3R) - isomer		442.2 (M-1)
54		D,L-threo-diastereomer pair		472.1 (M-1)
55		racemate	174.5-175.5	346.1

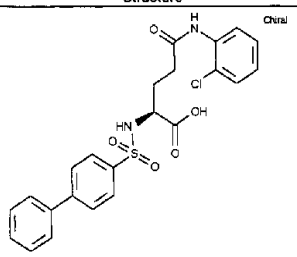
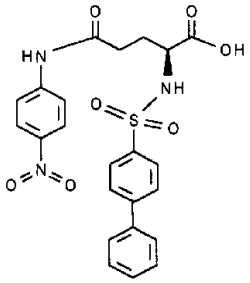
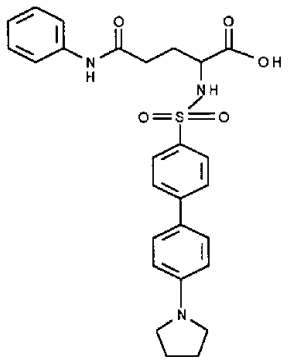
Example	Structure	Note	M.p. (°C)	MS (M+ H)
56	 Chiral	In each case S -isomer	93-95	477.2
57	 Chiral	S isomer	183.4	363.2
58	 Chiral	S isomer	159-161	495.2
59	 Chiral	S-isomer	205-207	378.2

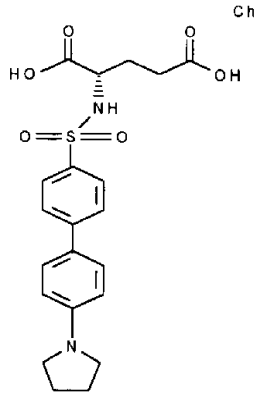
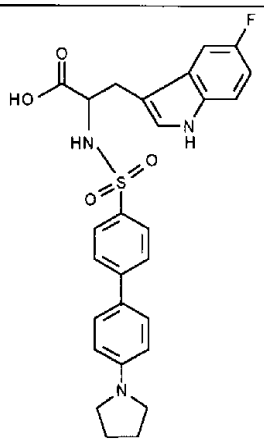
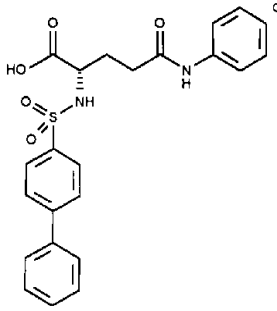
Example	Structure	Note	M.p. (°C)	MS (M+ H)
60	 Chiral	S isomer	145-146	362.1 (M-H)
61	 Chiral	R isomer	155-158	362.1 (M-H)
62	 Chiral	in each case S isomer	121	538.2
63		racemate	195-196	337.2

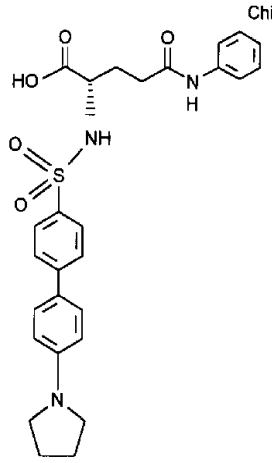
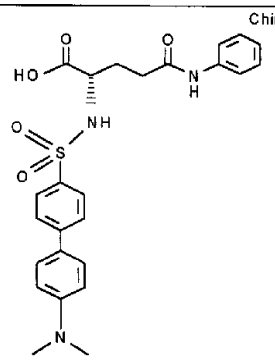
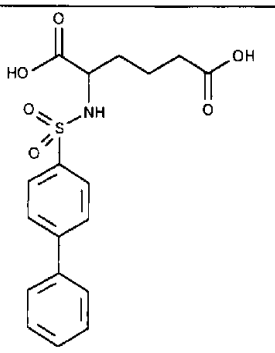
Example	Structure	Note	M.p. (°C)	MS (M+ H)
64	 Chiral	S isomer	138-139	304.1
65		racemate	> 230 (dec.)	485.3
66	 Chiral	R isomer	258-260	464.2
67	 Chiral	R isomer	155.5-156.5	357.1

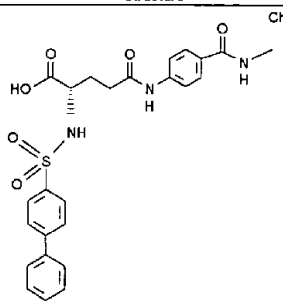
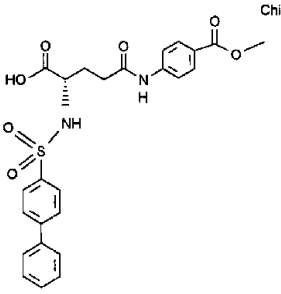
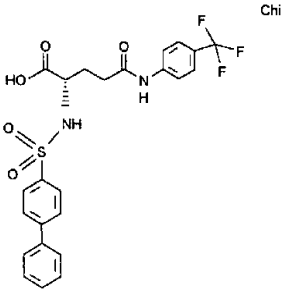
Example	Structure	Note	M.p. (°C)	MS (M+ H)
68	 Chiral	R isomer	131-134	412.1
69		racemate	238-239	473.1/475.1
70	 Chiral	S isomer	> 108 (dec.)	407.2

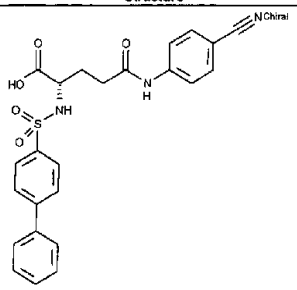
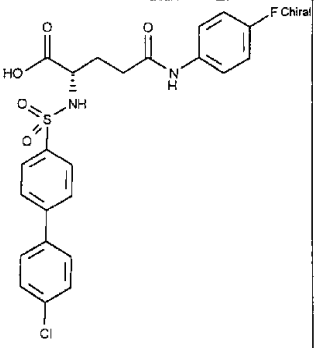
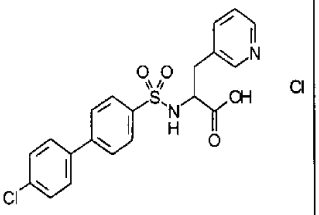
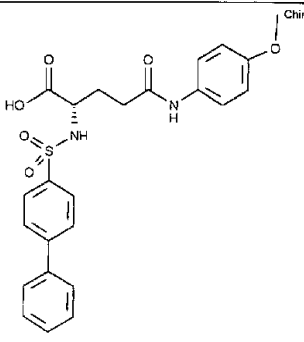
Example	Structure	Note	M.p. (°C)	MS (M+ H)
71		R isomer	> 145 (dec.)	490.3
72		R isomer	179.180.5	363.1
73		S isomer	181.5 - 182.5	516.3

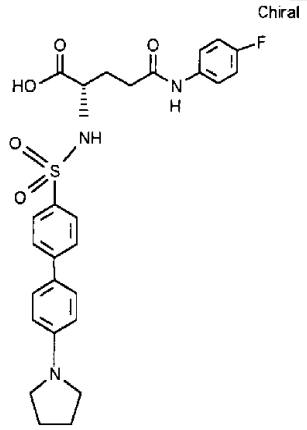
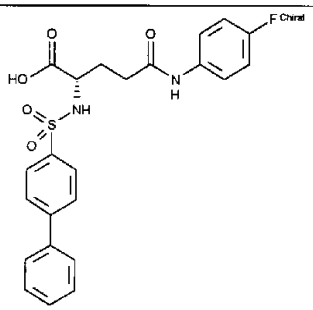
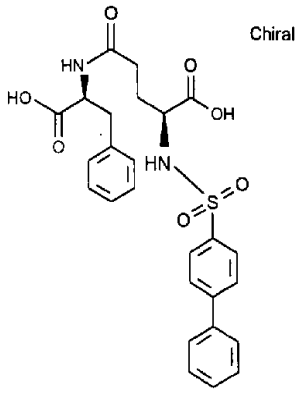
Example	Structure	Note	M.p. (°C)	MS (M+ H)
74		S isomer	187.5-188.5	473.2
75		S isomer	232-233	484.2
76		racemate	234-236 (dec.)	508.2

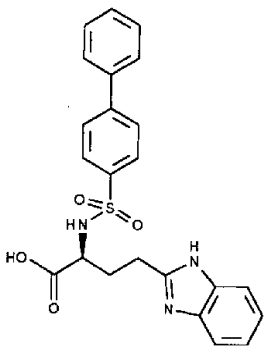
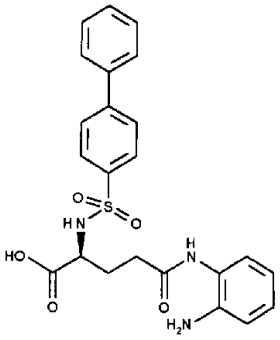
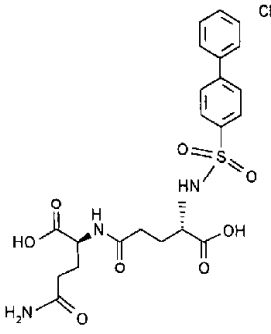
Example	Structure	Note	M.p. (°C)	MS (M+ H)
77	 Chiral	S isomer	> 220 (dec.)	433.3
78		racemate	> 230 (dec.)	508.2
79	 Chiral	S isomer	234.5-235.5	439.2

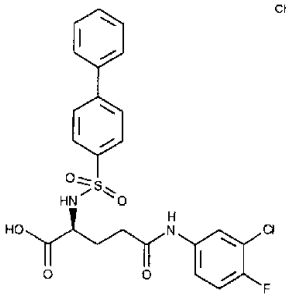
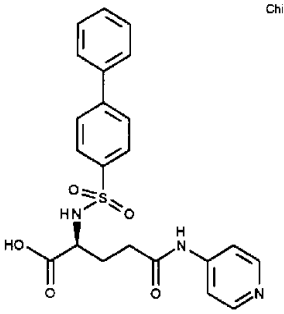
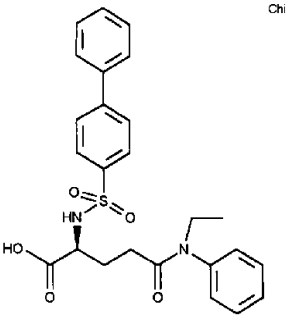
Example	Structure	Note	M.p. (°C)	MS (M+ H)
80	 Chiral	S isomer	> 228 (dec.)	508.3
81	 Chiral	S isomer	240.5-241.5 (dec.)	482.3
82		racemate	171.5-172	378.2

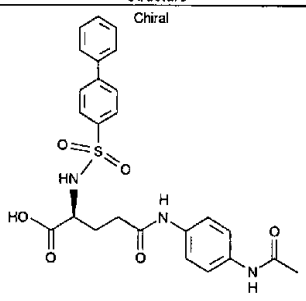
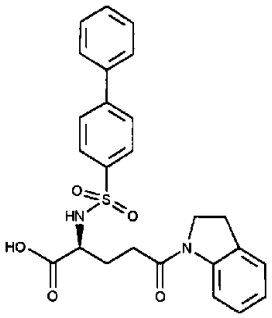
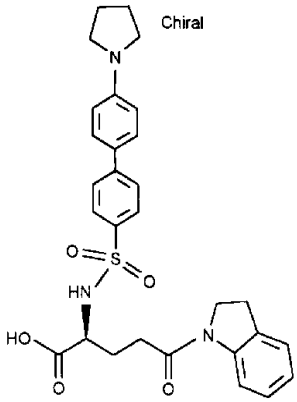
Example	Structure	Note	M.p. (°C)	MS (M+ H)
83	Chiral 	S isomer	250-250.5	496.2
84	Chiral 	S isomer	245-245.5	497.2
85	Chiral 	S isomer	265	507.3

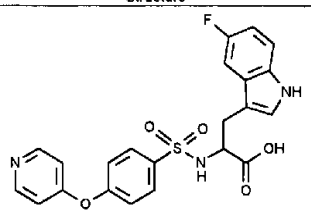
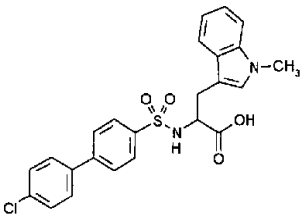
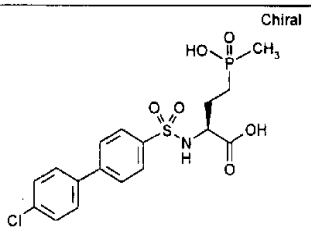
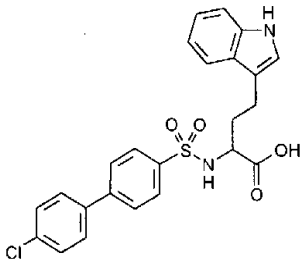
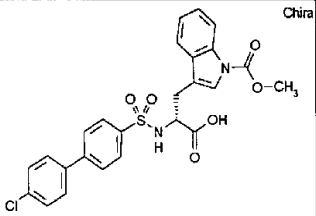
Example	Structure	Note	M.p. (°C)	MS (M+ H)
86		S isomer	220	464.0
87		S isomer	> 245 (dec.)	491.0
88		racemate		417.1
89		S isomer	219-221	469.2

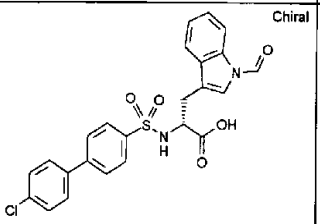
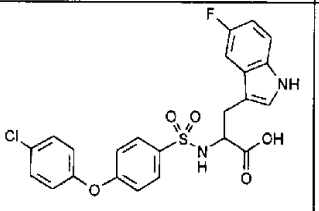
Example	Structure	Note	M.p. (°C)	MS (M+ H)
90	 Chiral	S isomer	> 245 (dec.)	526.3
91	 F Chiral	S isomer	> 258 (dec.)	457.0
92	 Chiral	in each case S isomer	123.5-124.5	511.2

Example	Structure	Note	M.p. (°C)	MS (M+ H)
93	 Chiral	S isomer	> 250.0 (dec.)	436.3
94	 Chir	S isomer	111-112	545.2
95	 Chiral	in each case S isomer	> 110 (dec.)	492.2

Example	Structure	Note	M.p. (°C)	MS (M+ H)
96	Chiral 	S isomer	>245 (dec.)	491.0
97	Chiral 	S isomer	> 290 (dec.)	440.1
98	Chiral 	S isomer	> 155 (dec.)	465.0 (M-1)

Example	Structure	Note	M.p. (°C)	MS (M+ H)
99	Chiral 	S isomer	> 230 (dec.)	496.2
100	Chiral 	S isomer	182.5-183.5	462.9 (M-1)
101	Chiral 	S isomer	> 130 (dec.)	532.2 (M-1)

Example	Structure	Note	M.p. (°C)	MS (M+ H)
102		S isomer		456.1
103		racemate		469.1
104		S isomer		432.1
105		racemate		469.2
106		R isomer		513.2

Example	Structure	Note	M.p. (°C)	MS (M+ H)
107	 Chiral	R isomer		583.2
108		racemate		489.1

Pharmacological examples

Preparation and determination of the enzymatic activity of the catalytic domains of human stromelysin and of neutrophil collagenase.

The two enzymes -stromelysin (MMP-3) and neutrophil collagenase (MMP-8) - were prepared according to Ye et al. (Biochemistry; 31 (1992) pages 11231-11235). To measure the enzyme activity or the enzyme inhibitor action, 70 µl of buffer solution and 10 µl of enzyme solution are incubated for 15 minutes with 10 µl of a 10% strength (v/v) aqueous dimethyl sulfoxide solution, which optionally contains the enzyme inhibitor. After addition of 10 µl of a 10% strength (v/v) aqueous dimethyl sulfoxide solution which contains 1 mmol/l of the substrate, the enzyme reaction is monitored by fluorescence spectroscopy (328 nm (ex) / 393 nm(em)).

The enzyme activity is shown as the extinction increase/minute. The IC_{50} values listed in Table 2 are determined as those inhibitor concentrations which in each case lead to a 50% inhibition of the enzyme.

The buffer solution contains 0.05% Brij (Sigma, Deisenhofen, Germany) and also 0.1 mol/l tris/HCl, 0.1 mol/l NaCl, 0.01 mol/l $CaCl_2$ and 0.1 mol/l piperazine-N,N'-bis[2-ethanesulfonic acid] (pH=6.5).

The enzyme solution contains 5 µg/ml of one of the enzyme domains prepared according to Ye et al. The substrate solution contains 1 mmol/l of the fluorogenic substrate (7-methoxycoumarin-4-yl)acetyl-Pro-Leu-Gly-Leu-3-(2',4'-dinitrophenyl)-L-2,3-diaminopropionyl-Ala-Arg-NH_2 (Bachem, Heidelberg, Germany).

Table 2

Example No.	Stromelysin IC_{50} (M)	Neutr. collagenase IC_{50} (M)
1	$4x10^{-7}$	$1x10^{-8}$
2	$1x10^{-7}$	$9x10^{-8}$
3	$2x10^{-5}$	$2x10^{-7}$
6	$2x10^{-7}$	$2x10^{-8}$
7	$2x10^{-7}$	$4x10^{-8}$

8	$3x10^{-7}$	$1x10^{-8}$
9	$3x10^{-7}$	$2x10^{-8}$
10	$9x10^{-8}$	$1x10^{-8}$
11	$9x10^{-8}$	$3x10^{-9}$
15	$1x10^{-7}$	$1x10^{-8}$
16	$7x10^{-8}$	$7x10^{-9}$
17	$1x10^{-7}$	$2x10^{-8}$
19	$5x10^{-7}$	$5x10^{-8}$
20	$4x10^{-7}$	$2x10^{-8}$
23	$1x10^{-6}$	$6x10^{-7}$
25	$2x10^{-7}$	$4x10^{-8}$
26	$4x10^{-7}$	$4x10^{-8}$
27	$2x10^{-7}$	$1x10^{-8}$
28	$3x10^{-7}$	$6x10^{-8}$
29	$8x10^{-8}$	$9x10^{-9}$
31	$1x10^{-6}$	$5x10^{-8}$
32	$2x10^{-7}$	$4x10^{-8}$
34	$2x10^{-7}$	$2x10^{-8}$
35	$1x10^{-7}$	$1x10^{-8}$
36	$2x10^{-7}$	$1x10^{-8}$
40	$7x10^{-8}$	$2x10^{-9}$
41	$2x10^{-7}$	$3x10^{-8}$
42	$4x10^{-7}$	$3x10^{-8}$
44	$9x10^{-8}$	$1x10^{-8}$
51	$5x10^{-8}$	$5x10^{-9}$
55	$8x10^{-7}$	$4x10^{-8}$
56	$3x10^{-8}$	$5x10^{-9}$
58	$4x10^{-8}$	$6x10^{-9}$
60	$6x10^{-7}$	$2x10^{-8}$
61	$4x10^{-7}$	$2x10^{-8}$
62	$7x10^{-9}$	$2x10^{-9}$
63	$3x10^{-6}$	$6x10^{-7}$
65	$1x10^{-7}$	$3x10^{-9}$
66	$2x10^{-8}$	$2x10^{-9}$
67	$1x10^{-6}$	$2x10^{-7}$
68	$4x10^{-7}$	$1x10^{-7}$

69	$1x10^{-8}$	$4x10^{-9}$
70	$1x10^{-7}$	$3x10^{-9}$
71	$1x10^{-8}$	$2x10^{-9}$
72	$6x10^{-7}$	$2x10^{-8}$
73	$3x10^{-7}$	$2x10^{-8}$
74	$1x10^{-7}$	$1x10^{-8}$
75	$3x10^{-7}$	$2x10^{-8}$
76	$5x10^{-9}$	$3x10^{-9}$
77	$4x10^{-9}$	$4x10^{-9}$
78	$2x10^{-8}$	$2x10^{-9}$
79	$2x10^{-8}$	$4x10^{-9}$
80	$7x10^{-9}$	$2x10^{-9}$
81	$1x10^{-8}$	$2x10^{-9}$
82	$1x10^{-7}$	$1x10^{-8}$
83	$1x10^{-6}$	$2x10^{-8}$
84	$5x10^{-6}$	$2x10^{-9}$
85	$3x10^{-6}$	$3x10^{-8}$
86	$3x10^{-7}$	$1x10^{-8}$
87	$3x10^{-8}$	$5x10^{-9}$
88	$1x10^{-7}$	$7x10^{-9}$
89	$3x10^{-7}$	$2x10^{-8}$
90	$1x10^{-8}$	$2x10^{-9}$
91	$3x10^{-7}$	$1x10^{-8}$
92	$3x10^{-8}$	$4x10^{-9}$
93	$2x10^{-7}$	$2x10^{-8}$
94	$2x10^{-7}$	$3x10^{-8}$
95	$3x10^{-7}$	$2x10^{-8}$
96	$6x10^{-7}$	$2x10^{-8}$
97	$1x10^{-6}$	$3x10^{-8}$
98	$4x10^{-7}$	$3x10^{-8}$
99	$7x10^{-7}$	$5x10^{-8}$
100	$5x10^{-7}$	$2x10^{-8}$
101	$4x10^{-8}$	$4x10^{-9}$
104	$4x10^{-8}$	$5x10^{-9}$
105	$3x10^{-8}$	$1x10^{-8}$
107	$4x10^{-8}$	$1x10^{-8}$

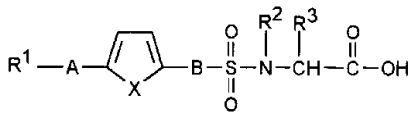
69	$1x10^{-8}$	$4x10^{-9}$
70	$1x10^{-7}$	$3x10^{-9}$
71	$1x10^{-8}$	$2x10^{-9}$
72	$6x10^{-7}$	$2x10^{-8}$
73	$3x10^{-7}$	$2x10^{-8}$
74	$1x10^{-7}$	$1x10^{-8}$
75	$3x10^{-7}$	$2x10^{-8}$
76	$5x10^{-9}$	$3x10^{-9}$
77	$4x10^{-9}$	$4x10^{-9}$
78	$2x10^{-8}$	$2x10^{-9}$
79	$2x10^{-8}$	$4x10^{-9}$
80	$7x10^{-9}$	$2x10^{-9}$
81	$1x10^{-8}$	$2x10^{-9}$
82	$1x10^{-7}$	$1x10^{-8}$
83	$1x10^{-6}$	$2x10^{-8}$
84	$5x10^{-6}$	$2x10^{-9}$
85	$3x10^{-6}$	$3x10^{-8}$
86	$3x10^{-7}$	$1x10^{-8}$
87	$3x10^{-8}$	$5x10^{-9}$
88	$1x10^{-7}$	$7x10^{-9}$
89	$3x10^{-7}$	$2x10^{-8}$
90	$1x10^{-8}$	$2x10^{-9}$
91	$3x10^{-7}$	$1x10^{-8}$
92	$3x10^{-8}$	$4x10^{-9}$
93	$2x10^{-7}$	$2x10^{-8}$
94	$2x10^{-7}$	$3x10^{-8}$
95	$3x10^{-7}$	$2x10^{-8}$
96	$6x10^{-7}$	$2x10^{-8}$
97	$1x10^{-6}$	$3x10^{-8}$
98	$4x10^{-7}$	$3x10^{-8}$
99	$7x10^{-7}$	$5x10^{-8}$
100	$5x10^{-7}$	$2x10^{-8}$
101	$4x10^{-8}$	$4x10^{-9}$
104	$4x10^{-8}$	$5x10^{-9}$
105	$3x10^{-8}$	$1x10^{-8}$
107	$4x10^{-8}$	$1x10^{-8}$

"Comprises/comprising" when used in this specification is taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

~~Patent Claims~~ HOE 97/F 130

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula I



(I)

and/or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerable salt of the compound of the formula I, where

R^1 is 1. phenyl,

2. phenyl, which is mono- or disubstituted by

2.1. $(C_1\text{-}C_6)$-alkyl, which is linear, cyclic or branched,

2.2. -OH,

2.3. $(C_1\text{-}C_6)$-alkyl-C(O)-O-,

2.4. $(C_1\text{-}C_6)$-alkyl-O-,

2.5. $(C_1\text{-}C_6)$-alkyl-O-$(C_1\text{-}C_4)$-alkyl-O-,

2.6. halogen,

2.7. $-CF_3$,

2.8. -CN,

2.9. $-NO_2$,

2.10. HO-C(O)-,

2.11. $(C_1\text{-}C_6)$-alkyl-O-C(O)-,

2.12. methylenedioxo,

2.13. R^4-(R^5)N-C(O)- or

2.14. R^4-(R^5)N-, or

3. a heteroaromatic from the following group 3.1. to 3.15., which is unsubstituted or substituted as described under 2.1 to 2.14,

3.1. pyrrole,

3.2. pyrazole,

3.3. imidazole,
3.4. triazole,
3.5. thiophene,
3.6. thiazole,
3.7. oxazole,
3.8. isoxazole,
3.9. pyridine,
3.10. pyrimidine,
3.11. indole,
3.12 benzothiophene,
3.13. benzimidazole,
3.14. benzoxazole or
3.15. benzothiazole,

R^2, R^4 and R^5 are identical or different and are

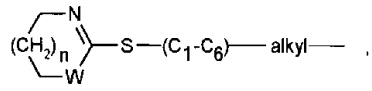
1. a hydrogen atom,
2. $(C_1\text{-}C_6)$-alkyl-,
3. HO-C(O)-$(C_1\text{-}C_6)$-alkyl-,
4. phenyl-$(CH_2)_n$-, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1 to 2.14 or is substituted by -NH-C(O)-$(C_1\text{-}C_3)$-alkyl and n is the integer zero, 1 or 2, or
5. picolyl or
6. R^4 and R^5 together with the ring amino group form a 4- to 7-membered ring, in which one of the carbon atoms is optionally replaced by -O-, -S- or -NH- or two adjacent carbon atoms of the 4- to 7-membered ring are part of a benzyl radical,

R^3 is
1. a hydrogen atom,
2. $(C_1\text{-}C_{10})$-alkyl, in which alkyl is unsubstituted, and/or a hydrogen atom of the alkyl radical is replaced by -OH,
3. $(C_2\text{-}C_{10})$-alkenyl, in which alkenyl is linear or branched,

4. R^2-O-(C_1-C_6)-alkyl,

5. R^2-S(O)$_n$-(C_1-C_6)-alkyl, where n has the abovementioned meaning,

6. R^2-S(O)(=NH)-(C_1-C_6)-alkyl-,

7. 

in which n is the integer zero, 1 or 2 and
W is a nitrogen, oxygen or sulfur atom,

8. phenyl-$(CH_2)_m$-, in which m is the integer zero, 1, 2, 3, 4, 5 or 6 and/or a hydrogen atom of the -$(CH_2)_m$- chain is replaced by -OH and phenyl is unsubstituted or mono- or disubstituted by

8.1 as described under 2.1. to 2.14.,

8.2 -O-$(CH_2)_m$-phenyl, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and m is the integer zero, 1, 2, 3, 4, 5 or 6,

8.3 -C(O)-$(CH_2)_m$-phenyl, in which phenyl is as defined under 8.2,

9. heteroaryl-$(CH_2)_m$-, in which heteroaryl is as defined under 3.1. to 3.15., m is as defined above and/or a hydrogen atom of the -$(CH_2)_m$-chain is replaced by -OH and heteroaryl is unsubstituted or mono- or disubstituted by

9.1 as described under 2.1 to 2.14 or

9.2 -CH(O),

9.3 -SO_2-phenyl, in which phenyl is unsubstituted or is as defined under 8.2 or 8.3,

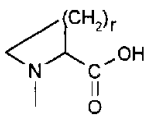
9.4 -O-$(CH_2)_m$-phenyl,

10. $-(CH_2)_m-P(O)(OH)-(C_1-C_3)$-alkyl, in which m is as defined above, or

11. $R^6-C(O)-(C_1-C_6)$-alkyl, in which R^6 is

1. a hydrogen atom,
2. (C_1-C_6)-alkyl-, in which alkyl is linear, branched or cyclic,
3. phenyl, in which phenyl is unsubstituted or substituted as described under 2.1 to 2.14,
4. heteroaryl, in which heteroaryl is as defined under 3.1. to 3.15.and/or is substituted as described under 2.1 to 2.14 or is substituted by $-(C_1-C_4)$-alkyl-COOH,
5. HO-,
6. R^2O-, in which R^2 has the abovementioned meaning,
7. $R^4-(R^5)N$-, in which R^4 and R^5 are as defined above,
8. heteroaryl-$(CH_2)_m$-NH-, in which heteroaryl is as defined under 3.1 to 3.15. and/or as described under 2.1. to 2.14 and m is as defined above or is substituted by $-(C_1-C_4)$-alkyl-COOH,
9. $R^4-(R^5)N-NH$-, in which R^4 and R^5 are as defined above, or
10. HO-C(O)-CH(R^3)-NH-, in which R^3 is as defined above, or

R^2 and R^3 together form a ring having a ring carboxyl group, of the subformula II



(II)

in which r is the integer zero, 1, 2 or 3 and/or one of the carbon atoms in the ring is replaced by -O-, -S- or -(R^7)N-, in which

R^7 is 1. a hydrogen atom,

2. (C_1-C_6)-alkyl,

3. phenyl, in which phenyl is unsubstituted or is substituted as described under 2.1 to 2.14,

4. benzyl, in which benzyl is unsubstituted or substituted as described under 2.1 to 2.14, or

5. R^2N-C(=NH)-, where R^2 has the abovementioned meaning,

and/or the carbon atoms in the ring of the subformula II are mono- or polysubstituted by (C_1-C_6)-alkyl-, phenyl-, phenyl-(CH_2)$_m$- or -OH,

A is a) a covalent bond,

b) -O-,

c) -CH=CH- or

d) -C≡C-,

B is a) -(CH_2)$_m$-, in which m has the abovementioned meaning,

b) -O-(CH_2)$_p$, in which p is an integer from 1 to 5, or

c) -CH=CH- and

X is -CH=CH-, an oxygen atom or a sulfur atom.

2. A compound of the formula I as claimed in claim 1, wherein

R^1 is 1. phenyl or

2. phenyl which is monosubstituted by

2.1. (C_1-C_6)-alkyl-, in which alkyl is linear, cyclic or branched,

2.2. -OH,

2.3. (C_1-C_6)-alkyl-C(O)-O-,

2.4. (C_1-C_6)-alkyl-O-,

2.5. (C_1-C_6)-alkyl-O-(C_1-C_4)-alkyl-O-,

2.6. halogen,

2.7. $-CF_3$ or

2.8. R^4-(R^5)N-,

R^2, R^4 and R^5 are identical or different and are

1. a hydrogen atom or
2. (C_1-C_6)-alkyl-,

R^3 is

1. (C_1-C_{10})-alkyl-, in which alkyl is linear, branched or cyclic, and/or in which a hydrogen atom of the alkyl radical is replaced by -OH,
2. $R^{2'}$-$S(O)_n$-(C_1-C_6)-alkyl-, in which $R^{2'}$ (C_1-C_6)-alkyl- or phenyl-$(CH_2)_n$- and n is the integer zero or 1,
3. phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and/or a hydrogen atom of the -$(CH_2)_m$- chain is replaced by -OH and m is the integer 1, 2, 3, 4 or 5,
4. heteroaryl-$(CH_2)_m$-, in which heteroaryl has the meaning mentioned under 3.3, 3.5, 3.6, 3.9 or 3.11 and/or is substituted as described under 2.1. to 2.14. and/or a hydrogen atom of the -$(CH_2)_m$-chain is replaced by -OH and m is the integer 1, 2, 3 or 4, or
5. R^6-C(O)-(C_1-C_6)-alkyl-, in which

R^6 is

1. -OH,
2. R^2O-, in which R^2 is as defined above,
3. R^4-(R^5)N-, in which R^4 and R^5 are as defined above, or

4. R^4 and R^5 together with the ring amino group form a 5- to 6-membered ring in which one of the carbon atoms is optionally replaced by -O-, -S- or -NH- or two adjacent carbon atoms of the 5- to 6-membered ring are part of a benzyl radical,

6. R^2 and R^3 together form a ring having a ring carboxyl group, of the subformula II, in which n is the integer 1 or 2 and/or one of the carbon atoms in the ring is replaced by -O- or -(R^7)N-, and

R^7 is 1. a hydrogen atom,

2. (C_1-C_6)-alkyl,

3. phenyl, in which phenyl is unsubstituted or substituted as described under 2.1 to 2.14,

4. benzyl, in which benzyl is unsubstituted or substituted as described under 2.1 to 2.14, or

5. R^2N-C(=NH)-, in which R^2 is as defined above, and/or the carbon atoms in the ring of the subformula II are monosubstituted by phenyl or -OH,

A is a) a covalent bond or

b) -O-,

B is a) -$(CH_2)_m$-, in which m is the integer zero, 1 or 2, or

b) -O-$(CH_2)_p$, in which p is an integer 1 or 2, and

X is -CH=CH-.

3. A compound of the formula I as claimed in claim 1, wherein

R^1 is 1. phenyl or

2. phenyl which is monosubstituted by

2.1. chlorine or fluorine or

2.2. R^4-(R^5)N-, in which R^4 and R^5 are identical or different and are

2.2.1. (C_1 -C_3)-alkyl or

2.2.2. R^4 and R^5 together with the ring amino group form a 5- to 6-membered ring, one of the carbon atoms optionally being replaced by -O- or -N-, ,

R^2 is a hydrogen atom,

R^3 is 1. heteroaryl-$(CH_2)_m$ -, in which heteroaryl is as defined under 3.5, 3.11 or 3.13 and the heteroaryl is unsubstituted or monosubstituted as described under 2.1 to 2.14 and m is the integer 1 or 2, or

2. R^6-C(O)-(C_2-C_3)-alkyl, in which

R^6 is 1. -OH,

2. R^2-O-, in which R^2 is as defined above or

3. R^4-(R^5)N-, in which R^4 and R^5 are identical or different and are

3.1. a hydrogen atom,

3.2. (C_1 -C_3)-alkyl-,

3.3. phenyl-(CH_2)-, where phenyl is unsubstituted or mono- or disubstituted as described under 2.1 to 2.14 and n is the integer zero, 1 or 2,

3.4. R^4 and R^5 together with the ring amino group form a 5- to 6-membered ring, where one of the carbon atoms is optionally replaced by -O- or -NH-, or form an indoline radical, or

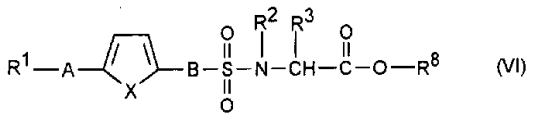
3.5. HO-C(O)-CH(R^3)-NH-, in which R^3 is as defined above,

A is a covalent bond,

B is $-(CH_2)_o-$, in which o is zero and

X is -CH=CH-.

4. A compound of the formula VI

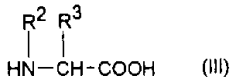


(VI)

and/or a stereoisomeric form of the compound of the formula VI and/or a physiologically tolerable salt of the compound of the formula VI, R^1, A, X, B, R^2 and R^3 having the meaning mentioned in the compound of the formula I as claimed in claim 1, in which R^8 is a hydrogen atom, $(C_1 - C_6)$ - alkyl, phenyl or benzyl

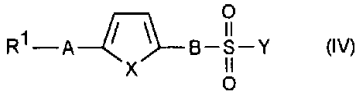
5. A process for the preparation of the compound of the formula I as claimed in one or more of claims 1 to 4, which comprises

a) reacting an aminocarboxylic acid of the formula III,



(III)

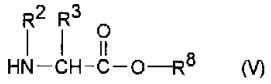
in which R^2 and R^3 are as defined in formula I, with a sulfonic acid derivative of the formula IV,



(IV)

in which R^1, A and B are as defined in formula I and Y is a halogen atom, imidazolyl or $-OR^8$, in which R^8 is a hydrogen atom, (C_1-C_6)-alkyl, phenyl or benzyl, if appropriate substituted, in the presence of a base or optionally of a dehydrating agent to give a compound of the formula I, or

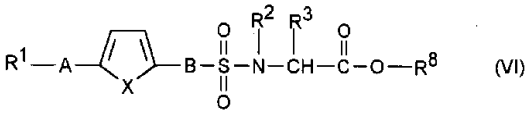
b) reacting an aminocarboxylic acid ester of the formula V,



(V)

in which R^2, R^3 and R^8 have the abovementioned meaning,

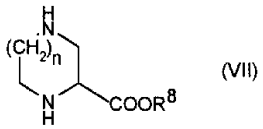
with a sulfonic acid derivative of the formula IV under the abovementioned conditions to give a compound of the formula VI



(VI)

and converting the compound of the formula VI into a compound of the formula I with removal of the radical R^8, preferably in the presence of a base or acid, or

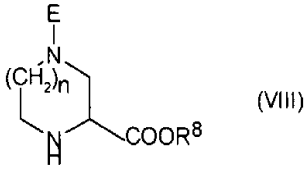
c) reacting the compound of the formula VII,



(VII)

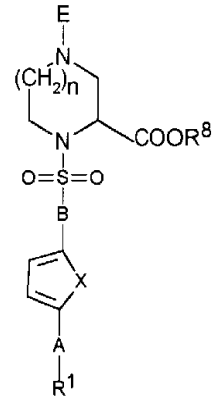
where n is the integer zero, 1 or 2,

with the aid of a protective group E to give a compound of the formula VIII,



(VIII)

converting the compound of the formula VIII with the sulfonic acid derivative of the formula IV under the abovementioned conditions into a compound of the formula IX



(IX)

and then converting the compound of the formula IX into the compound of the formula I with removal of the protective group E and of the radical R^8 with the aid of suitable cleavage reagents

or

d) resolving a compound of the formula I, which on account of its chemical structure occurs in enantiomeric forms, prepared by process a), b) or c) into the pure enantiomers by salt formation with enantiomerically pure acids or bases, chromatography on chiral stationary phases or derivatization by means of chiral enantiomerically pure compounds such as amino acids, separation of the diastereomers thus obtained, and removal of the chiral auxiliary groups, or

e) isolating the compound of the formula I prepared by process a), b), c) or d) either in free form or, in the case of the presence of acidic or basic groups, converting it into physiologically tolerable salts.

6. A pharmaceutical, comprising an efficacious amount of at least one compound of the formula I as claimed in one or more of claims 1 to 4 together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

7. The use of at least one compound of the formula I as claimed in one

or more of claims 1 to 4 for the production of pharmaceuticals for the propylaxis and therapy of disorders in the course of which an increased activity of matrix-degrading metalloproteinases is involved.

8. The use as claimed in claim 7 for the treatment of degenerative joint disorders such as osteoarthroses, spondyloses, chondrolysis after joint trauma or relatively long immobilization of the joint after meniscus or patella injuries or tears of the ligaments, disorders of the connective tissue such as collagenoses, periodontal disorders, wound healing disorders and chronic disorders of the locomotory apparatus such as inflammatory, immunologically or metabolically related acute and chronic arthritides, arthropathies, myalgias and disorders of the bone metabolism, ulceration, atherosclerosis and stenoses, but also for the treatment of inflammations, carcinomatous disorders, formation of tumor metastases, cachexia, anorexia and septic shock.

9. A process for the production of a pharmaceutical which comprises bringing at least one compound of the formula I as claimed in one or more of claims 1 to 4 into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, other suitable active compounds, additives or auxiliaries.

10. A method of treatment or prophylaxis of disorders in the course of which an increased activity of matrix-degrading metalloproteinases is involved, comprising administering to a patient in need of such treatment or prophylaxis an efficacious amount of at least one compound as defined in formula I as claimed in any one of claims 1 to 4.

11. A method of treatment or prophylaxis of degenerative joint disorders such as osteoarthroses, spondyloses, chondrolysis after joint trauma or relatively long immobilization of the joint after meniscus or patella injuries or tears of the ligaments, disorders of the connective tissue such as collagenoses, periodontal

disorders, wound healing disorders and chronic disorders of the locomotory apparatus such as inflammatory, immunologically or metabolically related acute and chronic arthritides, arthropathies, myalgias and disorders of the bone metabolism, ulceration, atherosclerosis and stenoses, but also for the treatment of inflammations, carcinomatous disorders, formation of tumor metastases, cachexia, anorexia and septic shock, comprising administering to a patient in need of such treatment or prophylaxis an efficacious amount of at least one compound as defined in formula I as claimed in any one of claims 1-4.

DATED this 22nd day of February 2001

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