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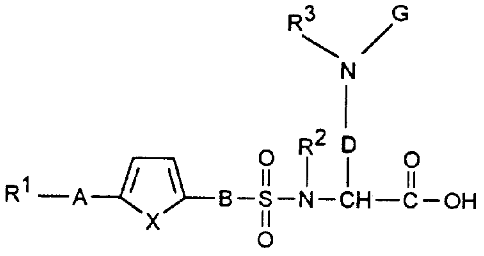
(54) DERIVES DE SUBSTITUTION D'ACIDES DIAMINOCARBOXYLIQUES

(54) SUBSTITUTED DIAMINOCARBOXYLIC ACIDS



(I)

(57) Dérivés de substitution d'acides diaminocarboxyliques de formule I (voir formule I), utiles pour l'obtention de produits pharmaceutiques permettant de prévenir et de traiter les troubles liés à une activité accrue des métalloprotéinases détruisant la matrice.

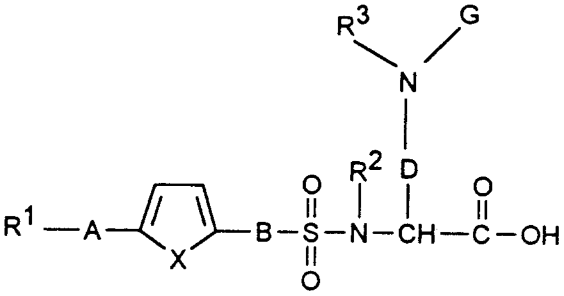
(57) Substituted diaminocarboxylic acids Compounds of the formula I (see formula I) are suitable for the production of pharmaceuticals for the prophylaxis and therapy of disorders in the course of which an increased activity of matrix-degrading metalloproteinases is involved.

Abstract

HOE 97/F 131K

Substituted diaminocarboxylic 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.

Description

Substituted diaminocarboxylic acids

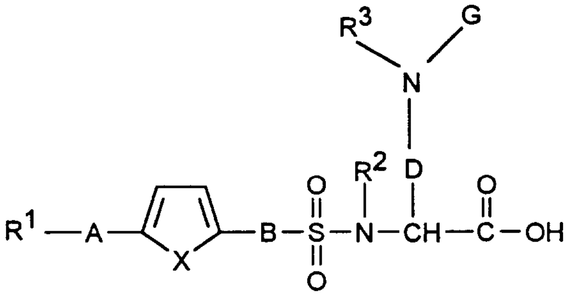
The invention relates to novel substituted diaminocarboxylic acids, processes for their preparation and use thereof as pharmaceuticals.

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 active compounds for the treatment of connective tissue disorders, it has now been found that the diaminocarboxylic acids according to the invention are strong inhibitors of matrix metalloproteinases. Particular value is placed here on the inhibition of stromelysin (matrix metalloproteinase 3) and neutrophil collagenase (MMP-8), since both enzymes are substantially involved, as important constituents of the cartilaginous tissue, in particular 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. $(C_1\text{-}C_7)$-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)-,
    - 2.14. R^4-(R^5)N-, or

3. a heteroaromatic from the following group 3.1. to 3.16., 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,
3.15. benzothiazole or
3.16 benzotriazole,

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

1. a hydrogen atom,
2. $(C_1 -C_6)$-alkyl-,
3. HO-C(O)-$(C_1$-$C_6)$-alkyl-,
4. phenyl-$(CH_2)_o$-, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and o is the integer zero, 1 or 2, or
5. is 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 carbonyl atoms is optionally replaced by -O-, -S- or -NH-,

R^3 and G are identical or different and are

1. a hydrogen atom,
2. $(C_1 -C_6)$-alkyl-, in which alkyl is linear, branched or cyclic,
3. $(C_2 -C_6)$-alkenyl-,
4. phenyl-$(CH_2)_m$-, 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 or 3,
5. heteroaryl-$(CH_2)_m$-, in which heteroaryl is substituted as defined under 3.1. to 3.16. and/or as described under 2.1 to 2.14 and m is the integer zero, 1, 2 or 3,
6. R^6-C(O)-, in which

R^6 is 6.1 (C_1-C_6)-alkyl-, in which alkyl is unsubstituted or substituted as described under 2.1. to 2.14. or by (C_3-C_6)-cycloalkyl

6.2 (C_3-C_6)-cycloalkyl, in which cycloalkyl is unsubstituted or substituted as desribed under 2.1. to 2.14.

6.3 (C_2-C_6)-alkenyl-, in which alkenyl is unsubstituted or mono- to trisubstituted by

6.3.1 phenyl, in which phenyl is unsubstituted or mono- to trisubstituted as described under 2.1. to 2.14.

6.3.2 heteroaryl-, in which heteroaryl is as defined under 3.1. to 3.16. and is unsubstituted or mono- to trisubstituted as described under 2.1. to 2.14. or

6.3.3 the radicals described under 2.1. to 2.14.,

6.4 phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- to trisubstituted as described under 2.1. to 2.14. by $-O-CF_3$, $-SO_2-NH_2$, $-NH-C(O)-CF_3$ or by benzyl and a hydrogen atom of the $-(CH_2)-$ radical is optionally substituted by the radical -COOH and m is the integer zero, 1, 2 or 3,

6.5 naphthyl,

6.6 adamantyl or

6.7 heteroaryl-$(CH_2)_m$-, in which heteroaryl is as defined under 3.1. to 3.16. and/or is substituted as described under 2.1. to 2.14. and m is the integer zero, 1, 2 or 3,

7. R^6-O-C(O)-, in which R^6 is defined as mentioned above,

8. R^6-CH(NH_2)-C(O)-, in which R^6 is defined as mentioned above,

9. R^8-N(R^7)-C(O)-, in which

R^8 is 9.1 a hydrogen atom

9.2 (C_1-C_6)-alkyl-,

9.3 phenyl-$(CH_2)_m$, 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 or 3, or

9.4 heteroaryl-$(CH_2)_m$, in which heteroaryl is as defined under 3.1. to 3.16. and/or is substituted as described under 2.1 to 2.14 and m is the integer zero, 1, 2 or 3, and in which

R^7 is a hydrogen atom or (C_1-C_6)-alkyl or in which

R^7 and R^8 together with the nitrogen atom to which they are bonded form a 4- to 7-membered ring and the ring is unsubstituted or a carbon atom in the ring is replaced by -O-, -S- or -NH-,

10. R^6-SO_2-, in which R^6 is defined as mentioned above,

11. $R^6-SO_2-N(R^7)-C(O)$-, in which R^6 and R^7 are defined as mentioned above,

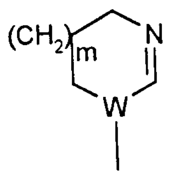
12. $R^6-NH-C(=NR^7)$-, in which R^6 and R^7 are defined as mentioned above or

12.1 (C_1-C_6)-alkyl-C(O)-,

12.2 $-NO_2$ or

12.3 $-SO_2-(CH_2)_q$-phenyl, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and q is the integer zero, 1, 2 or 3,

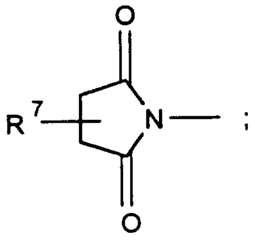
13.



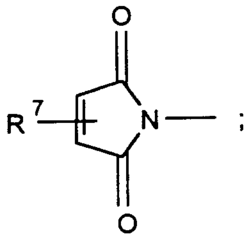
,

in which m is the integer zero, 1, 2 or 3 and W is a nitrogen, oxygen or sulfur atom, or

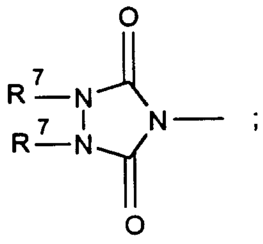
R^3 and G together with the nitrogen atom to which they are bonded form a ring of the subformula IIa to IIp,



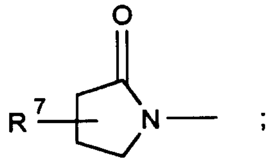
(IIa)



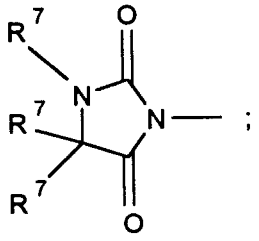
(IIb)



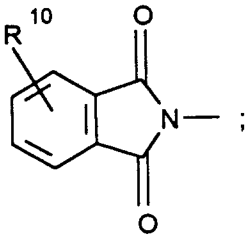
(IIc)



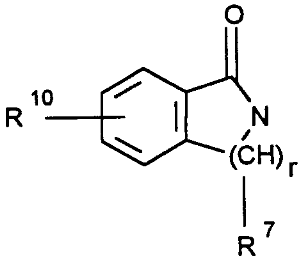
(IId)



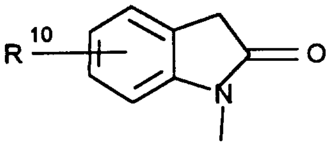
(IIe)



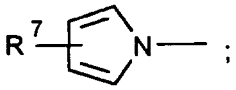
(IIf)



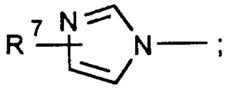
(IIg)



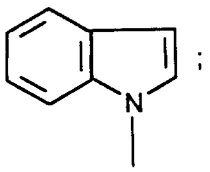
(IIh)



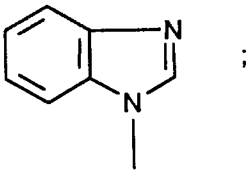
(IIi)



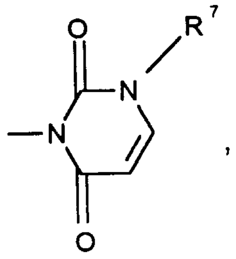
(IIj)



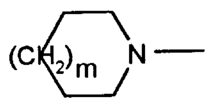
(IIk)



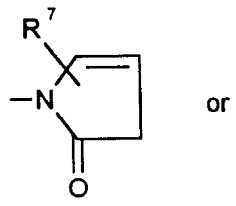
(IIl)



(IIm)

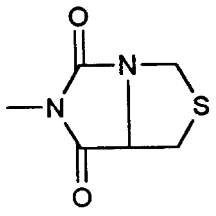


(IIn)



or

(IIo)



(IIp)

where r is the integer 1 or 2, R^{10} is a radical as described under 2.1. to 2.14. and R^7 and m have the abovementioned meaning and in the subformula IIg a carbon atom in the ring is optionally replaced by oxygen, sulfur, SO_2 or a nitrogen atom which is unsubstituted or substituted by R^2,

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) $-O-(CH_2)_q$, in which q is the integer 1, 2, 3, 4 or 5, or
c) -CH=CH-,

D is $-(CH_2)_m-$ in which m is the integer 1, 2, 3, 4, 5 or 6 and one of the chain carbon atoms is optionally replaced by an optionally substituted -NH-, -O- or -S- atom, 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
  - 1. halogen, in particular chlorine or fluorine or
  - 2. $R^4-(R^5)N-$, where R^4 and R^5 are identical or different and are
    - 2.1. (C_1-C_3)-alkyl or
    - 2.2. R^4 and R^5 together with the ring amino group form a 5-6-membered ring, where one of the carbon atoms is optionally replaced by -O- or -NH-,

R^2 is a hydrogen atom,

G and R^3 are different, where

G is a hydrogen atom or (C_1-C_4)-alkyl and

R^3 is 1. phenyl-$(CH_2)_m$, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1 to 2.14 and m is the integer 1,

2. is heteroaryl-$(CH_2)n$, in which heteroaryl is as defined under 3.10 and is unsubstituted or substituted as described under 2.1 to 2.14 and n is zero,

3. is R^6-C(O)-, in which

R^6 is 3.1 (C_1-C_6)-alkyl-, in which alkyl is linear, branched or cyclic,

3.2 phenyl-$(CH_2)_r$- in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1 to 2.14 and a hydrogen atom of the -(CH_2)- radical is optionally replaced by the radical -COOH and r is zero, 1, 2 or 3, or

3.3 heteroaryl-$(CH_2)_o$-, in which heteroaryl is as defined under 3.1 to 3.15 and is unsubstituted or substituted as described under 2.1 to 2.14 and o is zero, 1, 2, or 3, or

4. is R^8-N(R^7)-C(O)-, in which

R^8 and R^7 together with the nitrogen atom to which they are bonded form a 5- or 6-membered ring and the ring is unsubstituted or a ring carbon atom is replaced by an oxygen atom, or

R^3 and G together with the nitrogen atom to which they are bonded form a ring of the subformula IIg, in which r is 1,

A is a covalent bond,

B is -$(CH_2)_p$- and p is zero,

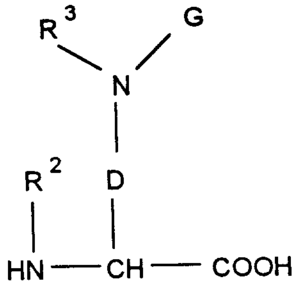
D is -$(CH_2)_q$- and q is an integer 2, 3 or 4, and

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 pyrrolidine, piperazine, morpholine, piperidine or thiomorpholine. 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. The alkenyl radicals can furthermore 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.

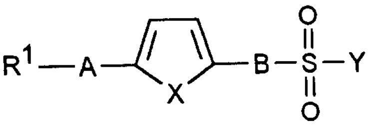
The invention furthermore relates to a process for the preparation of the compound of the formula I and/or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerable salt of the compound of the formula I, which comprises

a) reacting a diaminocarboxylic acid of the formula III



(III)

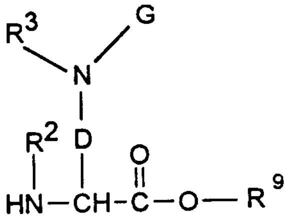
in which R^2, R^3, D and G are as defined in formula I, with a sulfonic acid derivative of the formula IV



(IV)

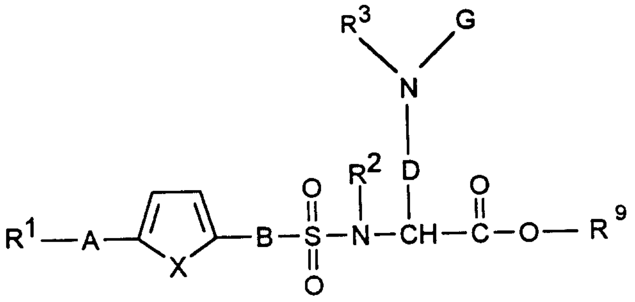
in which R^1, A and B are as defined in formula I and Y is a halogen atom, imidazolyl or $-OR^9$, in which R^9 is a hydrogen atom, $(C_1$-$C_6)$-alkyl, phenyl, succinimidyl, benzotriazolyl or benzyl, optionallly substituted, in the presence of a base or if appropriate of a dehydrating agent, to give a compound of the formula I, or

b) reacting a diaminocarboxylic acid ester of the formula V



(V)

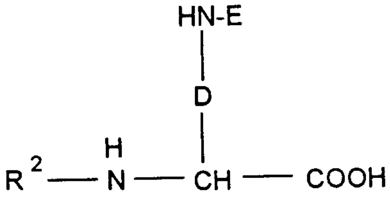
in which R^2, R^3, D, G and R^9 have the abovementioned meaning, with a sulfonic acid derivative of the formula IV under the abovementioned conditions to give a compound of the formula VI



(VI)

and converting the compound of the formula VI into a compound of the formula I with removal of the radical R^9, preferably in the presence of a base or acid,

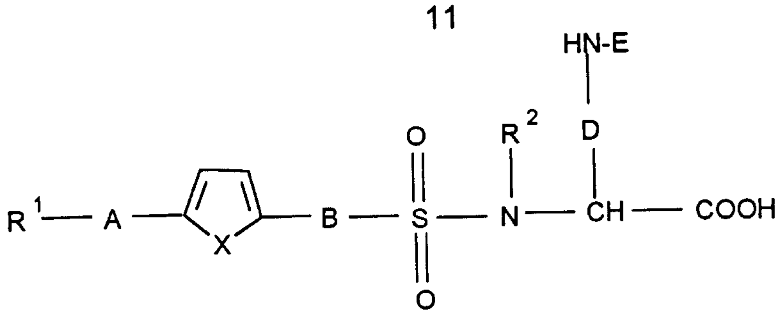
c) reacting the protected diaminocarboxylic acids of the formula VII,



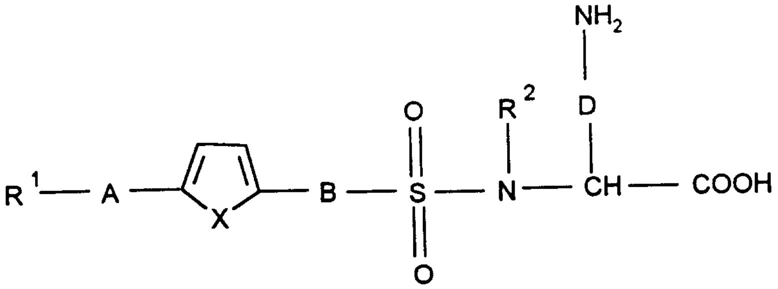
$$R^2-\underset{}{\overset{H}{N}}-\underset{}{\overset{\overset{\overset{HN-E}{|}}{D}}{\overset{|}{CH}}}-COOH$$

(VII)

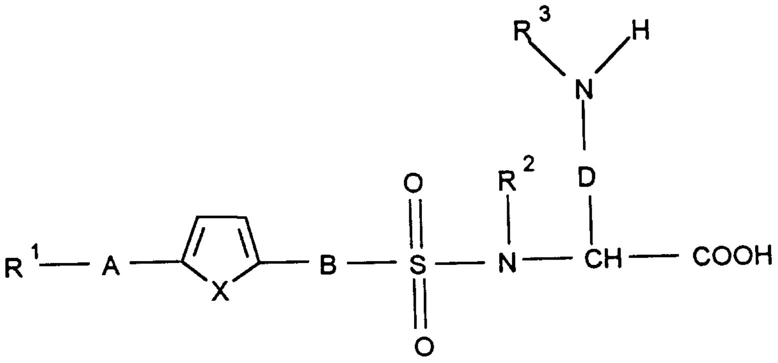
in which R^2 and D have the abovementioned meanings and E is a protective group of the amino function, with a sulfonic acid derivative of the formula IV to give a compound of the formula VIII


(VIII)

then converting the compound of the formula VIII, with removal of the protective group E with the aid of suitable cleavage agents, into a compound of the formula I

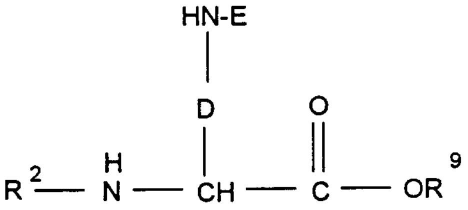

(I)

in which R^1, R^2, A, B, D and X have the abovementioned meaning and R^3 and G are a hydrogen atom, and reacting this compound of the formula I if appropriate with the aid of R^3-Y, in which R^3 and Y have the meanings indicated above, in the presence of a base to give a compound of the formula I,


(I)

in which R^1, R^2, R^3, A, B and X have the abovementioned meanings and G is a hydrogen atom, or

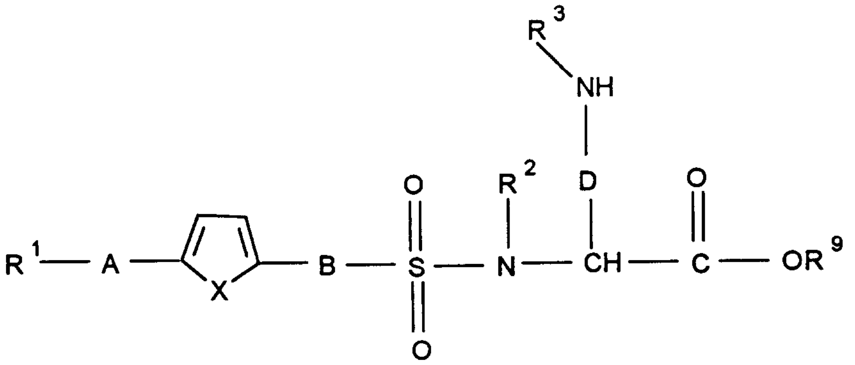
d) as starting compounds, converting protected diamino acid esters of the formula IX,



$$R^{2}-NH-CH(D-NH-E)-C(=O)-OR^{9}$$

(IX)

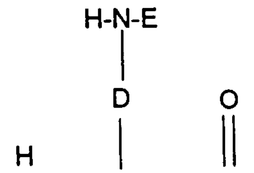
in which R^2, R^9, D and E have the abovementioned meaning, in the same manner as described in process variant c), into the esters of the formula X,



(X)

which are optionally converted into the corresponding compounds of the formula I according to process variant b), or

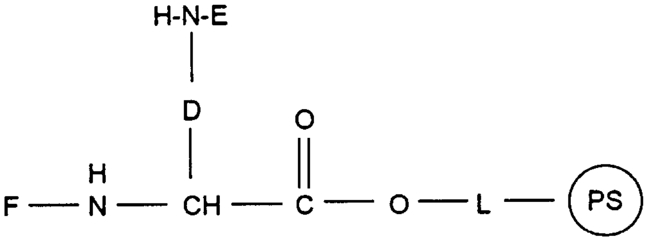
e) coupling a diaminocarboxylic acid of the formula XI,



$$F-NH-CH(D-NH-E)-C(=O)-OH$$

(XI)

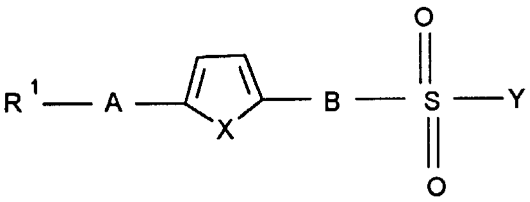
in which D is defined as in formula I and E and F are N-amino protective groups which are different from one another, by its carboxyl group via an intermediate chain L to a polymeric resin of the formula PS, a compound of the formula XII



$$\mathrm{F}-\overset{\mathrm{H}}{\mathrm{N}}-\overset{\substack{\mathrm{H\text{-}N\text{-}E}\\ | \\ \mathrm{D}\\ |}}{\mathrm{CH}}-\overset{\substack{\mathrm{O}\\ \|}}{\mathrm{C}}-\mathrm{O}-\mathrm{L}-\text{(PS)}$$

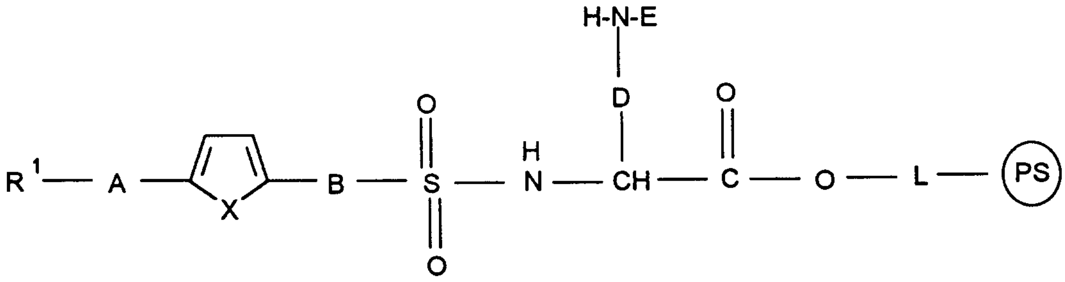
(XII)

resulting, which, after selective removal of the protective group F, is reacted with a sulfonic acid derivative of the formula IV



(IV)

where R^1, A, B and Y have the abovementioned meanings, in the presence of a base or, if appropriate, of a dehydrating agent to give a compound of the formula XIII

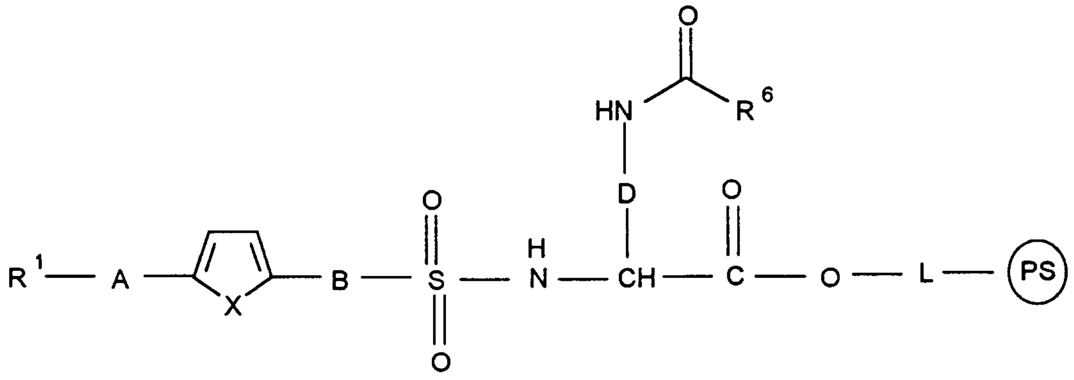


(XIII)

and reacting the compound of the formula XIII, after removal of the protective group E, with a carboxylic acid derivative of the formula XIV

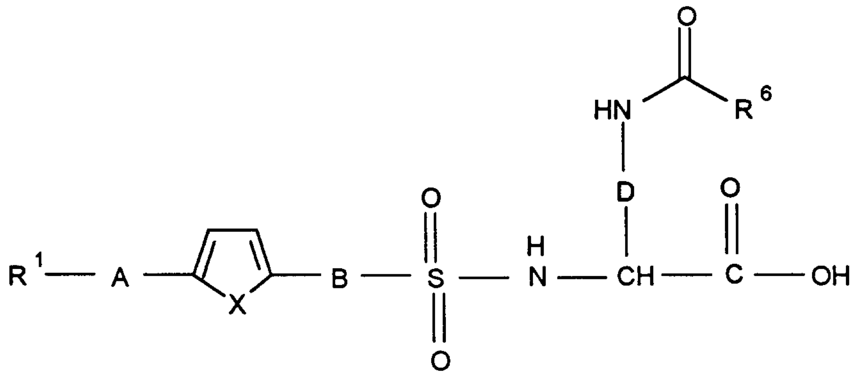
$$R^6\text{-C(O)-Y} \qquad \text{(XIV)}$$

in which R^6 and Y have the abovementioned meaning, in the presence of a base or of a dehydrating agent, to give a compound of the formula XV



(XV)

and converting this, after removal from the support material, into a compound of the formula I,



(I)

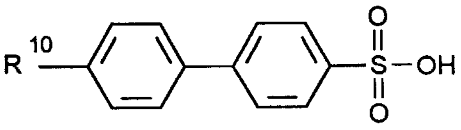
in which R^1, R^6, A, B, D and X have the abovementioned meaning.

Starting compounds of the formula III employed in which R^2, R^3 and G are a hydrogen atom are preferably 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, ornithine, lysine and homolysine. If R^3 and G, together with the amino function, are a guanidyl group, arginine is preferably used.
If, as in process variants c), d) and e), the amino functions of the starting compounds of the formulae VII, IX and XI are provided with a protective group E or F, this selective amino group derivatization is carried out according to methods such as are described in Houben-Weyl "Methoden der Org. Chemie" [Methods of Organic Chemistry], Volume 15/1.

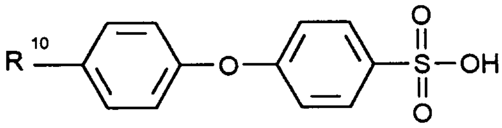
Suitable protective groups E and F for this purpose are preferably the N-protective groups customarily used in peptide chemistry, for example protective groups of the urethane type, such as benzyloxycarbonyl (Z), t-butoxycarbonyl (Boc), 9-fluorenylmethoxycarbonyl (Fmoc) and allyloxycarbonyl (Aloc) or of acid amide type, in particular formyl, acetyl or trifluoroacetyl or of alkyl type such as benzyl. The (trimethylsilyl)ethoxycarbonyl (Teoc) group has proven particularly suitable for this purpose (P. Kociénski, Protecting Groups, Thieme Verlag 1994). Many of the selectively derivatized compounds are also commercially available, so the preparation of the compounds of the formula I according to the invention, as is described in process variant c), consists in carrying out, after the introduction of the sulfonic acid ester into the α-amino group, the removal of the side-chain protective group E, which can optionally be followed by a multi-stage derivatization of the free amino group in the side chain. During this procedure, the carboxyl group can be present in free form or in the form of an ester with the radical $-OR^9$. In the case in which the radical $-OR^9$ is a straight-chain (C_1-C_3)-alkyl radical, this ester of the formula I can also be employed in therapy in this form (prodrug).

In the case in which R^9 is a tert-butyl radical, the ester cleavage is preferably carried out according to known methods using HCl in diethyl ether or trifluoroacetic acid in the last synthesis stage.

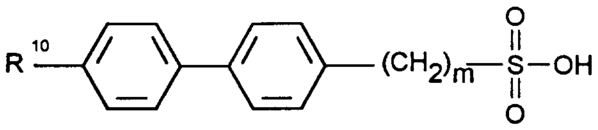
Starting materials for the preparation of the sulfonic acid derivatives of the formula IV are preferably sulfonic acids or their salts of the formula XVIa - XVIg, for example



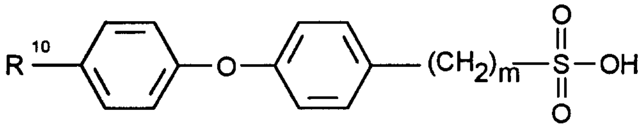
(XVIa)



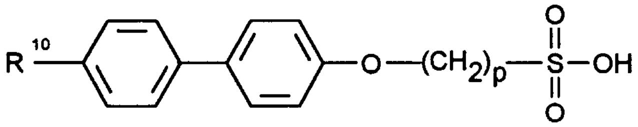
(XVIb)



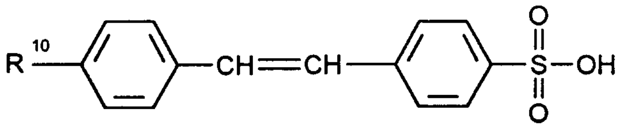
(XVIc)



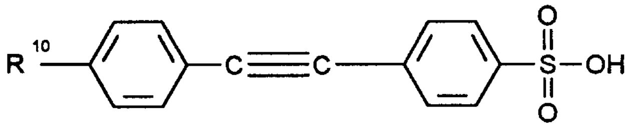
(XVId)



(XVIe)



(XVIf)



(XVIg)

R^{10} being a radical described under phenyl 2.1. to 2.14..

For the preparation of the arylsulfonic acids of the formulae XVIa and b, use is preferably made of the sulfonation processes using concentrated sulfuric acid described in Houben-Weyl „Methoden der Organischen Chemie“ [Methods of Organic Chemistry], Volume 9, pp. 450-546, if appropriate in the presence of a catalyst, sulfur trioxide and its addition compounds or halosulfonic acids, such as chlorosulfonic acid. Particularly in the case of the diphenyl ether of the formula XVIb, the use of concentrated sulfuric 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 formulae XVIc, XVId, or XVIe can be prepared in a manner known per se in which the corresponding arylalkyl halide is reacted with sulfites such as sodium sulfite or ammonium sulfite in aqueous or aqueous/alcholic 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 solvent such as phosphorus oxytrichloride 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, VII or IX according to process variant a), b), c) or d) proceeds advantageously in the manner of a 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 diisopropyl ethyl amine, is especially used, possibly in the presence of N,N-dimethylaminopyridine as the catalyst.

In another variant, the aminocarboxylic acids of the formula III, V, VII or IX 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 polymeric support designated by PS in the formula XII is a crosslinked polystyrene resin having a linker designated L as an intermediate chain, known as a Wang resin (S.W. Wang, Journal of the American Chemical Society (1973), 1328 p-benzyloxybenzyl alcohol polystyrene resin). Alternatively, other polymeric supports such as glass, cotton or cellulose having various intermediate chains L can be employed.

The intermediate chain designated by L is covalently bonded to the polymeric support and allows a reversible, ester-like bonding with the diamino acid of the formula XI, which during the further reaction remains stably bonded to the diaminocarboxylic acid, but under strong acidic reaction conditions, e.g. pure trifluoroacetic acid, releases the group located on the linker again.

The release of the desired compound of the formula I from the linker can be carried out in various places in the reaction sequence.

1.) In the case of a compound of the formula I in which R^3 and G are hydrogen, the α-sulfonylamino-ω-carboxylic acid derivative, after removal of the protective group E, is liberated by treatment of the resin with trifluoroacetic acid.

2.) If a compound of the formula I where R^3 is hydrogen and G is R^6-C(O)- is to be obtained, the release of the compound from the resin is carried out after simple acylation with R^6-C(O)-Y, as in 1).

3.) For the case of a compound of the formula I in which R^3 and G are R^6-C(O)-, the removal is only carried out after thorough diacylation with the aid of an acylating catalyst, e.g. dimethylaminopyridine, as in 1).

4) This procedure furthermore allows the radicals 2 to 13 defined in formula I for R^3 and G to be coupled at this position in the reaction sequence to the α-sulfonylamido-ω-aminocarboxylic acid bonded to the solid support using suitable reagents, e.g. alkyl halides, alkenyl halides, chloroformates, isocyanates, sulfonic acid derivatives or cyclic anhydrides. After removal of the resulting compounds from the solid support, the corresponding substituted

amines, urethanes, ureas, sulfonamides or amides, for example, are thus also obtained.

A. General procedure for the coupling of protected diaminocarboxylic acids of the formula XI to the solid support according to procedure e):

2 g of Wang resin (Nova-Biochem; loading 0.5 mmol/g) are allowed to swell in 20 ml of dry dichlormethane for 30 min (50 ml PET syringe with a Teflon filter on the syringe bottom). After filtering the solvent, the syringe is filled with a solution of 3.5 mmol of the appropriate ω-Teoc-α-Fmoc diaminocarboxylic acid (prepared according to D.H. Rich et al., Synthesis 198; 346), 3.5 mmol of diisopropylcarbodiimide and 0.5 mmol of N,N-dimethylaminopyridine in approximately 10 ml of dry dichloromethane and shaken at room temperature (RT) for 16 hours (h).

After filtering off the reaction mixture, the resin is washed several times with dichloromethane and dried and weighed to determine the yield.

B. Removal of the α-Fmoc protective group

The resin prepared as in A. is allowed to swell in the syringe in approximately 20 ml of dry dimethylformamide (DMF) and then, after filtering off the solvent, treated with 25 % strength piperidine/DMF solution and shaken at RT for 45 minutes (min). The resulting mixture is filtered and the resin remaining in the syringe is washed several times with dry DMF. (The filtrate and all wash solutions can be stored to determine the Fmoc removal; for implementation see: Solid Phase Peptide Synthesis - a practical approach, E. Atherton and R.C. Sheppard, IRL Press at Oxford University Press 1989).

C. Sulfonation of the free α-amino group

The contents of the syringe are then uniformly distributed into 4 smaller syringes provided with an inserted filter plate and treated with solutions of various sulfonic acid derivatives of the formula IV (in each case 1 mmol) and diisopropylethylamine (in each case 1 mmol) in 3 ml of dry DMF and shaken at

RT for 24 h. The reagent solution is then washed out and the resin is washed several times with DMF.

D. Removal of the Teoc protective group

The resin prepared as in C. is treated with a molar N-tetrabutylammonium fluoride solution in DMF (in each case approximately 3 ml) and shaken at RT for 2 hours. The reagent solutions are filtered and the remaining resin is washed several times with DMF. The syringe contents of each of the 4 individual syringes are then distributed, for example, into each of a further 3 prepared syringes. (In each case 1x 0.05 mmol and 2x 0.1 mmol).

E.

1: Removal from the solid support

In each case approximately 1/5 of the contents of a syringe is washed with dichloromethane (approximately 10 ml) to remove the substance from the solid support, dried and shaken at RT for 1 hour with approximately 1 ml of a solution of 95% trifluoroacetic acid, 2% H_2O and 3% triisopropylsilane.

The filtered solution from the syringe is evaporated, and precipitated with diethyl ether. The solid residue is filtered for further purification and dried.

2: Acylation with carboxylic acid derivatives of the formula R^6-C(O)-Y:

The other syringes are in each case filled with 1 molar solutions of acetic anhydride (1 equivalent based on liberated amine, or 3 equivalents for bis-acylations) and a corresponding amount of triethylamine in DMF and shaken at RT for 16 hours (completeness of the acylation can be checked, for example, by the Kaiser-Ninhydrin test/for implementation see: Solid Phase Peptide Synthesis - a practical approach, E. Atherton and R.C. Sheppard, JRL Press at Oxford University Press 1989).

3: Removal of the compounds of the formula XV from the solid support

The resins prepared in 2: are washed with dichloromethane as described in 1:, dried and treated at RT for 1 h with trifluoroacetic acid/H_2O/triisopropylsilane 95/2/3. The solutions obtained are worked up as described in 1:.

Physiologically tolerable salts are prepared from compounds of the formula I capable of salt formation, including their stereoisomeric forms, 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, trifluoromethylsulfonic, acetic, oxalic, tartaric, succinic or trifluoroacetic acid.

The invention also relates to pharmaceuticals comprising an efficacious content 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 inflammation, 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 solubiliizers 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 the formula I, daily doses of approximately 20 mg to 1000 mg, preferably approximately 100 mg to 500 mg, 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 are given in degrees Celsius, RT means room temperature (22-26°C). Abbreviations used are either explained or correspond to the customary conventions.

Example 1 (R)- (4-Chlorobiphenylsulfonyl)citrulline

Prepared according to process variant a)

1.7 g (9.7 mmol) of R-citrulline are dissolved in 19.4 ml of 0.5 N NaOH and, after addition of 40 ml of THF, slowly treated at 0 °C with a further 19.4 ml of the sodium hydroxide solution and at the same time 9.7 ml of a 1 molar solution of 4-chlorobiphenylsulfonyl chloride. After stirring at room temperature for 16 hours (h), the reaction mixture is concentrated on a rotary evaporator and treated with 20 ml of ethyl acetate. On acidification with 1 M HCl, a white precipitate is deposited, which is filtered off with suction and dried.

Yield: 2.26 g (54% of theory)

^{1}H-NMR (DMSO-d_6): 1.2-1.7 (2m, 4 H); 2.9 (dd, 2 H); 3.7 (dd, 1 H); 5.4 (s, 2 H); 5.9 (t, 1 H); 7.5-7.9 (2 d, s, 8 H); 8.2 (d, 1H)

Example 2 R-(4-Chlorobiphenylsulfonyl)- Lys(Boc)-OH

Prepared according to process variant c)

The reaction of 5.15g (21mmol) of H-D-Lys(Boc)-OH to give (4-chlorobiphenylsulfonyl)-R-Lys(Boc)-OH is carried out as described in Example 1; the workup, however, is carried out by extraction with ethyl acetate and evaporation of the solvent under reduced pressure.

Yield: 9.3 g (89% of theory)

^{1}H-NMR (DMSO-d_6): 1.1-1.7 (m,15H), 2.8 (dd,2H), 3.7 (m,1H), 6.7 (t,1H), 7.6; 7.8 (2d, 4H), 7.9 (m,4H), 8.2 (d,1H)

Example 3 R-(4-Chlorobiphenylsulfonyl)- Lys-OH

4.97g (10 mmol) of the compound from Example 2 are treated for 30 min at RT with 15 ml of 50% strength TFA in methylene chloride. Evaporation under reduced pressure affords the desired compound.

Yield: 3.73 g (94% of theory)

^{1}H-NMR (DMSO-d_6): 1.1-1.7 (m, 6H), 2.8 (dd,2H), 3.7 (m,1H), 6.6 (m,2H), 7.6; 7.8 (2d, 4H), 7.9 (m,4H), 8.2 (d,1H)

Example 4 4-Chlorobiphenylsulfonyl-N-epsilon-(5-methylisoxazol-4-carbonyl)- Lys-OH

0.15 g (0.345 mmol) of the (4-chlorobiphenylsulfonyl)lysine from Example 3 is stirred at RT for 6 h with 50.1 mg (0.345 mmol) of 5-methylisoxazole-4-carbonyl chloride and 86.9 mg (1.035 mmol) of $NaHCO_3$ in 5 ml of acetonitrile. The solvent is then distilled off under reduced pressure, the residue is taken up in ethyl acetate and the solution is extracted several times by shaking under hydrochloric acid and also neutral conditions. After drying the organic phase and filtering off the drying agent, the solution is evaporated under reduced pressure.

Yield: 0.11 g (63% of theory)

^{1}H-NMR (DMSO-d_6): 1.1-1.7 (mm, 7 H); 2.6 (2 s, 3 H); 2.8; 3.1 (2 m, 2 H);
3.7 (m, 1 H); 7.6; 7.8 (2 d, 4 H); 7.9 (m, 5 H);
8.2 (d, 1 H); 8.8 (2 s, 1 H)

Example 5 (4-Chlorobiphenylsulfonyl)-N-delta-(phenylsulfonylamino-carbonyl)-Orn-OH

Prepared according to process variant d)

5 a. Reaction of H-Orn(Z)-OtBu to give 4-chlorobiphenylsulfonyl-Orn(Z)-OtBu:

11.27 g (31.4 mmol) of H-Orn(Z)-OtBu-hydrochloride are reacted with 9.02 g (31.4 mmol) of 4-chlorobiphenylsulfonyl chloride and 10.7 ml (61.8 mmol) of diisopropylethylamine at 0 °C in 200 ml of THF. After 4 h, the batch is evaporated under reduced pressure and the residue is extracted, after taking it up in ethyl acetate, by shaking under hydrochloric acid, neutral and basic conditions (sodium carbonate solution). After drying the organic phase, the desired product is obtained after evaporation to dryness.

Yield: 16.7 g (93% of theory)

^{1}H-NMR (DMSO-d_6): 1.5 (s, 9 H); 1.3-1.5 (m, 4 H); 2.9 (m, 2 H); 3.6 (m, 1 H); 5.0 (s, 2 H); 7,3 (m, 6 H); 7,5; 7,7 (2d, 4 H); 7,8 (s, 4 H); 8,2 (d, 1 H)

5 b. Removal of the benzyloxycarbonyl protective group (Z)

16.7 g (29 mmol) of the product from 5a is dissolved in methanol-ethyl acetate 1:1 and hydrogenated with 4 g of 10% Pd/C under a slight overpressure for 16 h. The catalyst is then filtered off and the residue is evaporated under reduced pressure.
Yield: 11.2 g (91% of theory)
^{1}H-NMR: The characteristic signals of the protective group are absent (5.0; 7.3).

5 c. Reaction of 5b to give the phenylsulfonylurea derivative:

0.5 g (1.14 mmol) of the compound mentioned under 5 b is reacted with 0.23 ml of phenylsulfonyl isocyanate in dimethylacetamide at RT. After 16 h, the solvent is removed and the crystalline product precipitating from ethyl acetate is aftertreated with ether. Diethyl ether residues are removed under reduced pressure.
Yield: 0.53 g (75% of theory)

^{1}H-NMR (DMSO-d_6): 1.1 (s, 9 H); 1.3-1.5 (m, 4 H); 2.9 (m, 2 H); 3.6 (m, 1 H); 6.5 (t, 1 H); 7.4-7.9 (mm, 14 H); 8.2 (d, 1 H); 10.6 (s, 1 H)

5d. Removal of the protective group of Example 5c:

0.52 g of the abovementioned product 5 c is stirred at RT for 45 min with 5 ml of TFA. TFA is removed under reduced pressure; the residue is coevaporated twice wth toluene, suspended in diethyl ether and separated off as a white crystalline solid as in Example 5.

Yield: 0.4 g (84% of theory)

^{1}H-NMR (DMSO-d_6): 1.3-1.5 (m, 4 H); 2.9 (m, 2 H); 3.6 (m, 1 H); 6.5 (t, 1 H); 7.4-7.9 (mm, 14 H); 8.2 (d, 1 H); 10.6 (s, 1 H)

Example 6 2-(2R)-(4-Chlorobiphenylsulfonylamino)-5-phthalimidoyl-pentanoic acid

0.7 g (1.67 mmol) of 2-(2R)-(4-chlorobiphenylsulfonylamino)-5-amino-pentanoic acid hydrochloride (prepared according to process variant c) is heated to 150 °C for 1 hour with 0.358 g (2.42 mmol) of phthalic anhydride. After the evolution of gas has subsided, the reaction mixture is taken up in dichloromethane and chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether/glacial acetic acid 10/10/1).

Yield: 29.6 mg (34.6% of theory)

Melting point: 178°C

^{1}H-NMR (DMSO-d_6): 1.3 - 1.7 (m, 4H); 3.4 - 3.6 (t, 2H); 3.7 - 3.8 (m, 1H); 7.5 (d, 2H); 7.7 (d, 2H); 7.7 - 7.9 (m, 8H); 8.2 (d, 1H, NH); 12.6 (s, 1H, broad, OH)

Example 7 2-(2R)-(4 -Chlorobiphenylsulfonylamino)-5-(1-oxo-1,3-dihydro-isoindol-2-yl)pentanoic acid

0.32 g (0.76 mmol) of 2-(2R)-(4-chlorobiphenylsulfonylamino)-5-amino-pentanoic acid hydrochloride is dissolved in 30 ml of glacial acetic acid with 0.186 g (1.35 mmol) of phthalaldehyde and stirred at 100 °C for 3 hours. The solution is cooled to 0 °C, and the precipitate which is deposited is filtered off with suction and chromatographed on a silica gel column (eluent: ethyl acetate/petroleum ether/glacial acetic acid 10/10/2).

Yield: 185 mg (52% of theory)

Melting point: >234 °C (decomposition)

^{1}H-NMR (DMSO-d_6): 1.4 - 1.7 (m, 4H); 3.1 (m, 1H); 3.4 - 3.6 (m, 2H); 4.4 (d, 1H); 4.5 (d, 1H); 6.9 (s, 1H, broad, OH); 7.4 - 7.9 (m, 13H)

Example 8 R-(4-Biphenylethylsulfonyl)-Lys-OH

Prepared according to process variant e)
α-Fmoc-ε-Teoc-D-Lys-OH (0.18 mmol) is coupled under the abovementioned conditions to 100 mg of (0.05 mmol) Wang resin, and after removal of the α-Fmoc protective group is reacted with 0.18 mmol of 4-biphenylethylsulfonyl chloride/diisopropylethylamine. After removal of the ε-Teoc protective group with 1-molar tetrabutylammonium fluoride/DMF solution and removal of the resulting lysine derivative from the resin (trifluoroacetic acid (TFA)/H_2O/ triisopropylsilane, 95/2/3), the resulting solution is evaporated. The solid residue is washed with diethyl ether, dissolved in a 10% strength aqueous acetic acid and lyophilized to dryness, and yields 20 mg of the title compound in the form of an amorphous white powder.

HPLC (RP 18; UV 210 nm): Gradient 0-15 min. B = 5-70% (A = 100% H_2O/ 0.1% trifluoroacetic acid; B = 100% acetonitrile/ 0.1% trifluoroacetic acid)
T_R = 9.49 min. (95%)

Example 9 R-(4-Biphenylethylsulfonyl)-N-epsilon-acetyl-Lys-OH

As described in Example 8, 0.35 mmol of α-Fmoc-epsilon-Teoc-D-lysine is coupled to 200 mg (0.10 mmol) of Wang resin, Fmoc deprotected and reacted with 4-biphenylethylsulfonyl chloride/diisopropylethylamine. After removal of the ε-Teoc protective group, the resulting lysine derivative is stirred at room temperature for 15 hours with 0.15 mmol of acetic anhydride/0.15 mmol of diisopropylethylamine. After thorough washing with DMF, dichloromethane and drying of the resin (0.1 mm Hg) overnight, the desired compound is removed from the solid support using trifluoroacetic acid/ H_2O/ triisopropylsilane =

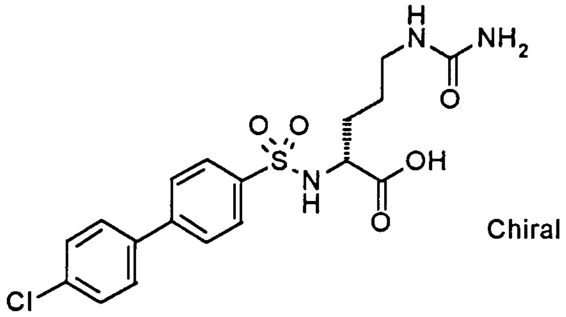
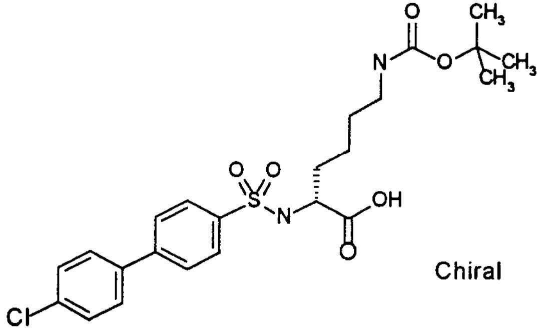
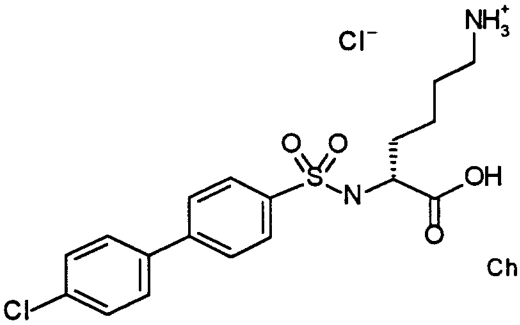
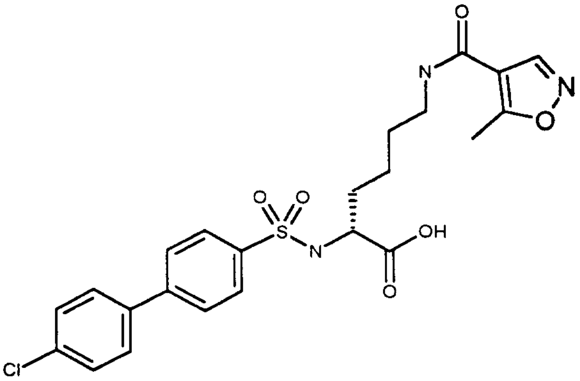
95/2/3 and worked up as in Example 8. 40 mg of the compound are obtained as an amorphous white powder.

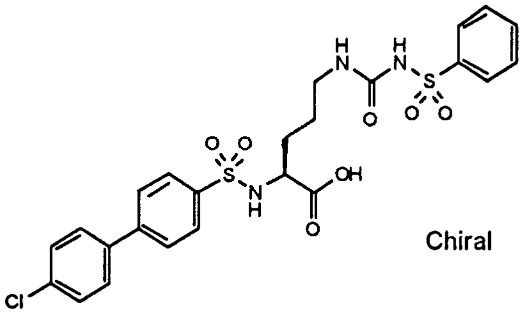
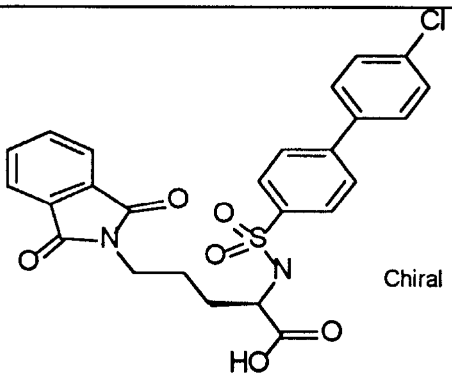
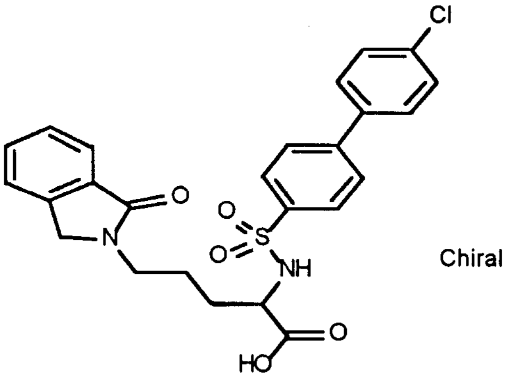
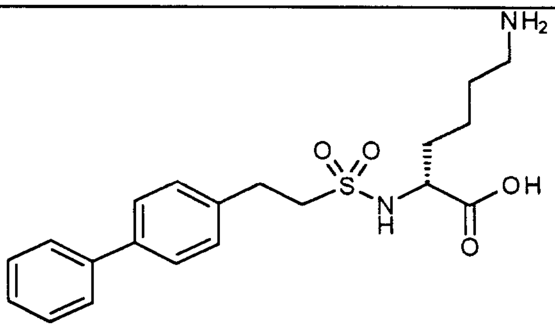
HPLC (RP 18; UV 210 nm): Gradient 0-15 min. B = 5-70% (A = 100% H_2O/ 0.1% trifluoroacetic acid; B = 100% acetonitrile/ 0.1% trifluoroacetic acid)

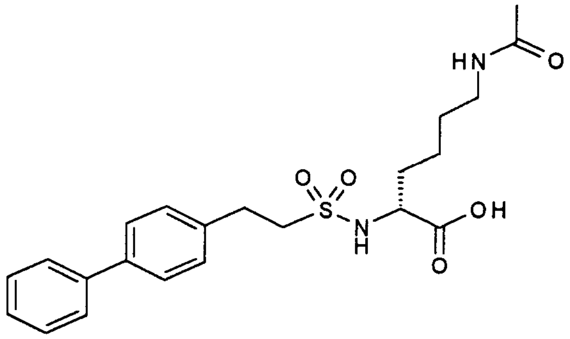
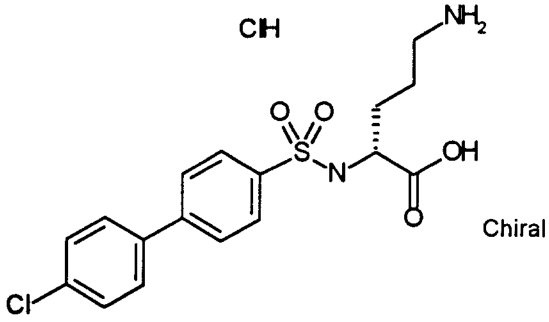
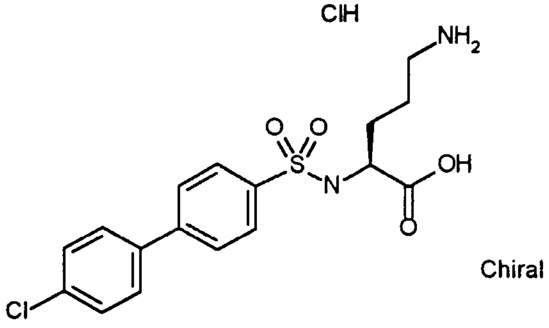
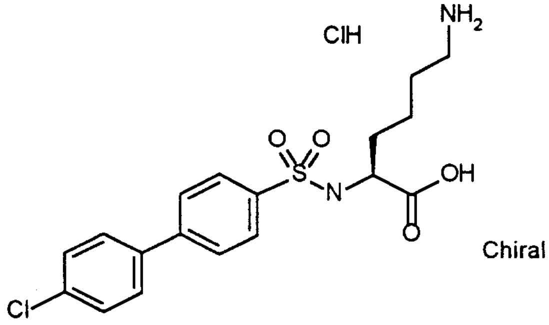
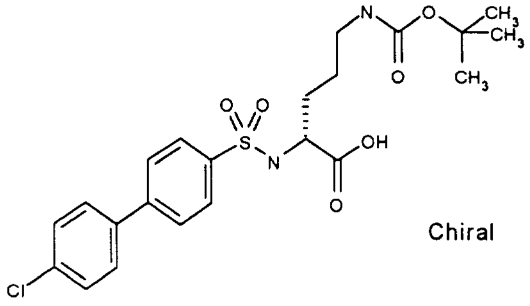
T_R = 10.39 min. (93%)

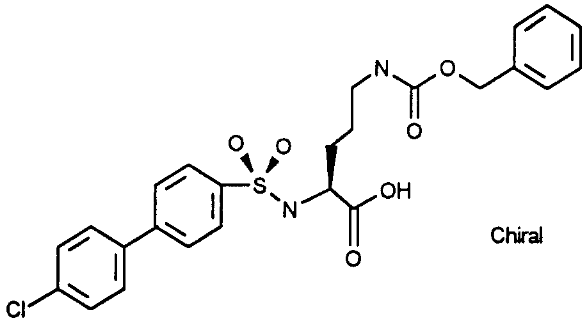
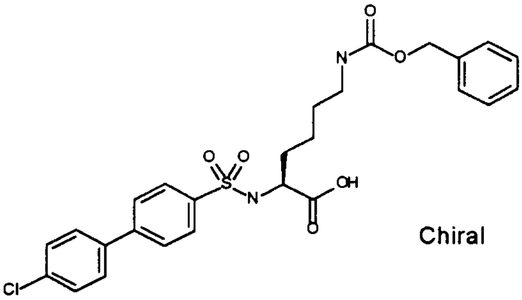
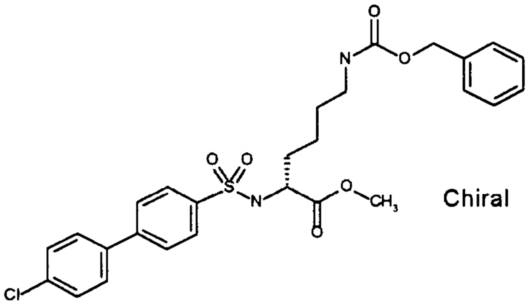
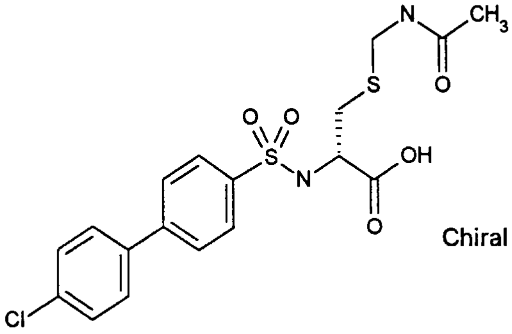
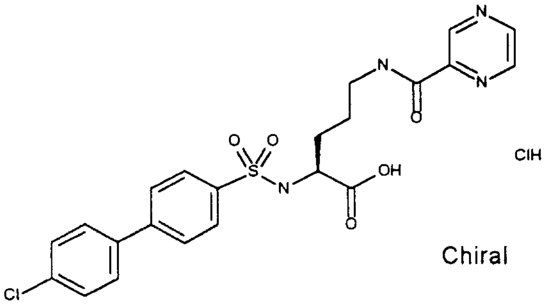
The examples mentioned in Table 1 which follows have been prepared analogously to the preceding examples.

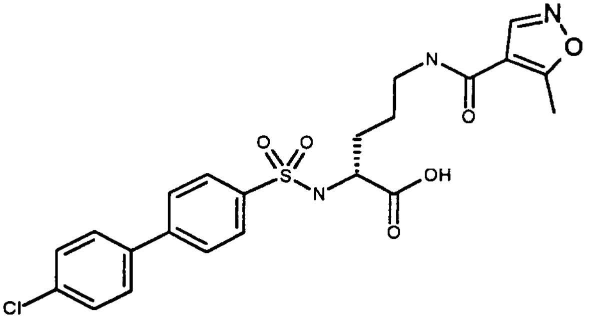
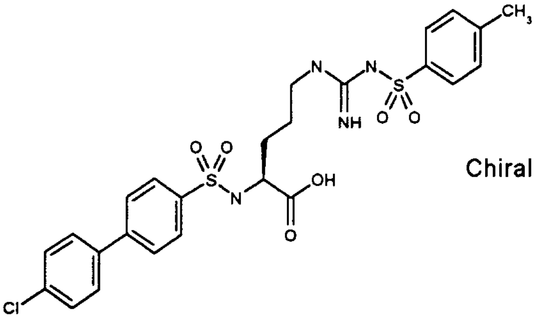
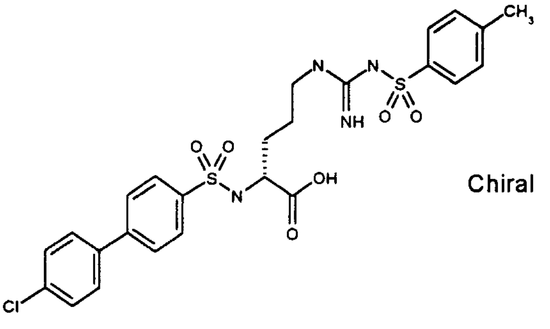
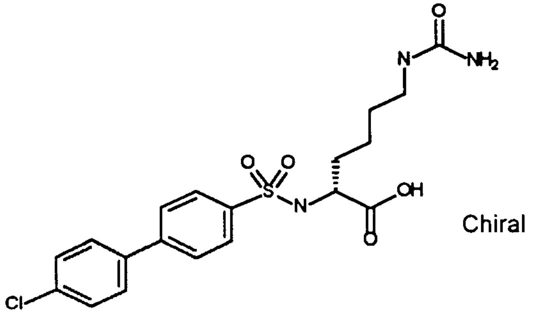
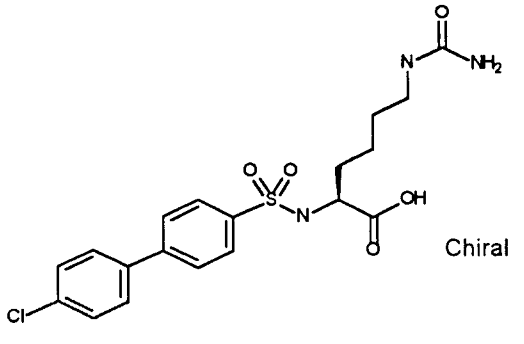
Table 1:

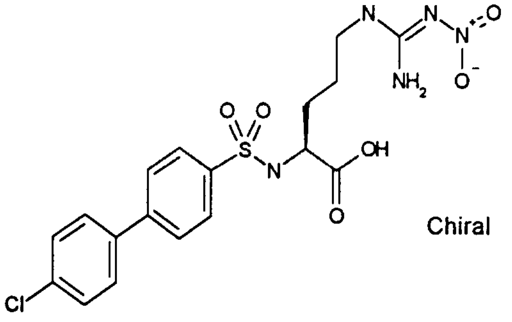
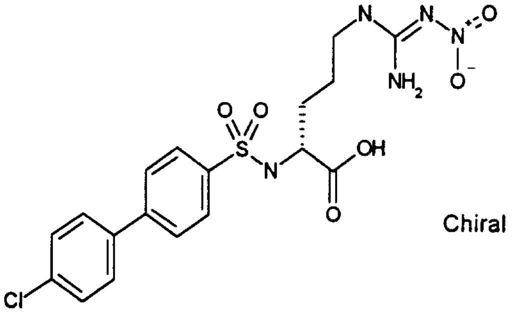
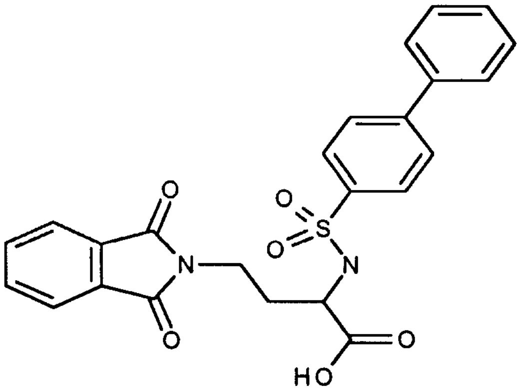
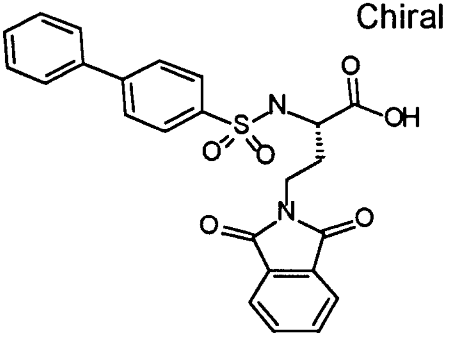
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
1			426.1	R isomer
2			497.2	R isomer
3			397.2	R isomer
4			506.1	R isomer

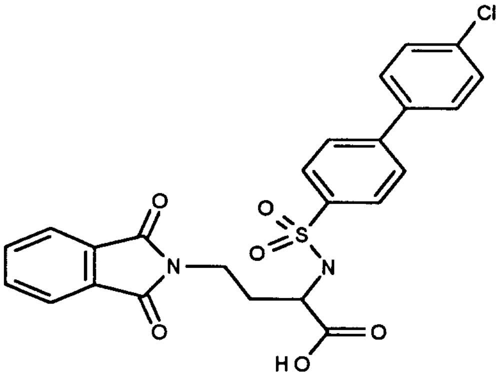
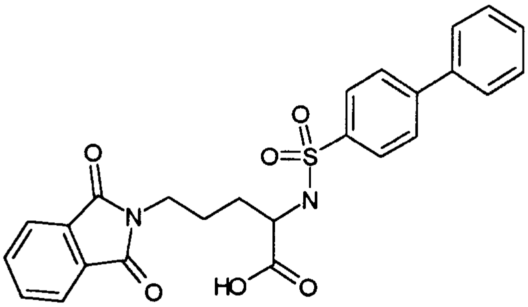
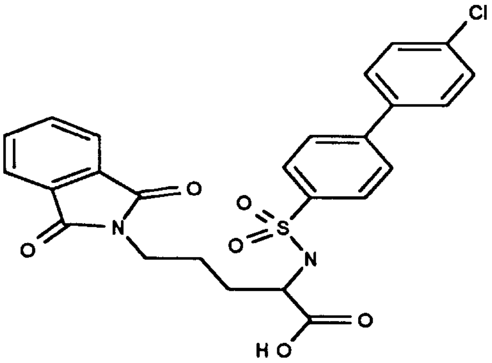
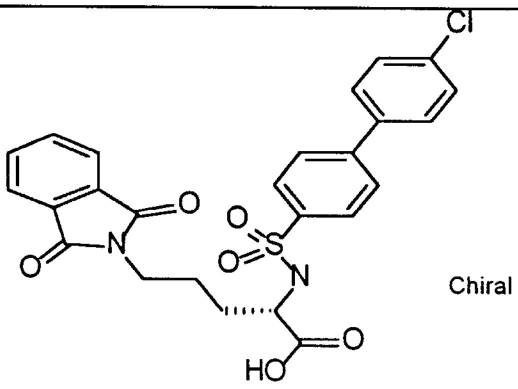
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
5			588.2 (M + Na)	S isomer
6		178	513.2	R isomer
7		233-35	521.1 (M+Na)	R isomer
8			391.2 (M + H)	R isomer

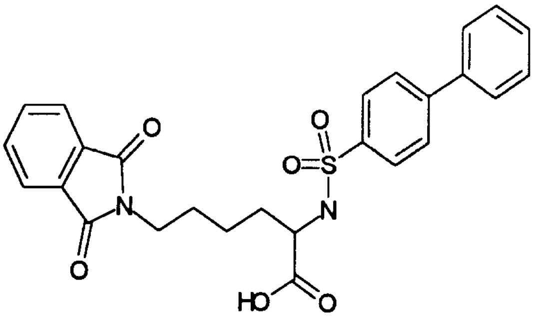
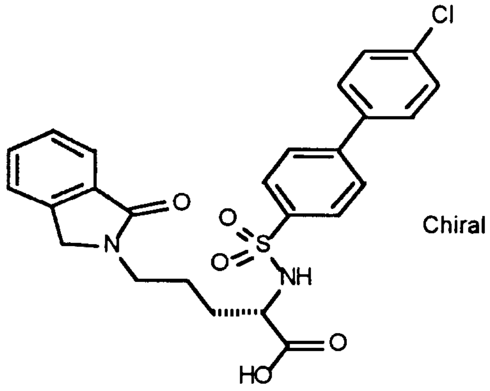
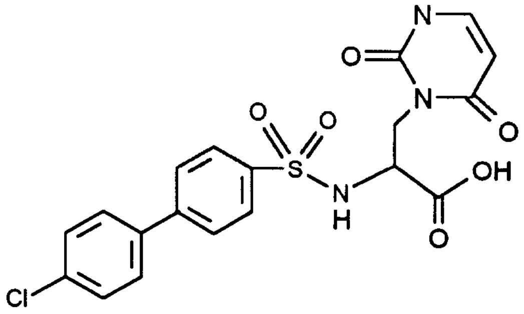
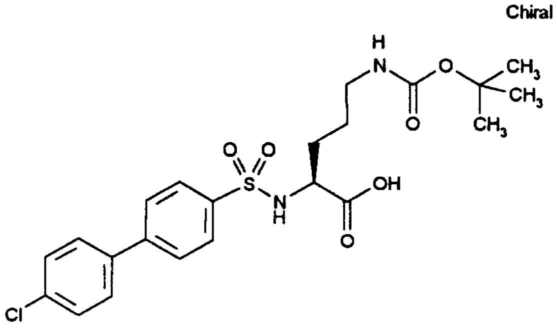
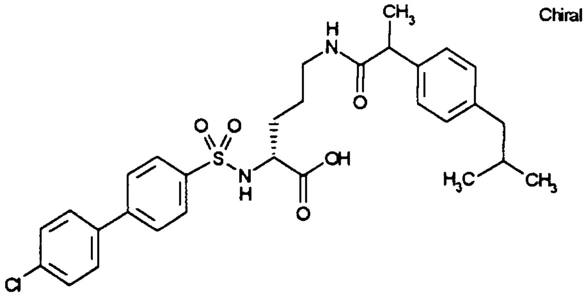
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
9			433.2 (M + H)	R isomer
10			383.1	R isomer
11			383.1	S isomer
12			397.2	S isomer
14			483.2	R isomer

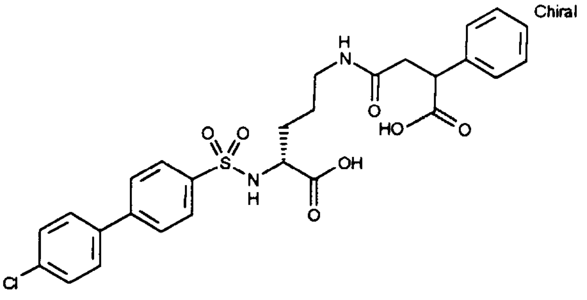
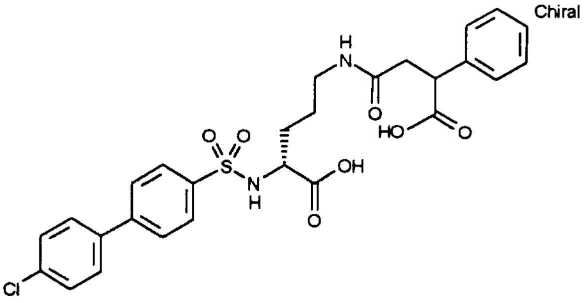
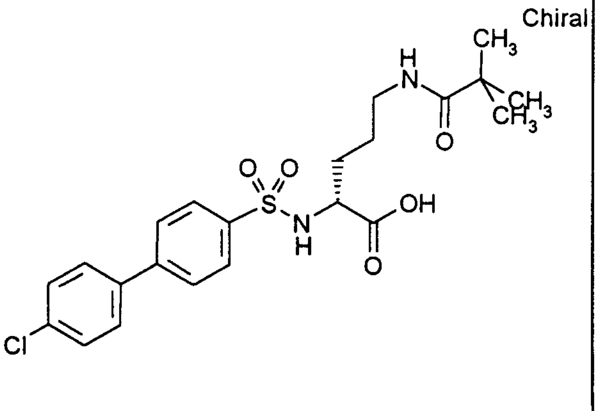
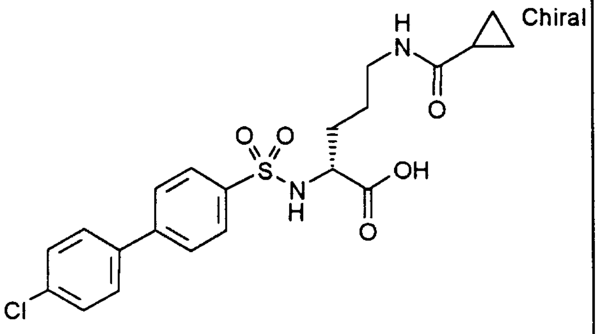
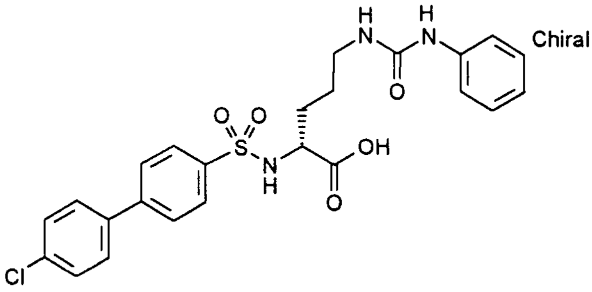
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
15			517.1	S isomer
16			529.2 (M - 1)	S isomer
17		69 - 70		R isomer
18			443.1	R isomer
19			489.1	S isomer

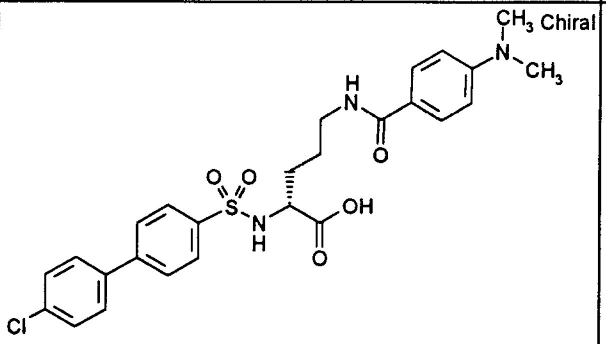
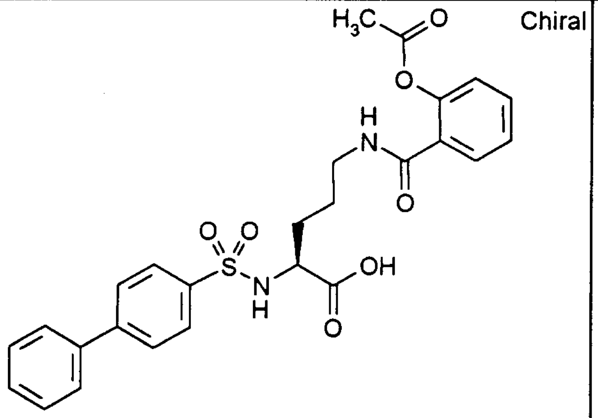
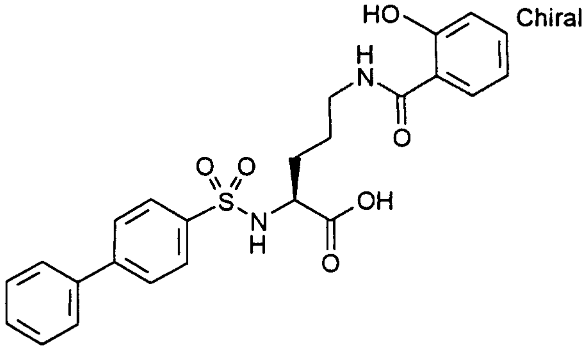
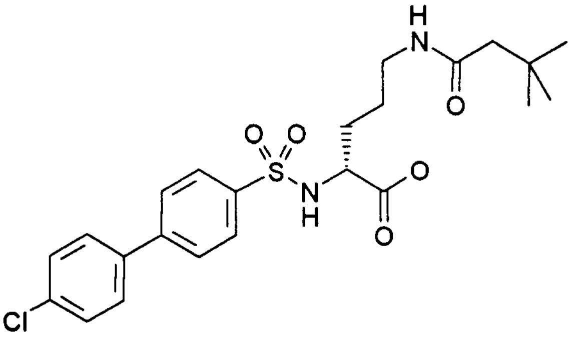
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
20			492.1	R isomer
21			579.2	S isomer
22			579.2	R isomer
23			440.1	R isomer
24			440.1	S isomer

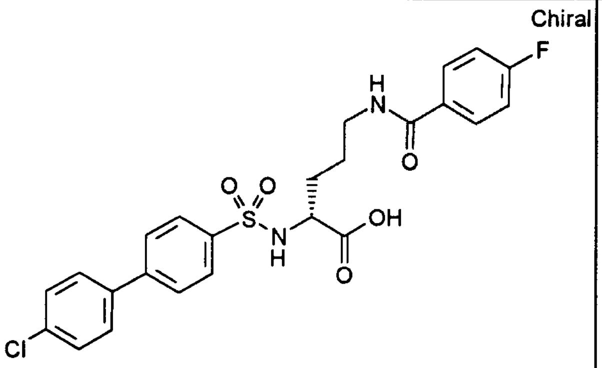
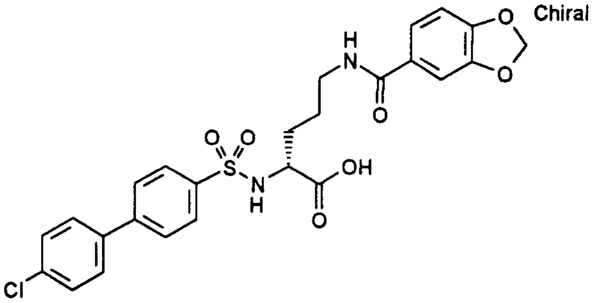
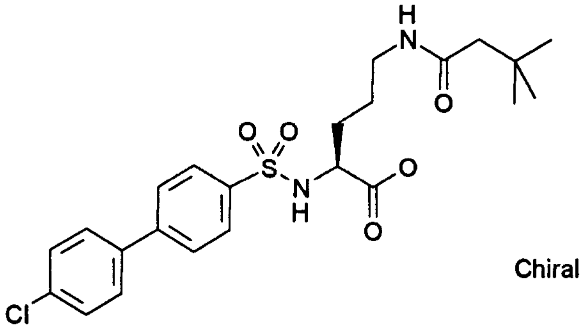
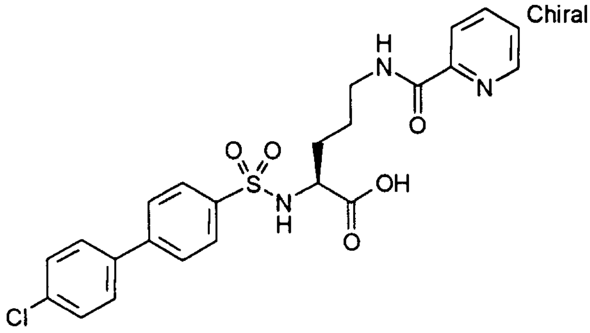
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
25			470.2	S isomer
26			470.2	R isomer
27		176	465.1	racemate
28		167	465.2	S isomer

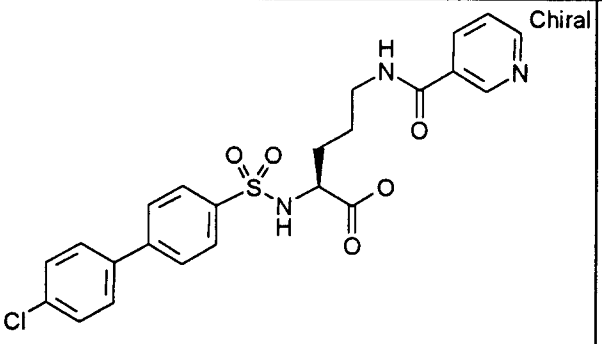
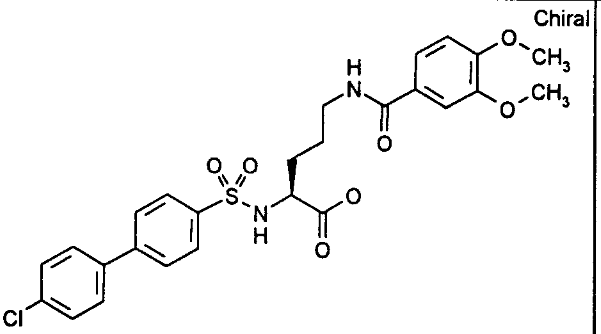
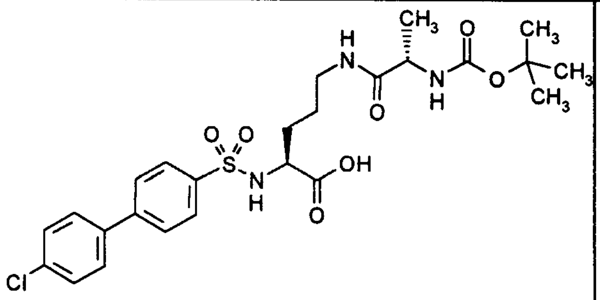
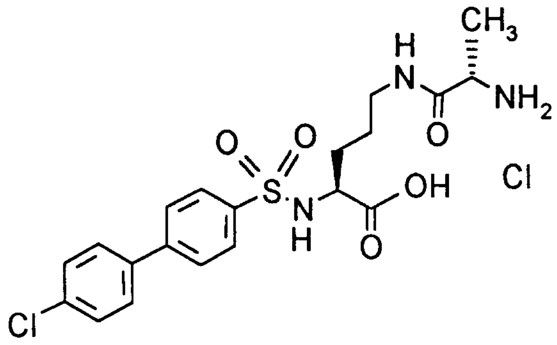
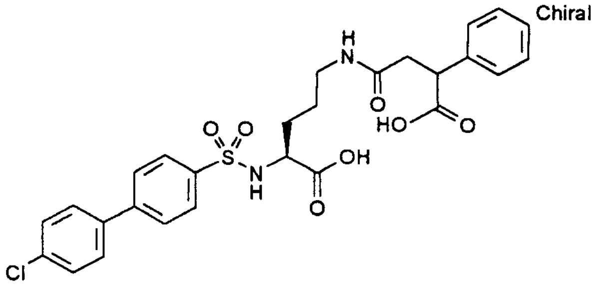
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
29		238	499.2	racemate
30		168	479.2	racemate
31		132	513.2	racemate
32		179	513.2	S isomer

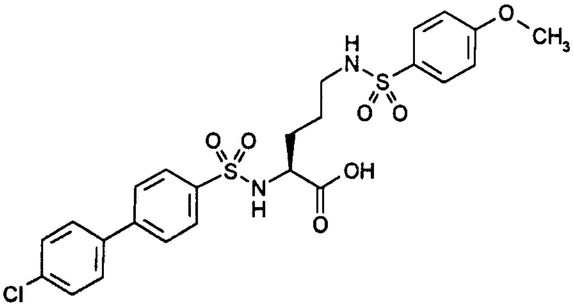
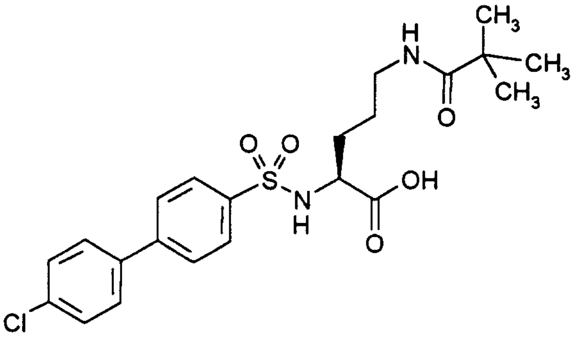
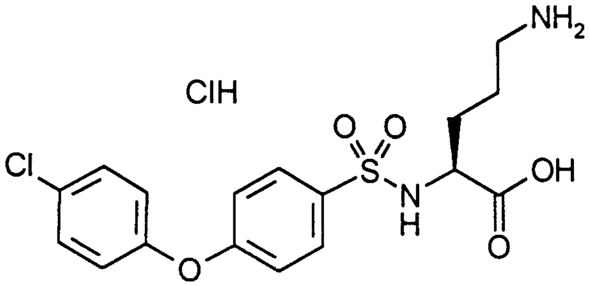
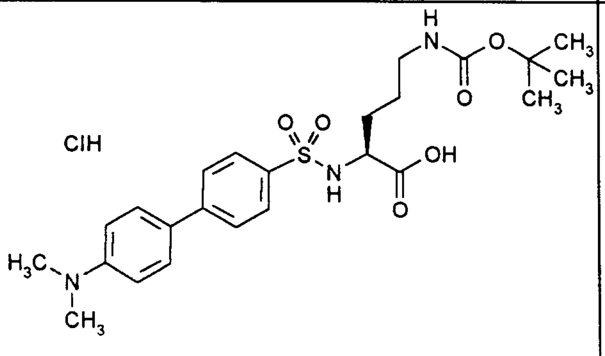
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
33		181	493.2	racemate
34		213-15	521.1 (M+Na)	S isomer
35			450.1 (M-1)	racemate
36			483.1	S
37			571.2	R,S/R,R

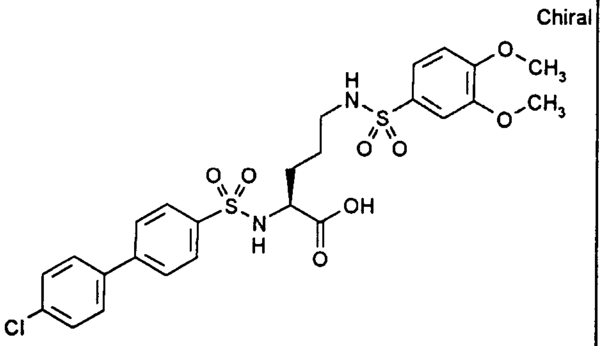
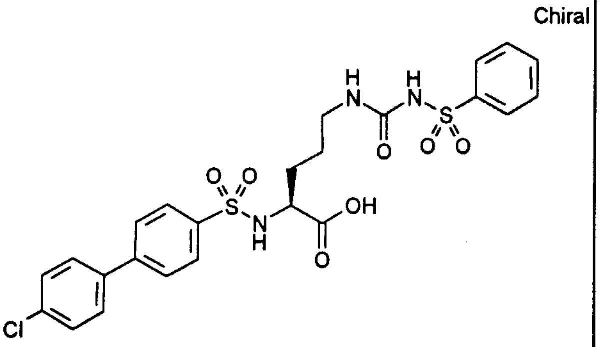
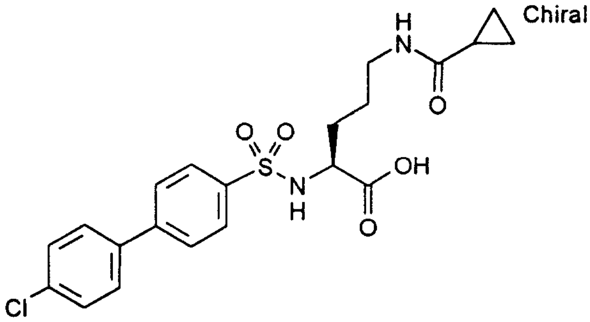
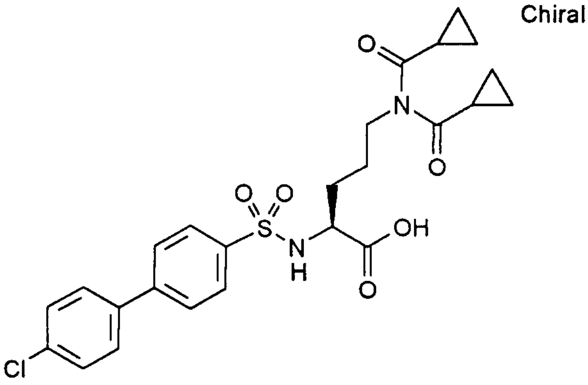
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
38			559.1	R(A)
39			559.2	R(B)
40			467.2	R
41			451.2	R
42			502.2	R

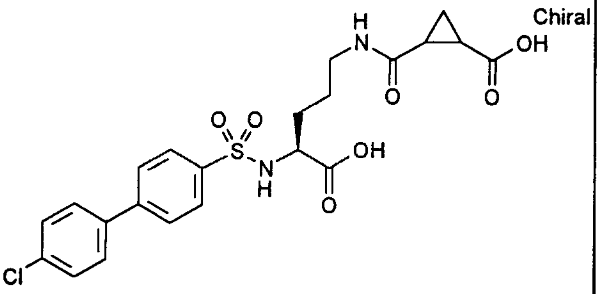
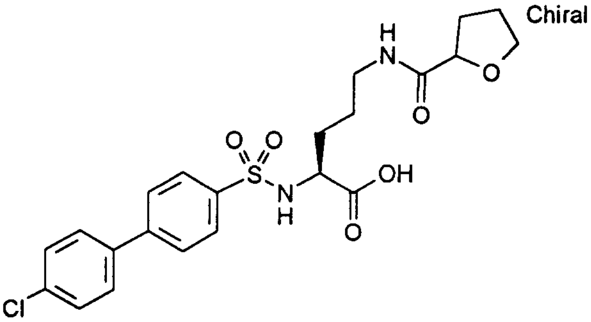
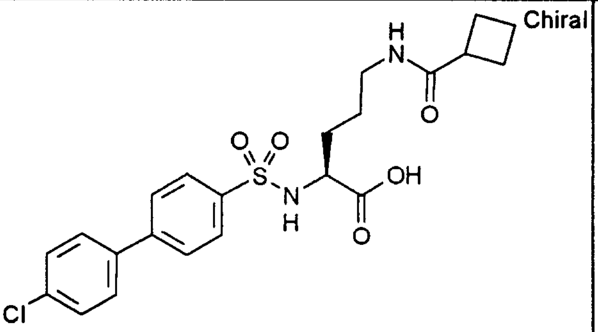
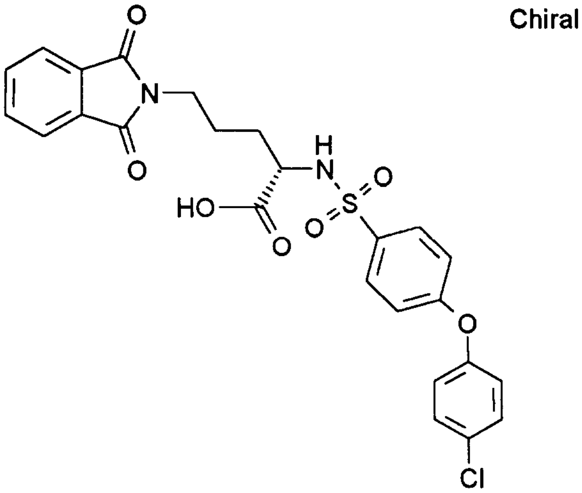
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
43			530.1	R
44			511.2	S
45			469.2	S
46			481.2	R

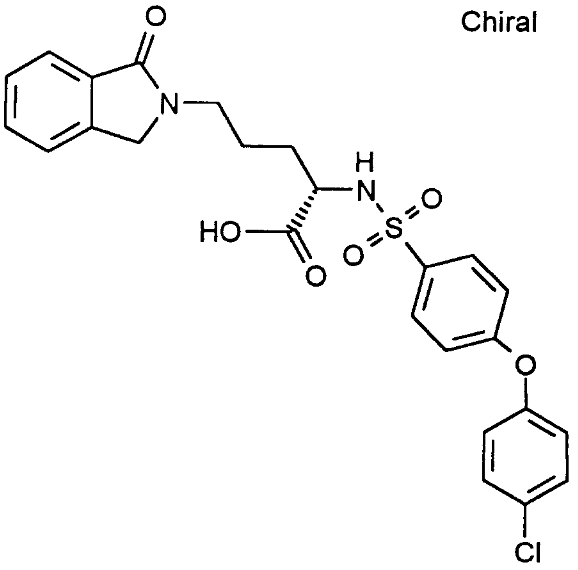
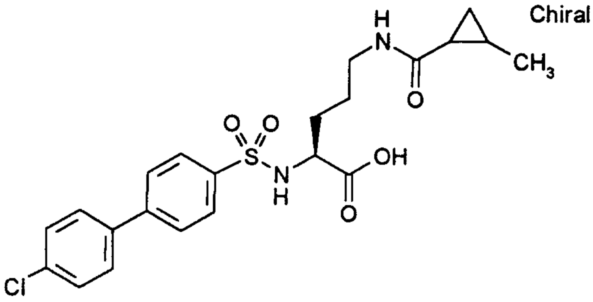
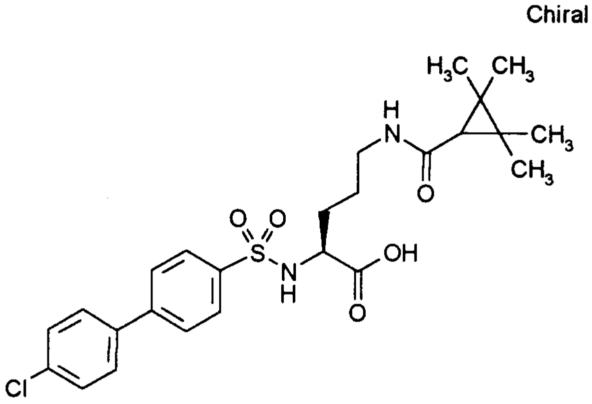
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
47			505.2	R
48			531.2	R
49			481.1	S
50			488.1	S

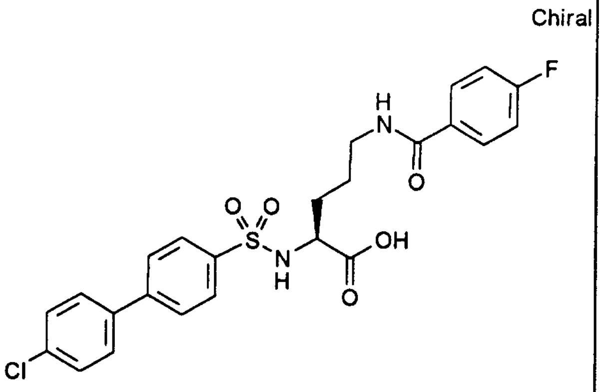
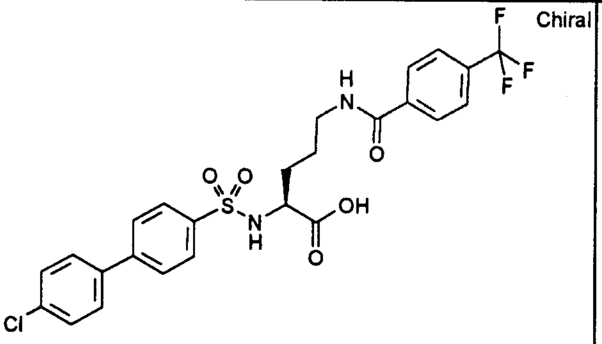
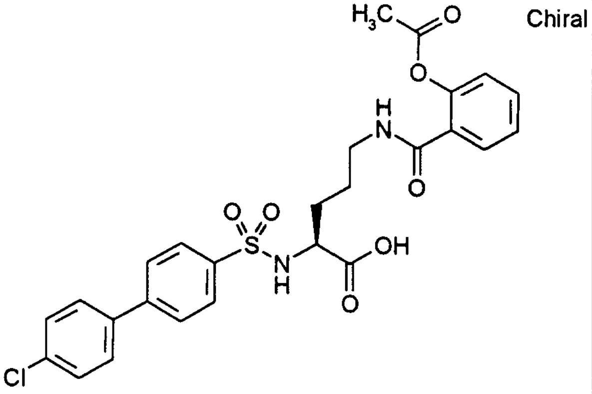
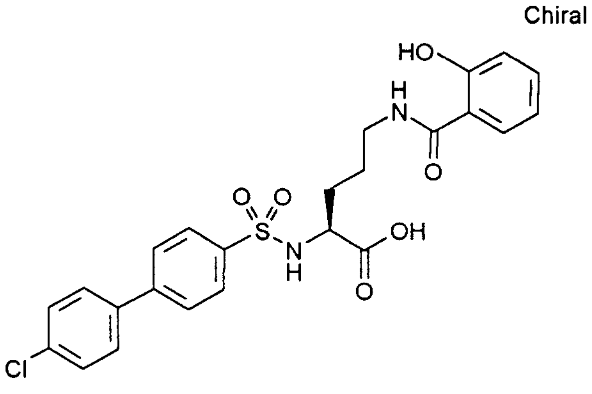
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
51			488.1	S
52			547.2	S
53			554.2	S,S
54			454.2	S,S
55			559.2	S,R/S,S

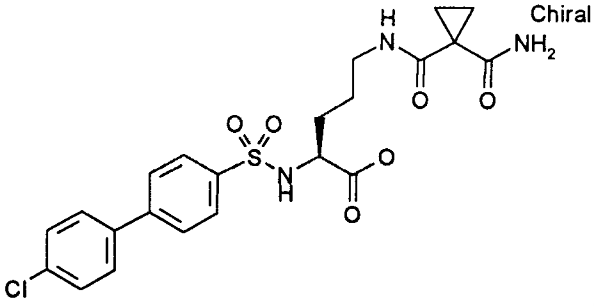
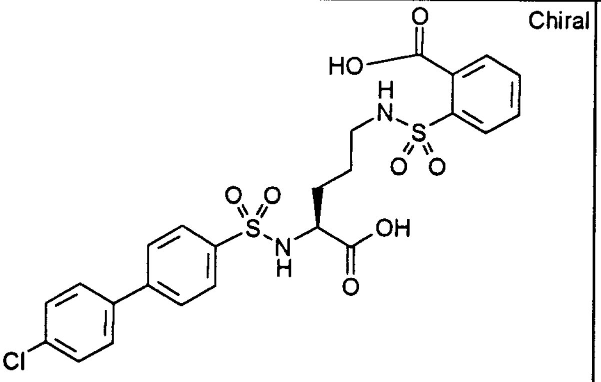
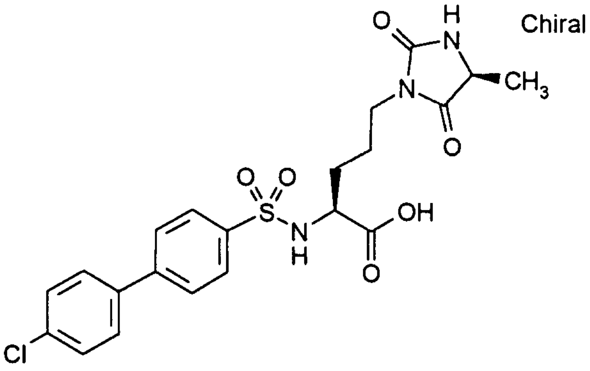
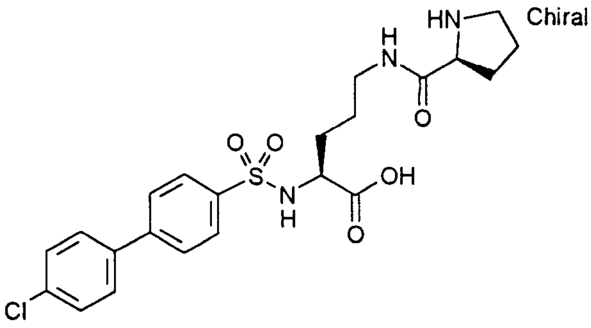
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
56	Chiral 		553.1	S
57	Chiral 		467.2	S
58			399.2	S
59			492.3	S

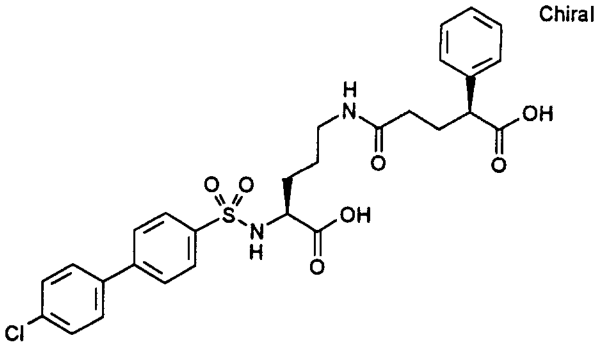
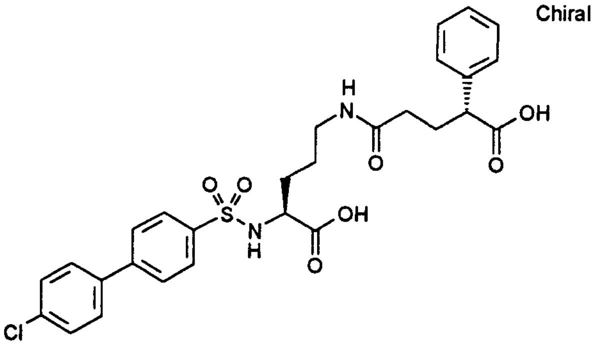
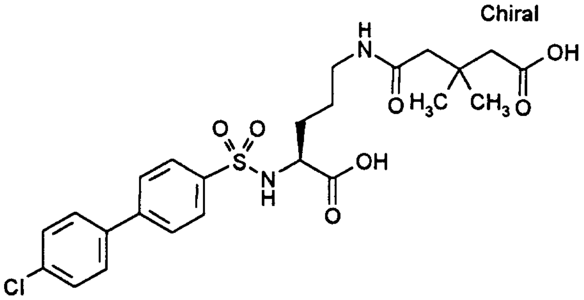
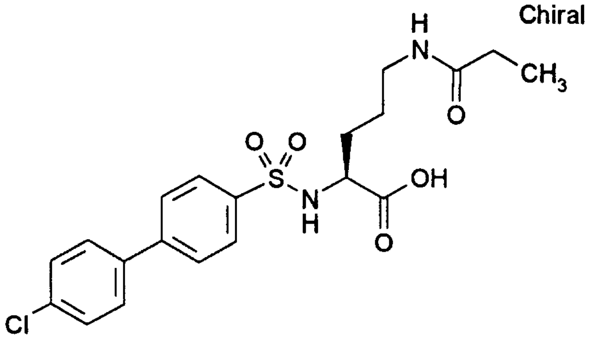
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
60			583.1	S
61			566.2	S
62			451.2	S
63			519.2	S

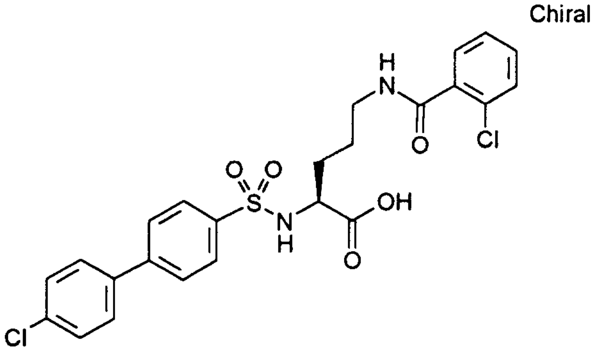
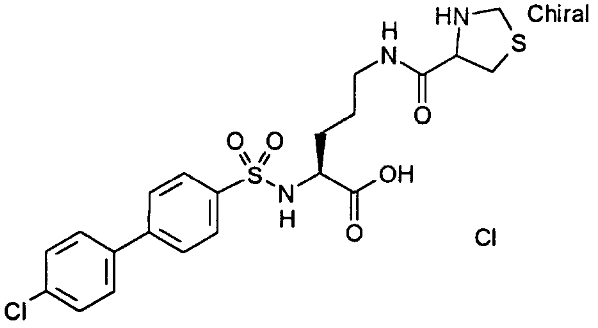
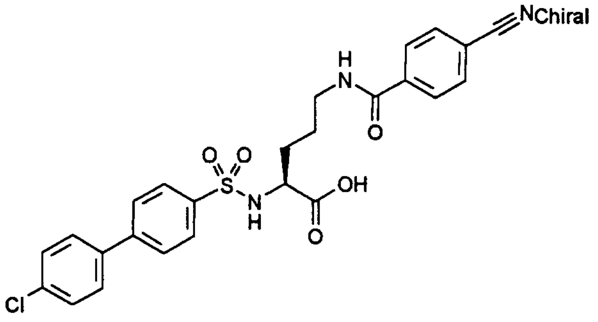
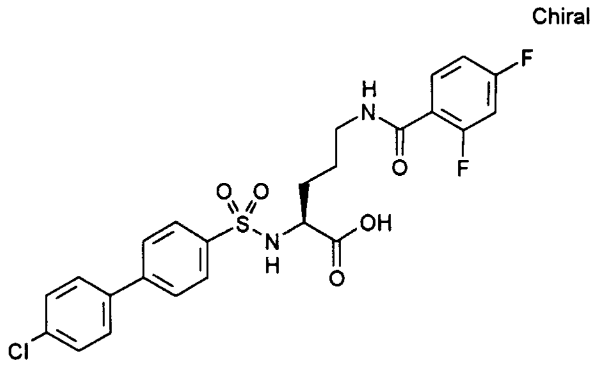
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
64			495.2	S
65			479.2	S
66			465.2	S
67			529.2	S

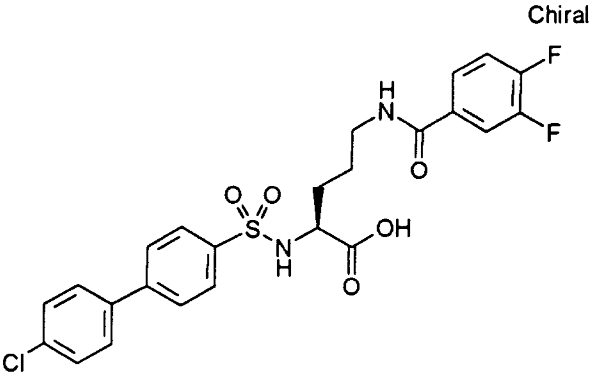
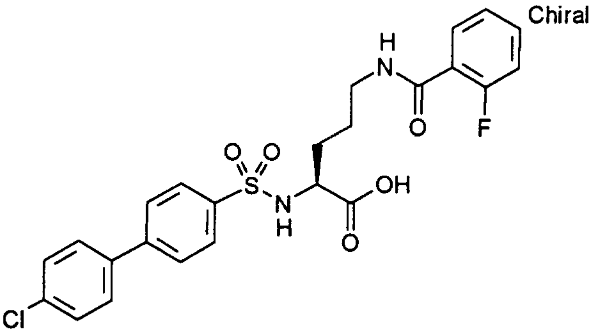
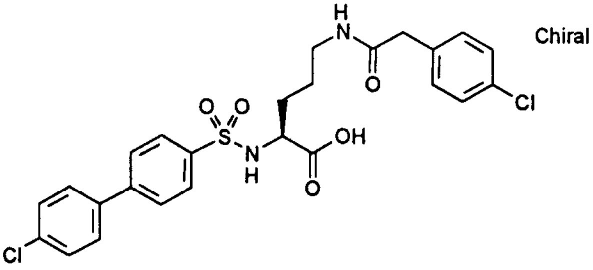
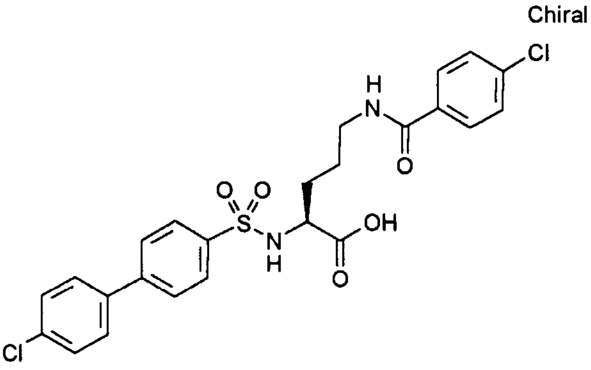
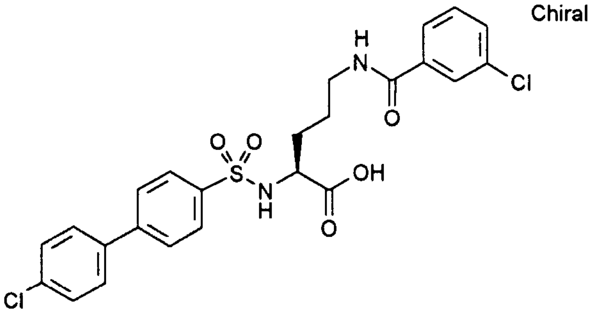
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
68		223-225°C		S
69			465.2	"S"
70			507.3	S

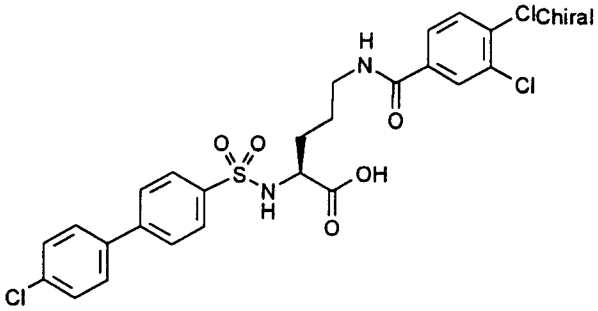
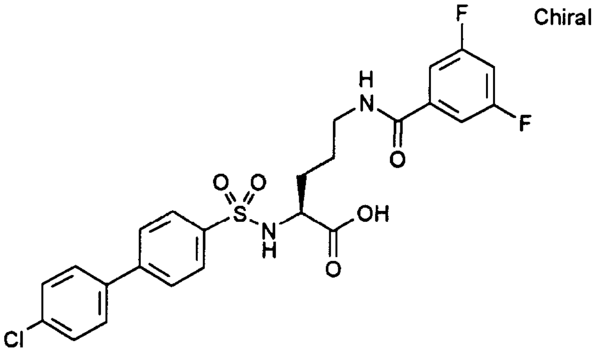
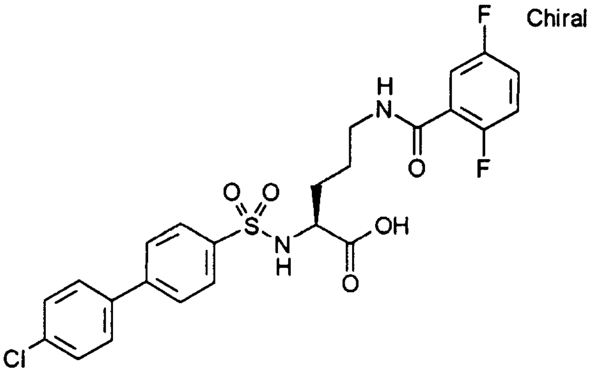
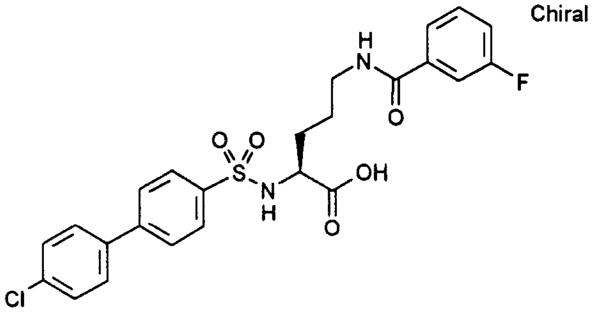
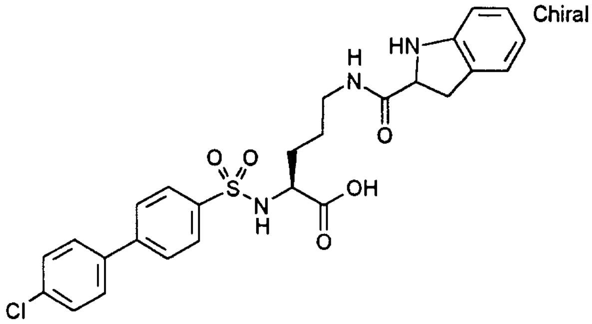
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
71			505.1	S
72			555.1	S
73			545.2	S
74			503.1	S

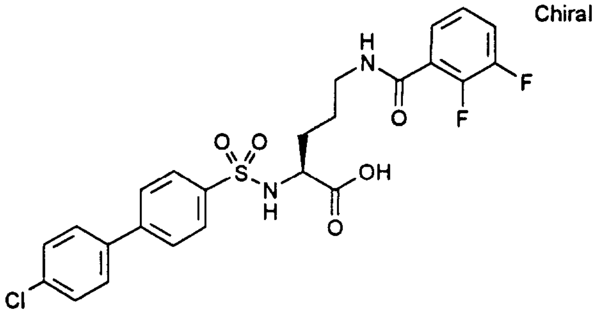
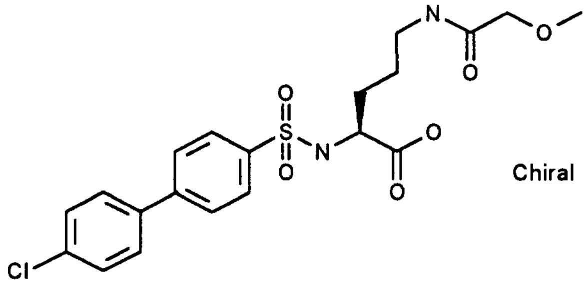
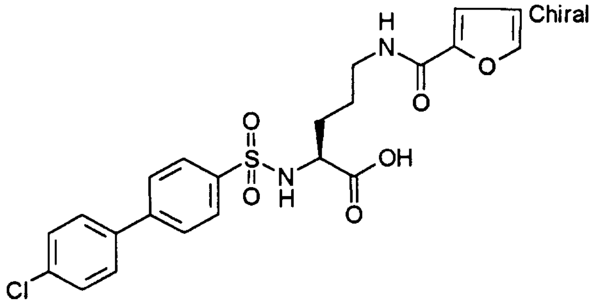
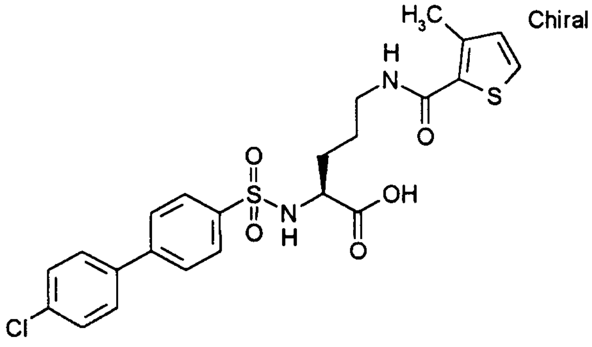
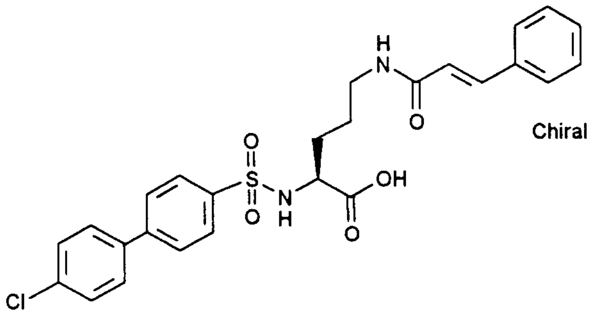
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
75			494.1	S
76			565.2M-H	S
77			480.2	S
78			478.2	S

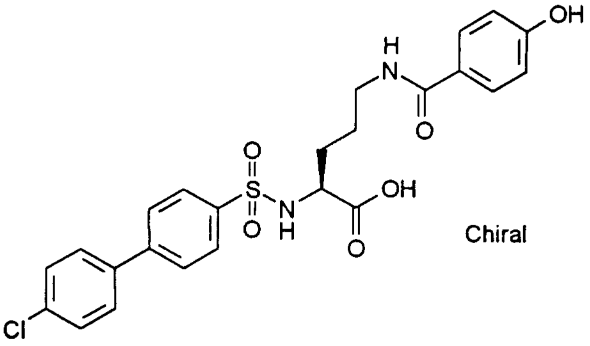
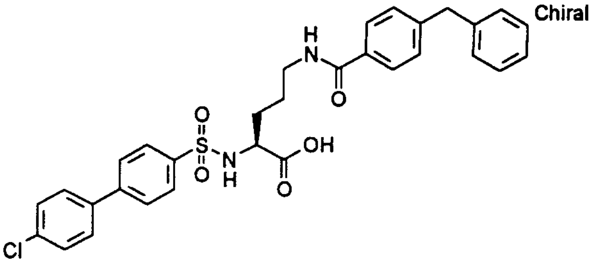
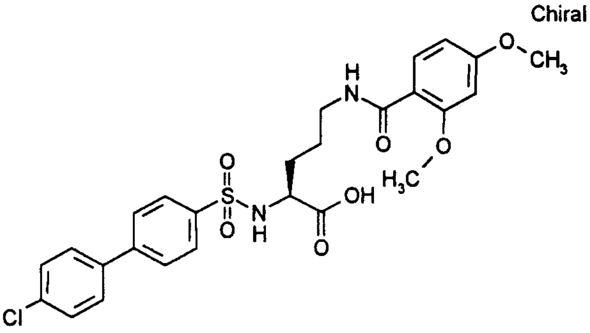
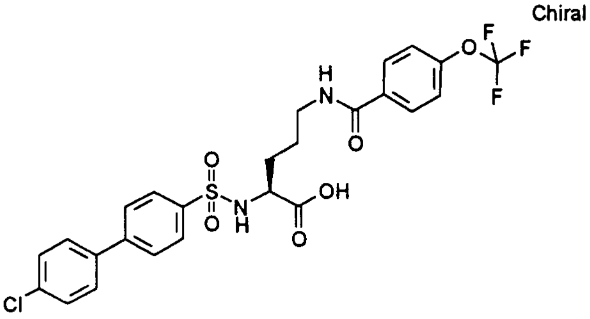
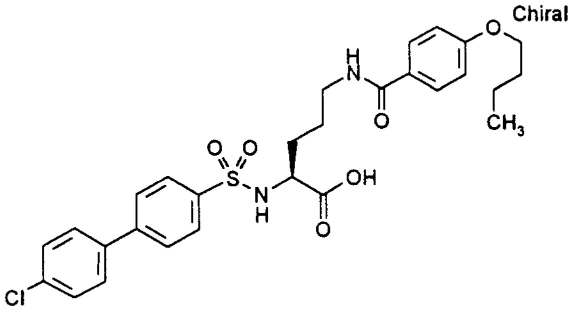
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
79			573.1	S
80			573.1	S
81			525.2	S
82			439.1	S

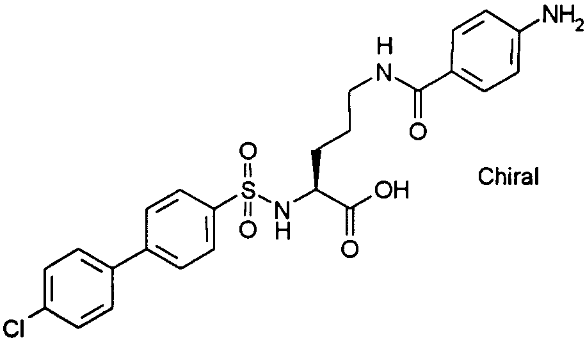
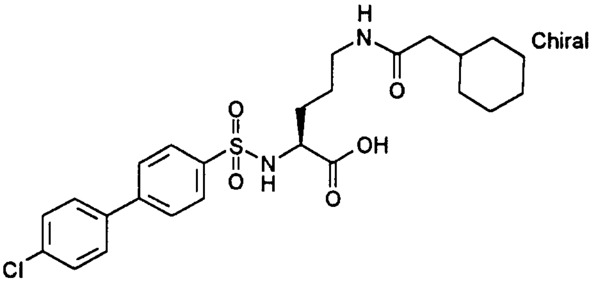
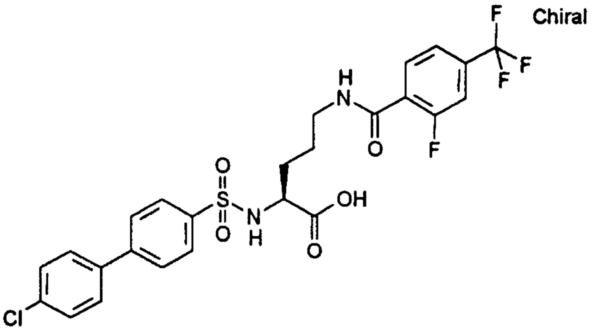
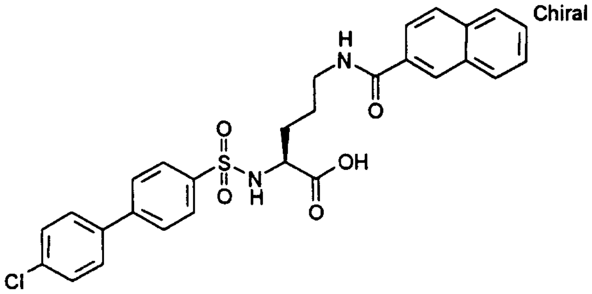
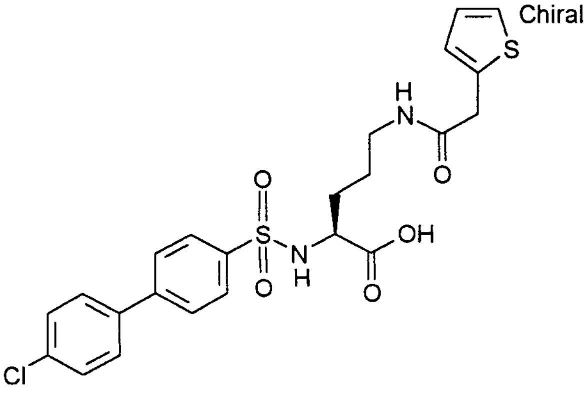
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
83			521.2	S
84			498.2	S
85			512.2	S
86			523.2	S

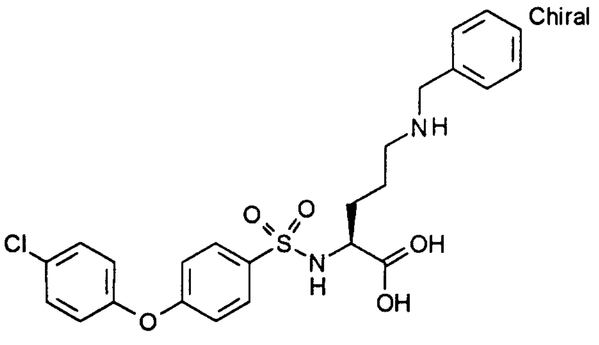
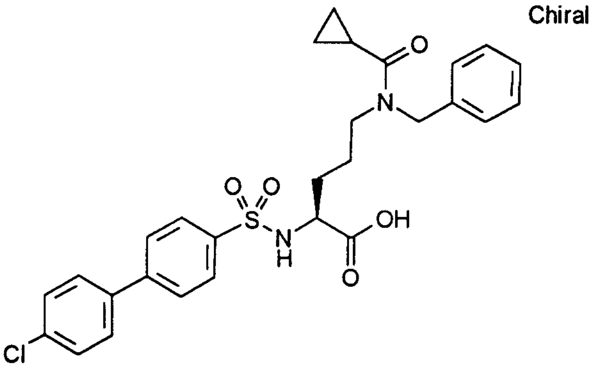
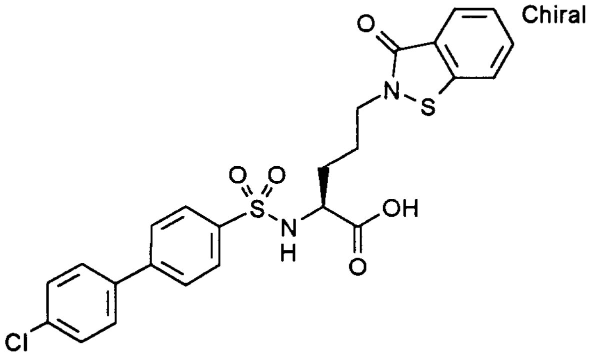
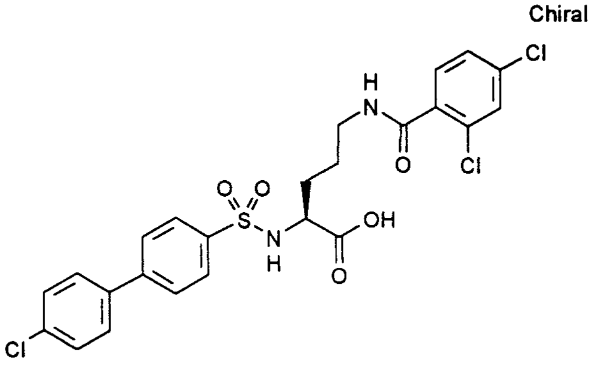
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
87			523.2	S
88			505.2	S
89			535.2	S
90			521.2	S
91			521.2	S

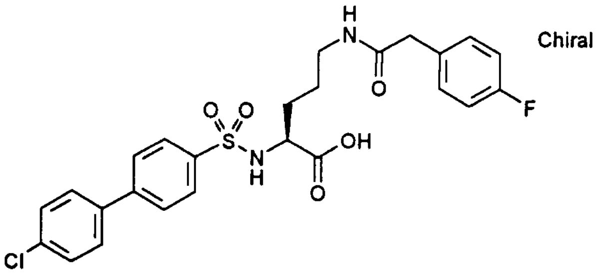
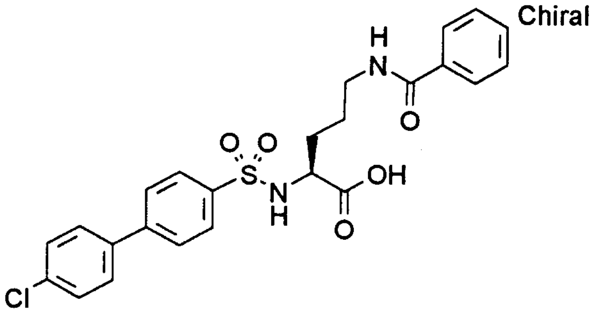
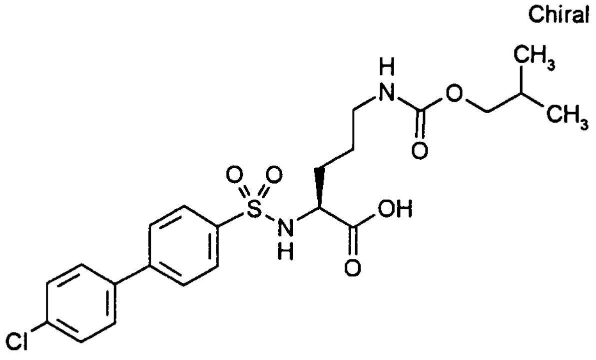
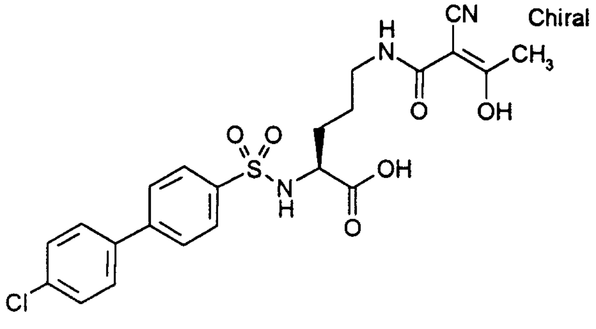
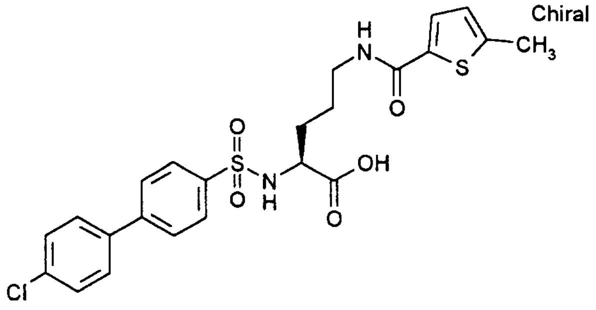
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
92			557.1	S
93			523.2	S
94			523.2	S
95			505.2	S
96			528.2	S

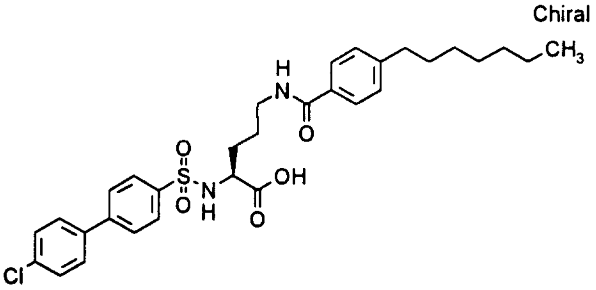
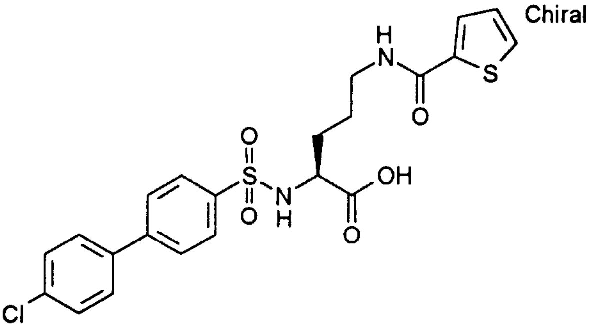
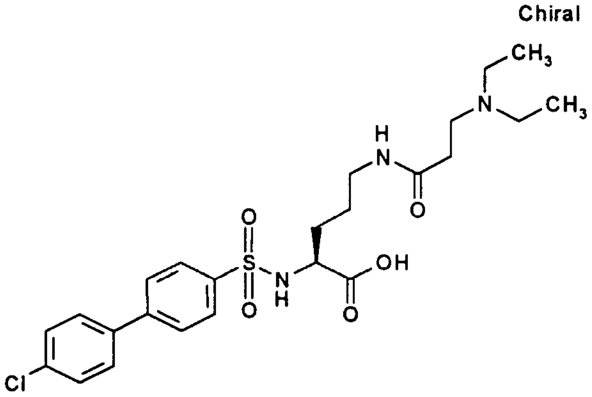
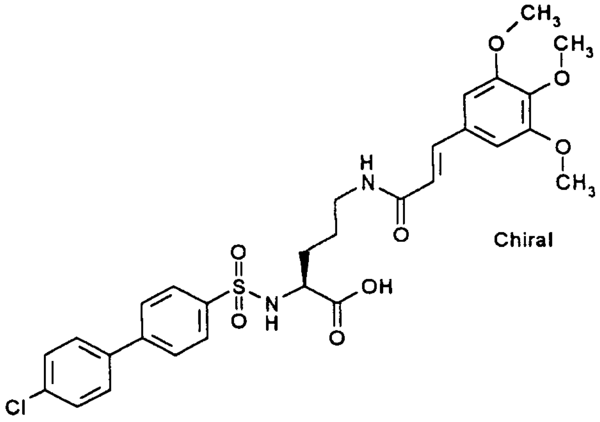
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
97			523.2	S
98			455.2	S
99			477.2	S
100			507.2	S
101			513.2	S

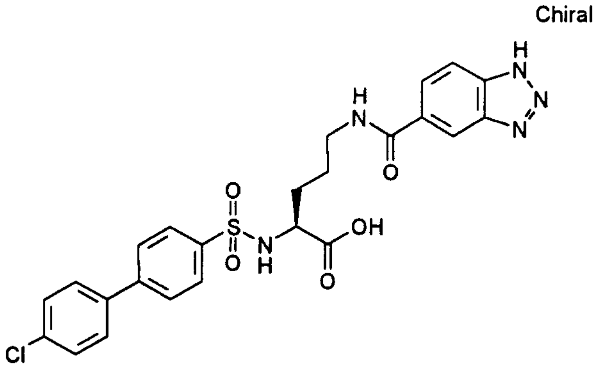
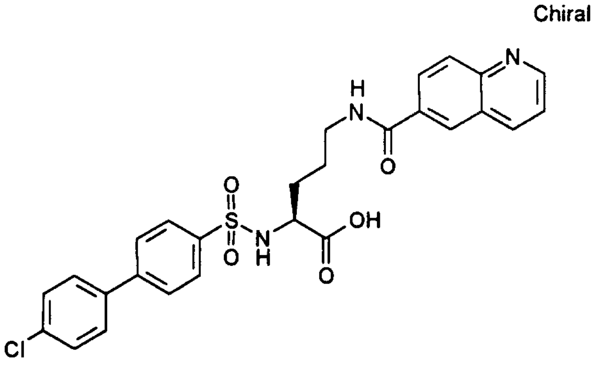
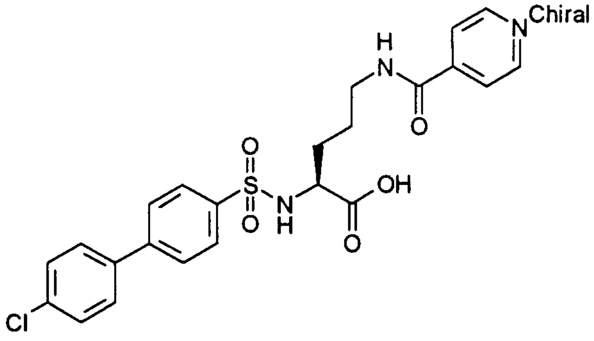
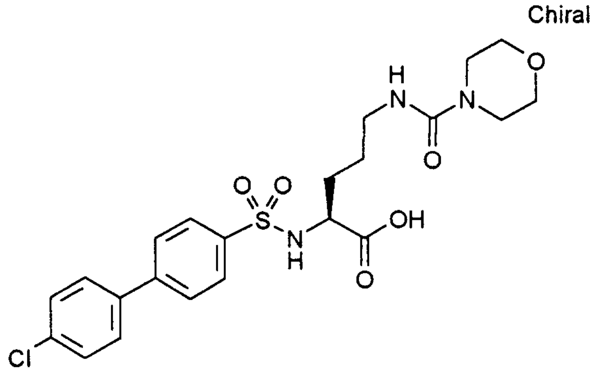
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
102			503.2	S
103			577.2	S
104			547.2	S
105			571.2	S
106			559.2	S

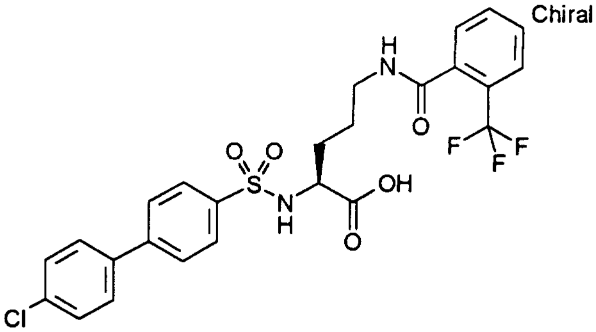
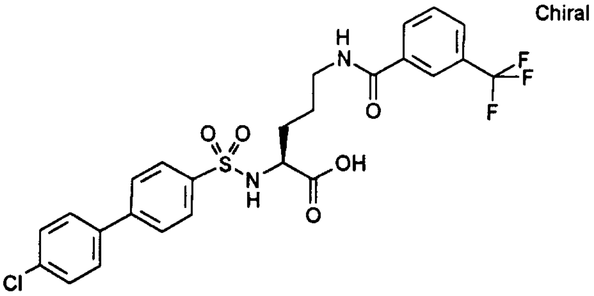
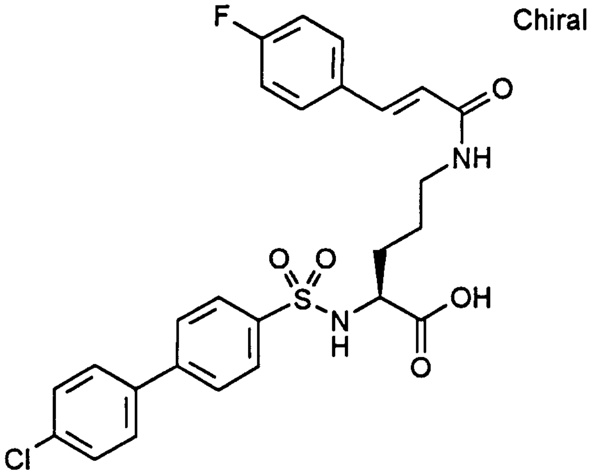
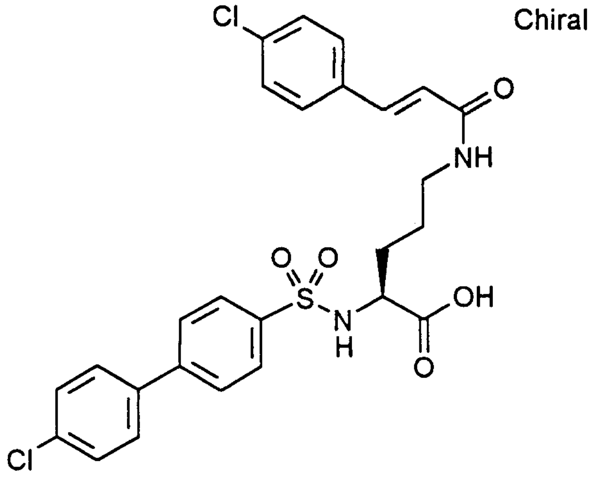
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
107			502.2	S
108			507.2	S
109			573.2	S
110			537.2	S
111			507.2	S

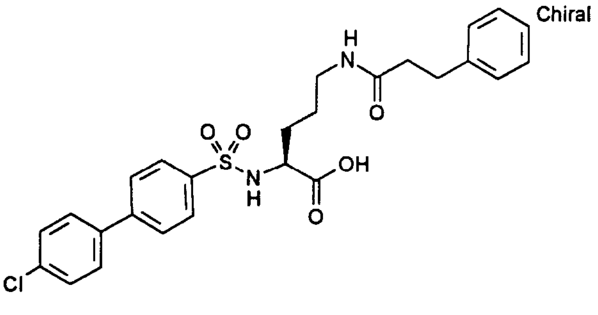
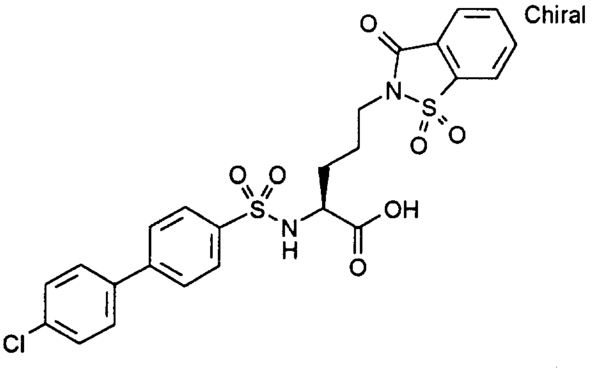
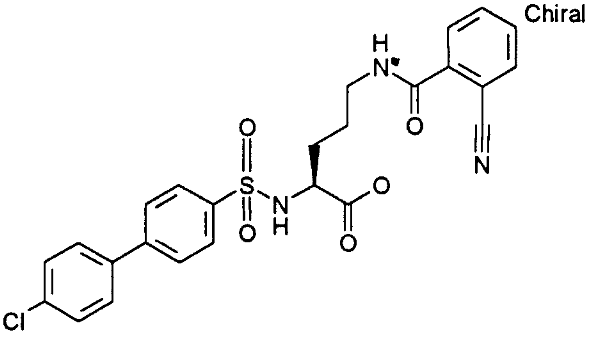
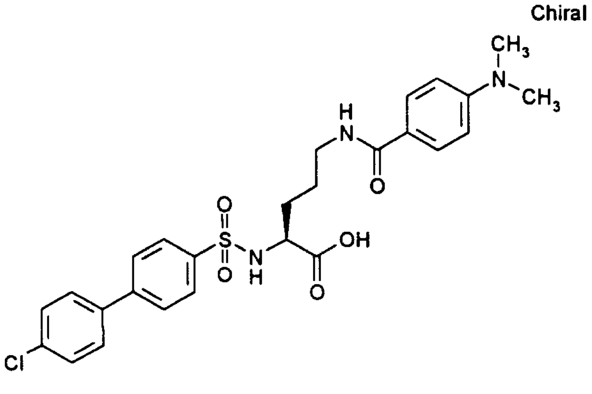
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
112			489	S
113			541.3	S
114			517.03	S
115			556.1	S

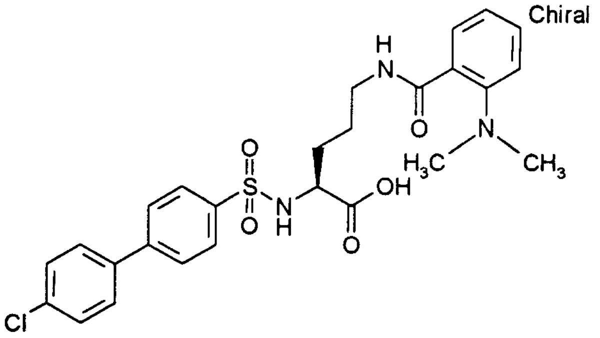
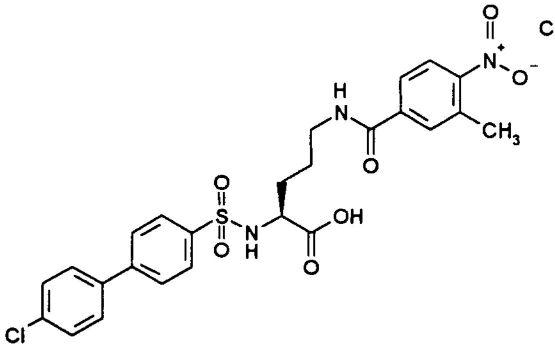
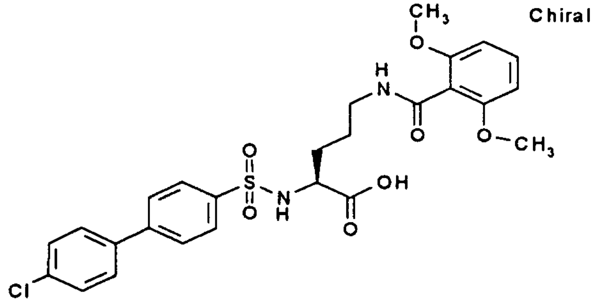
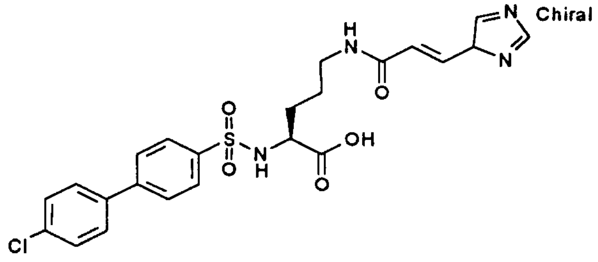
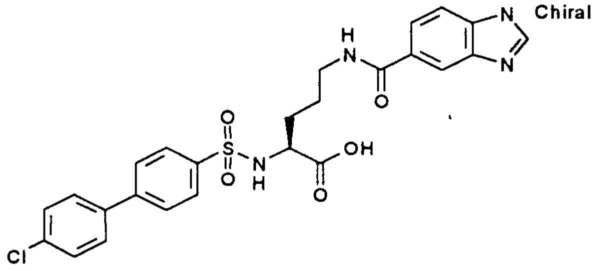
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
116			519.2	S
117			487.2	S
118			483.3	S
119			490.3	S
120			507.2	S

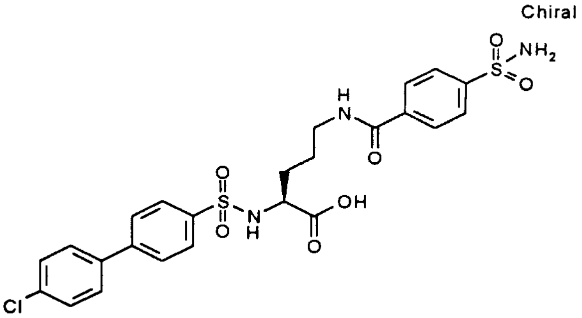
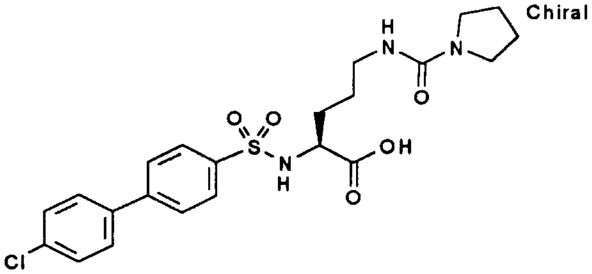
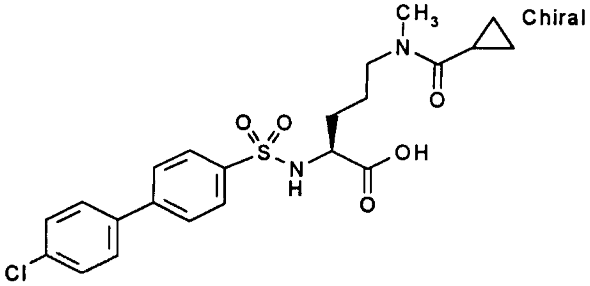
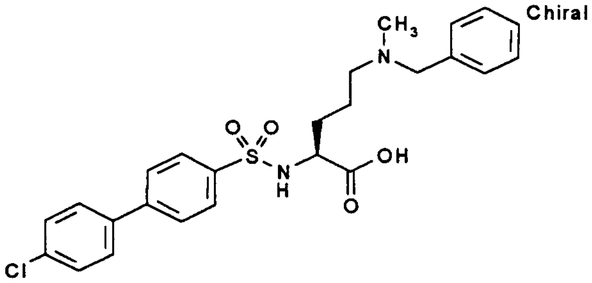
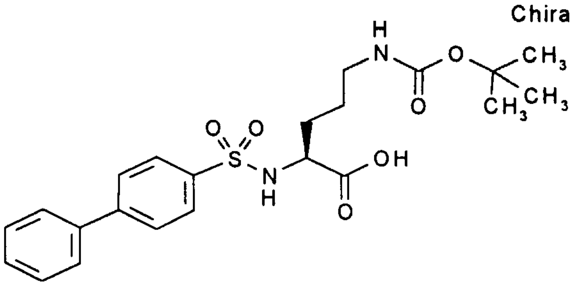
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
121			585.3	S
122			493.2	S
123			510.3	S
124			603.2	S

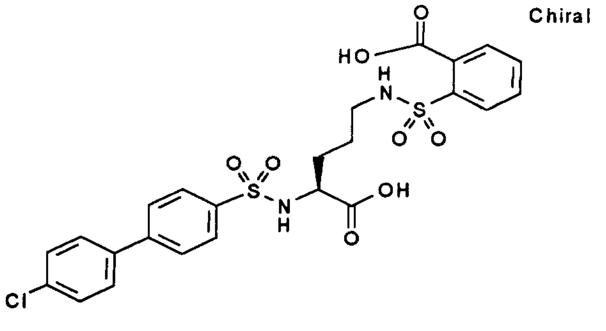
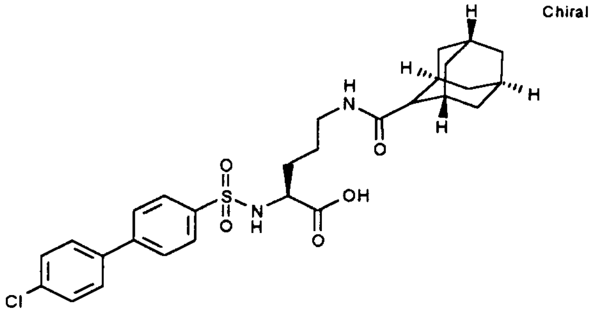
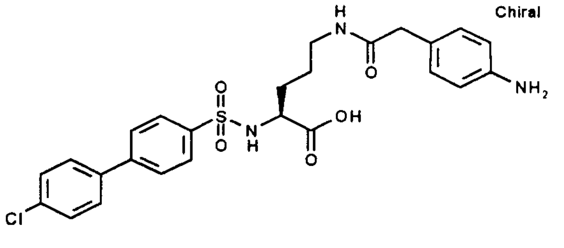
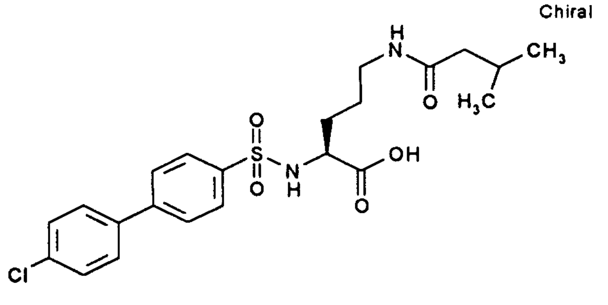
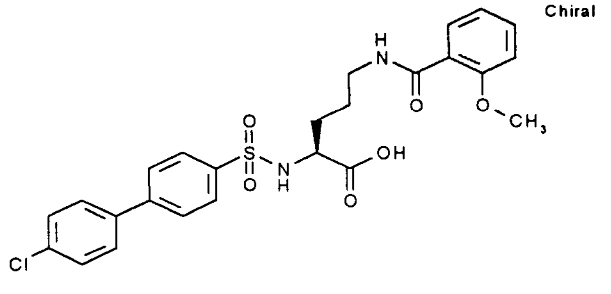
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
125			528.2	S
126			538.2	S
127			488.2	S
128			496.2	S

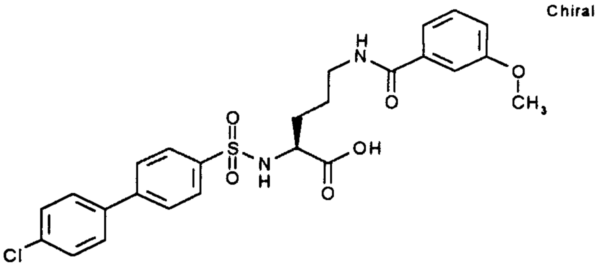
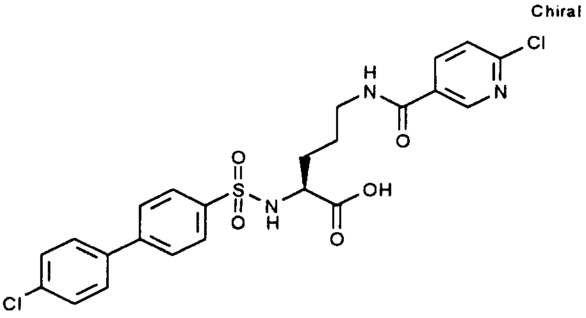
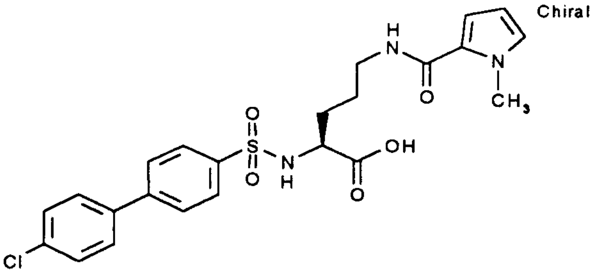
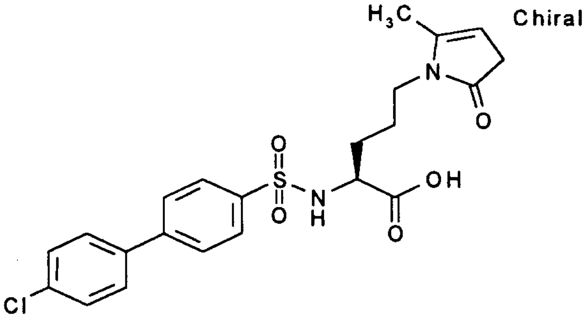
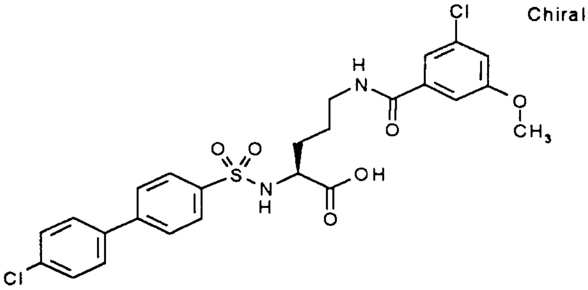
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
129			555.2	S
130			555.2	S
131			531.2	S
132			547.2	S

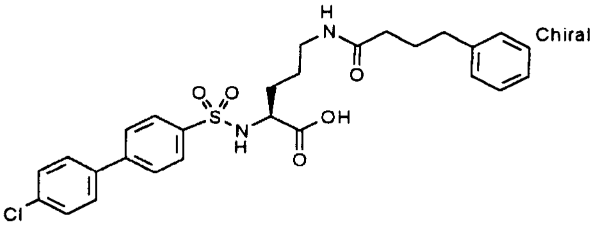
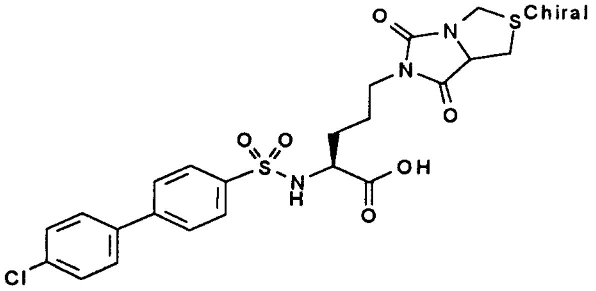
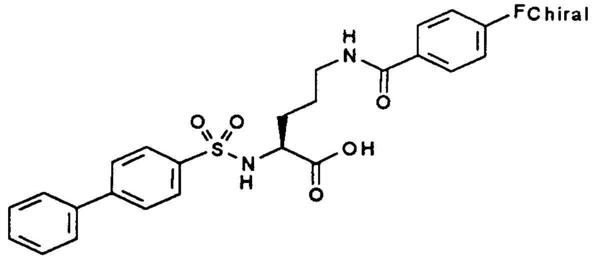
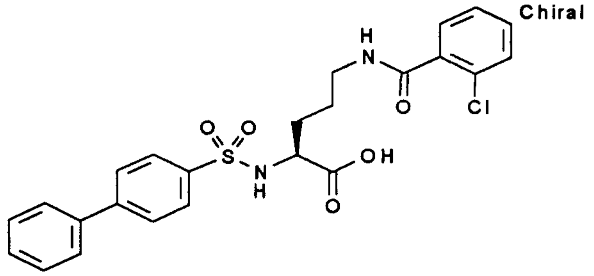
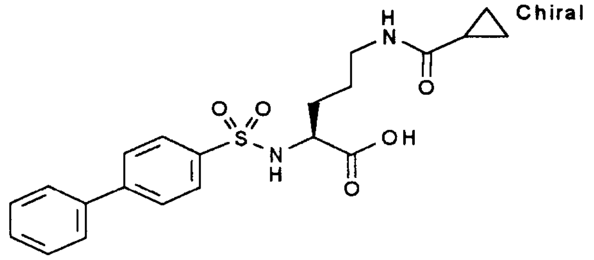
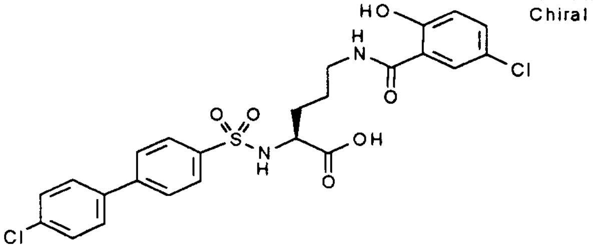
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
133			515.3	S
134			549.1	S
135			512.2	S
136			530.2	S

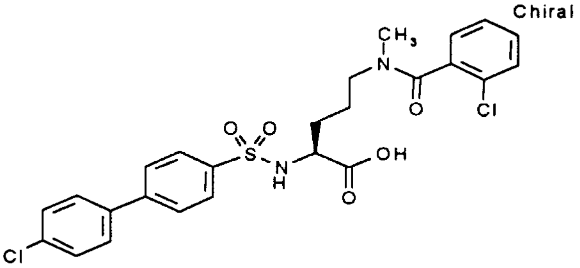
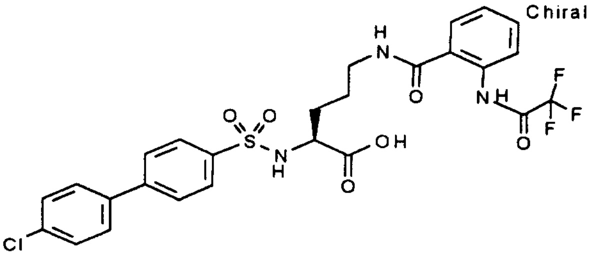
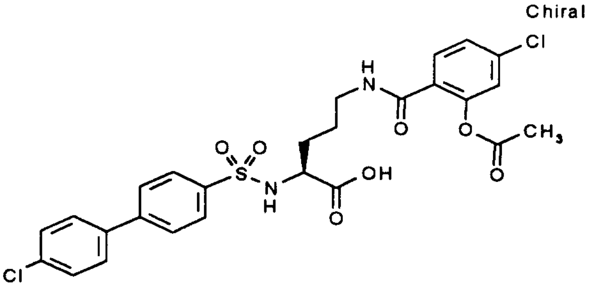
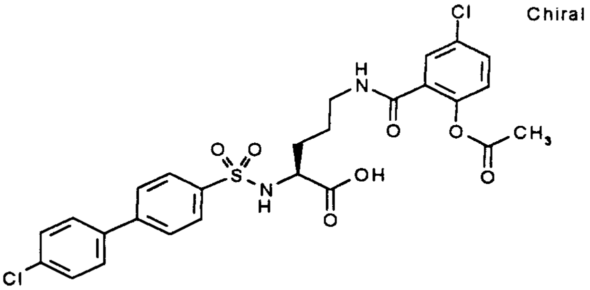
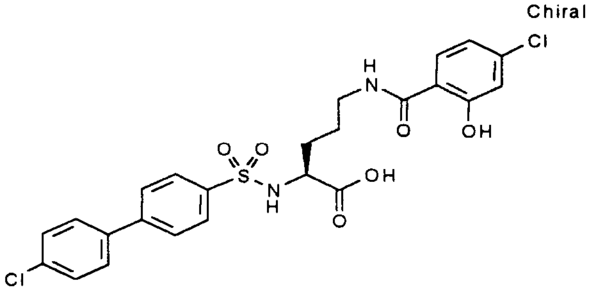
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
137			530.2	S
138			546.2	S
139			547.2	S
140			503.2	S
141			527.2	S

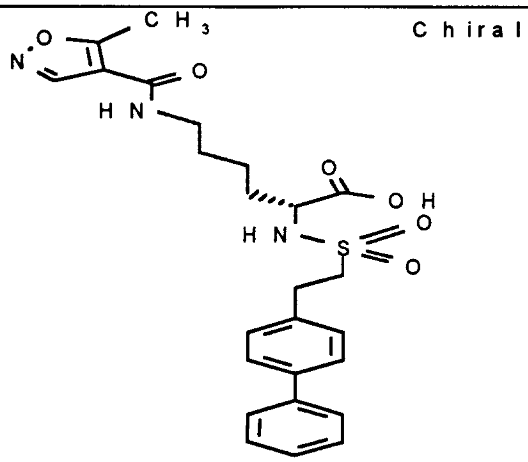
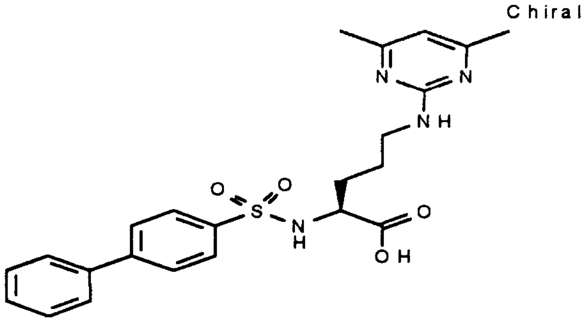
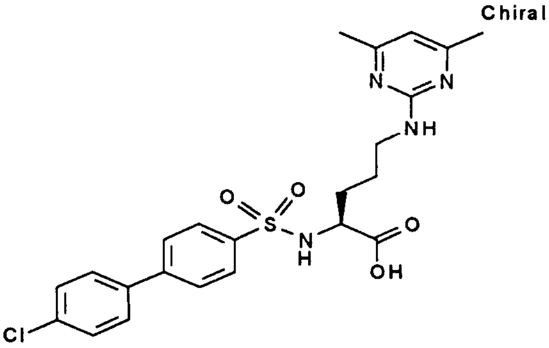
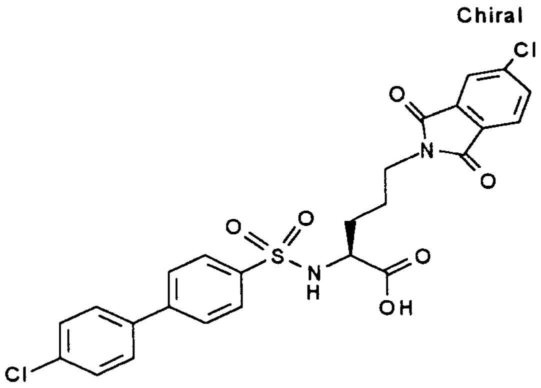
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
142			566.2	S
143			480.2	S
144			465.3	S
145			487.3	S
146			449.2	S

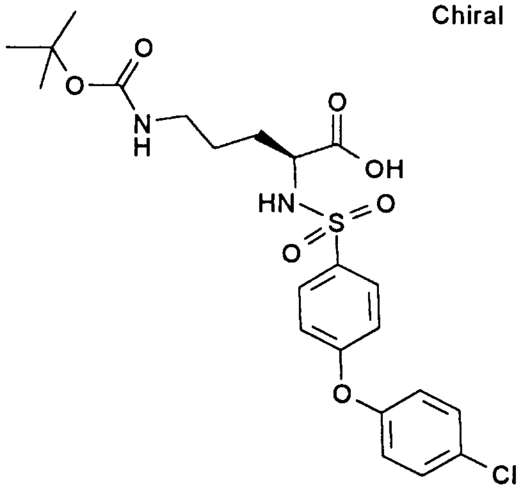
Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
147			458.2	S,S
148			545.3	S
149			516.2	S
150			467.2	S
151			517.2	S

Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
152			517.2	S
153			522	S
154			490.2	S
155			463	S
156			551.2	S

Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
157			529.2	S
158			524.0	S
159			471.2	S
160			487.1	S
161			417.2	S
162			537.1	S

Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
163			535.1	S
164			598.1	S
165			579.2	S
166			579.2	S
167			537.2	S

Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
168			500.2	R
169		226-227°C		S
170		177-179°C		S
171			547	S

Ex.	Structure	M.p. (°C)	MS (M+ H)	Notes
172		131-133°C		

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 substrates, 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	*IC50 MMP-3 [x 10^{-9} mol/l]*	*IC50 MMP-8 [x 10^{-9} mol/l]*
1	50	7
2	20	6
4	90	20
5	50	4
6	5	2
7	4	2
9	60	70
12	60	10
14	5	3
15	20	8
16	20	10
18	70	10
19	20	5
20	40	7
21	70	20
22	80	80
23	40	5
24	30	5
25	60	10
26	60	7
28	40	6
29	6	3
30	30	5
31	5	2
32	6	2
34	4	2
36	5	2
38	5	2
39	20	30
41	5	2
42	10	3
43	40	20

44	30	6
45	20	4
46	10	3
47	10	3
48	20	7
49	20	3
50	6	2
51	20	3
52	20	10
53	30	6
55	7	3
56	10	8
57	40	8
59	5	1
60	10	10
61	6	2
62	5	2
63	10	2
64	30	2
65	20	4
66	10	2
69	4	2
70	10	3
71	10	3
72	20	6
73	4	2
74	10	3
75	20	4
76	40	40
77	10	2
79	5	2
80	10	3
81	30	3
82	20	4
83	7	3
84	20	4

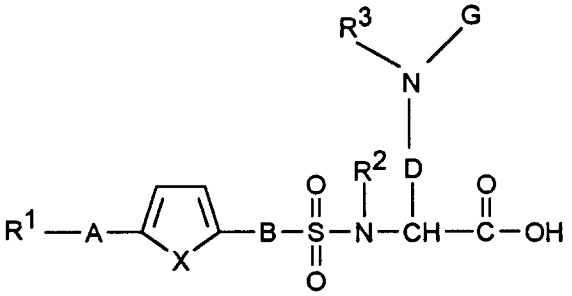
85	20	5
86	20	4
87	30	10
88	10	3
89	30	10
90	20	5
91	30	5
92	40	20
93	20	4
94	30	5
95	20	4
96	20	6
97	20	4
98	10	3
99	5	2
100	4	2
101	40	10
102	20	5
103	70	60
104	30	8
105	40	10
106	60	30
107	10	4
108	20	5
109	20	7
110	40	20
111	10	3
113	5	3
114	5	2
115	5	3
116	20	4
117	9	2
118	10	4
120	20	4
122	3	2
123	60	10

125	10	10
126	30	10
127	20	3
128	5	2
129	10	2
130	20	4
131	20	5
132	30	10
133	5	2
134	5	2
135	30	8
136	10	7
137	20	7
138	30	10
139	50	20
140	60	20
141	10	10
142	10	4
143	5	2
144	10	3
145	10	5
146	30	3
151	30	10
152	60	10
154	30	9
155	50	10
156	60	20
157	40	7
158	7	2
160	70	10
161	40	4
162	50	6
168	40	20
170	20	10
171	30	10

Patent Claims

HOE 97/F 131K

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 -C_7)-alkyl, which 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,

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 3.16., 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,
3.15. benzothiazole or
3.16 benzotriazole,

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

1. a hydrogen atom,
2. (C_1 -C_6)-alkyl-,
3. HO-C(O)-(C_1-C_6)-alkyl-,
4. phenyl-$(CH_2)_o$-, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and o 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 carbonyl atoms is optionally replaced by -O-, -S- or -NH-,

R^3 and G are identical or different and are

1. a hydrogen atom,
2. (C_1 -C_6)-alkyl-, in which alkyl is linear, branched or cyclic,
3. (C_2 -C_6)-alkenyl-,
4. phenyl-$(CH_2)_m$-, 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 or 3,

5. heteroaryl-$(CH_2)_m$-, in which heteroaryl is substituted as defined under 3.1. to 3.16. and/or as described under 2.1 to 2.14 and m is the integer zero, 1, 2 or 3,

6. R^6-C(O)-, in which

R^6 is 6.1 $(C_1\text{-}C_6)$-alkyl-, in which alkyl is unsubstituted or substituted as described under 2.1. to 2.14. or $(C_3\text{-}C_6)$-cycloalkyl,

6.2 $(C_3\text{-}C_6)$-cycloalkyl, in which cycloalkyl is unsubstituted or substituted as described under 2.1.to 2.14.,

6.3 $(C_2\text{-}C_6)$-alkenyl-, in which alkenyl is unsubstituted or mono- to trisubstituted by

6.3.1 phenyl, in which phenyl is unsubstituted or mono- to trisubstituted as described under 2.1. to 2.14.

6.3.2 heteroaryl , in which heteroaryl is as defined under 3.1. to 3.16. and is unsubstituted or mono- to trisubstituted as described under 2.1. to 2.14. or

6.3.3 the radicals described under 2.1. to 2.14,

6.4 phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- to trisubstituted as described under 2.1. to 2.14. by -O-CF_3, -SO_2-NH_2 , -NH-C(O)-CF_3 or by benzyl and a hydrogen atom of the -(CH_2)- radical is optionally substituted by the radical -COOH and m is the integer zero, 1, 2 or 3,

6.5 naphthyl,

6.6 adamantyl or

6.7 heteroaryl-$(CH_2)_m$-, in which heteroaryl is as defined under 3.1. to 3.16. and/or is substituted as described under 2.1. to 2.14. and m is the integer zero, 1, 2 or 3,

7. R^6-O-C(O)-, in which R^6 is defined as mentioned above,

8. R^6-CH(NH_2)-C(O)-, in which R^6 is defined as mentioned above,

9. R^8-N(R^7)-C(O)-, in which

R^8 is 9.1 a hydrogen atom

9.2 (C_1-C_6)-alkyl-,

9.3 phenyl-(CH_2)$_m$, 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 or 3, or

9.4 heteroaryl-(CH_2)$_m$, in which heteroaryl is as defined under 3.1. to 3.16. and/or is substituted as described under 2.1 to 2.14 and m is the integer zero, 1, 2 or 3, and in which

R^7 is a hydrogen atom or (C_1-C_6)-alkyl or in which

R^7 and R^8 together with the nitrogen atom to which they are bonded form a 4- to 7-membered ring and the ring is unsubstituted or a carbon atom in the ring is replaced by -O-, -S- or -NH-,

10. R^6-SO_2-, in which R^6 is defined as mentioned above,

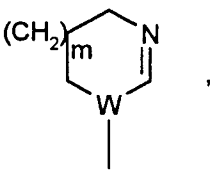
11. R^6-SO_2-N(R^7)-C(O)-, in which R^6 and R^7 are defined as mentioned above,

12. R^6-NH-C(=NR^7)-, in which R^6 and R^7 are defined as mentioned above or

12.1 (C_1-C_6)-alkyl-C(O)-,

12.2 -NO_2 or

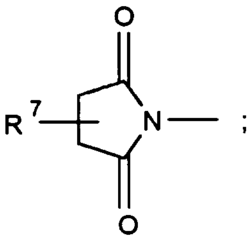
12.3 -SO_2-(CH_2)$_q$-phenyl, in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1. to 2.14. and q is the integer zero, 1, 2 or 3, 13.



,

in which m is the integer zero, 1, 2 or 3 and W is a nitrogen, oxygen or sulfur atom, or

R^3 and G together with the nitrogen atom to which they are bonded form a ring of the subformula IIa to IIp



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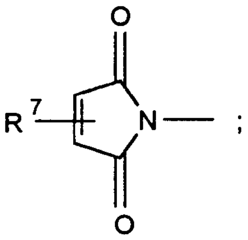
(IIa)



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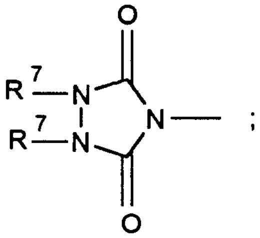
(IIb)



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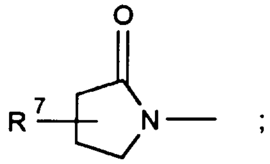
(IIc)



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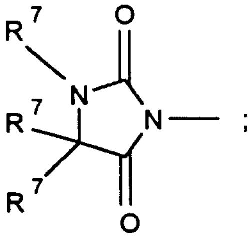
(IId)



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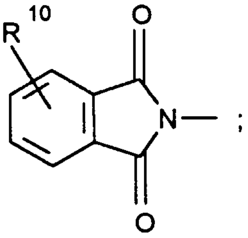
(IIe)



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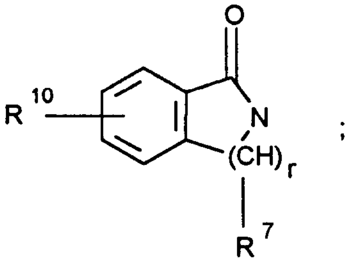
(IIf)



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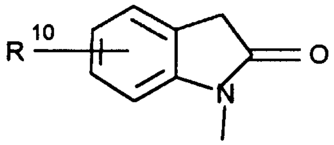
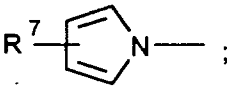
(IIg)



(IIh)



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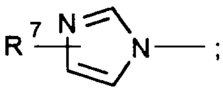
(IIi)



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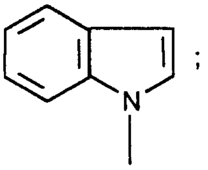
(IIj)



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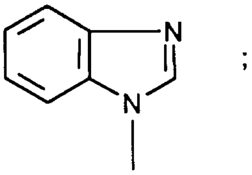
(IIk)



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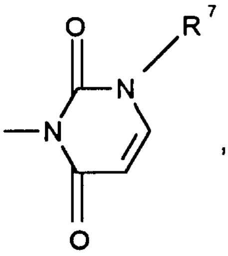
(IIl)



(IIm)

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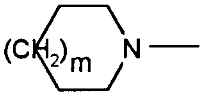

(IIn)

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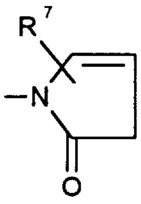
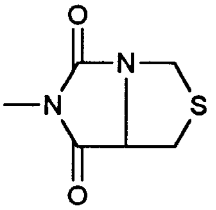


(IIo)

or



(IIp)

where r is the integer 1 or 2, R^{10} is a radical as described under 2.1. to 2.14. and R^7 and m have the abovementioned meaning and in the subformula IIg a carbon atom in the ring is optionally replaced by oxygen, sulfur, SO_2 or a nitrogen atom which is unsubstituted or substituted by R^2 ,

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) $-O-(CH_2)_q$, in which q is the integer 1, 2, 3, 4 or 5, or
c) -CH=CH-,

D is $-(CH_2)_m-$ in which m is the integer 1, 2, 3, 4, 5 or 6 and one of the chain carbon atoms is optionally replaced by an optionally substituted -N-, -O- or -S- atom, 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. halogen, in particular 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 5-6-membered ring, where one of the carbon atoms is optionally replaced by -O- or -NH-,

R^2 is a hydrogen atom,

G and R^3 are different where

G is a hydrogen atom or (C_1 -C_4)-alkyl and

R^3 is 1. phenyl-$(CH_2)_m$ in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1 to 2.14 and m is the integer 1,

2. is heteroaryl-(CH_2)n, in which heteroaryl is as defined under 3.10 and is unsubstituted or substituted as described under 2.1 to 2.14 and n is zero,

3. is R^6 -C(O)-, in which

R^6 is 3.1 (C_1 -C_6)-alkyl-, in which alkyl is linear, branched or cyclic,

3.2 phenyl-$(CH_2)_r$ - in which phenyl is unsubstituted or mono- or disubstituted as described under 2.1 to 2.14 and a hydrogen atom of the -(CH_2)- radical is optionally replaced by the radical -COOH and r is zero, 1, 2 or 3, or

3.3 heteroaryl-$(CH_2)_o$-, in which heteroaryl is as defined under 3.1 to 3.15 and is unsubstituted or substituted as described under 2.1 to 2.14 and o is zero, 1, 2, or 3, or

4. is R^8-N(R^7)-C(O)- , in which

R^8 and R^7 together with the nitrogen atom to which they are bonded form a 5- or 6-membered ring and the ring is unsubstituted or a ring carbon atom is replaced by an oxygen atom, or

R^3 and G together with the nitrogen atom to which they are bonded form a ring of the subformula IIg, in which r is 1 ,

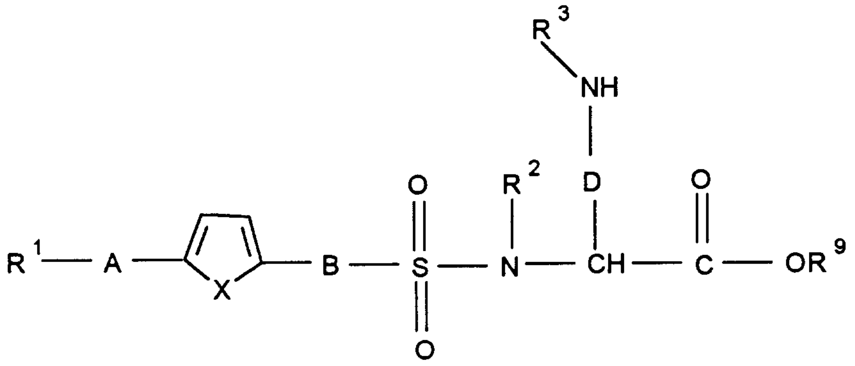
A is a covalent bond,

B is $-(CH_2)_p-$ and p is zero,

D $-(CH_2)_q-$ and q is an integer 2, 3 or 4, and

X is -CH=CH- .

3. A compound of the formula X

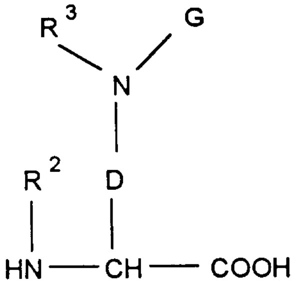


(X)

and/or a stereoisomeric form of the compound of the formula X and/or a physiologically tolerable salt of the compound of the formula X, where R^1, A, X, B, R^2, R^3 and D have the meaning mentioned in the compound of the formula I as claimed in claim 1 and R^9 is a hydrogen atom, (C_1-C_6)-alkyl, phenyl, succinimidyl, benzotriazolyl or benzyl.

4. A process for the preparation of the compound of the formula I as claimed in one or more of claims 1 to 3, which comprises

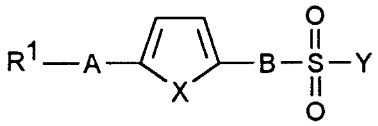
a) reacting a diaminocarboxylic acid of the formula III



$$R^2-NH-CH(-D-N(R^3)G)-COOH$$

(III)

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

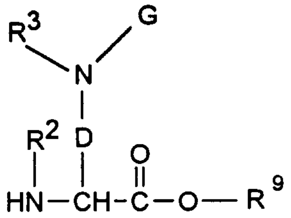


(IV)

in which R^1, A and B are as defined in formula I and Y is a halogen atom, imidazolyl or $-OR^9$, in which R^9 is a hydrogen atom, (C_1-C_6)-alkyl, phenyl, succinimidyl, benzotriazolyl or benzyl, optionallly substituted,

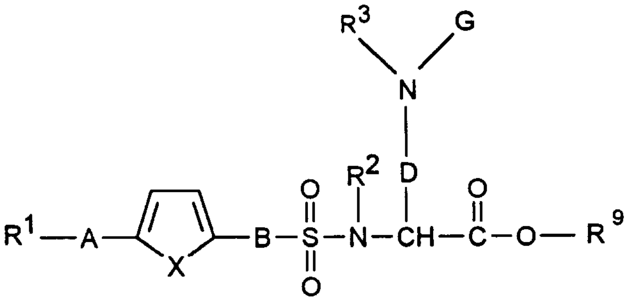
in the presence of a base or if appropriate of a dehydrating agent, to give a compound of the formula I, or

b) reacting a diaminocarboxylic acid ester of the formula V



(V)

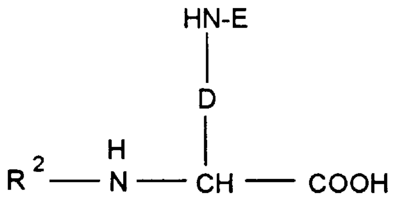
in which R^2, R^3, D, G and R^9 have the abovementioned meaning, with a sulfonic acid derivative of the formula IV under the abovementioned conditions to give a compound of the formula VI



(VI)

and converting the compound of the formula VI into a compound of the formula I with removal of the radical R^9, preferably in the presence of a base or acid, or

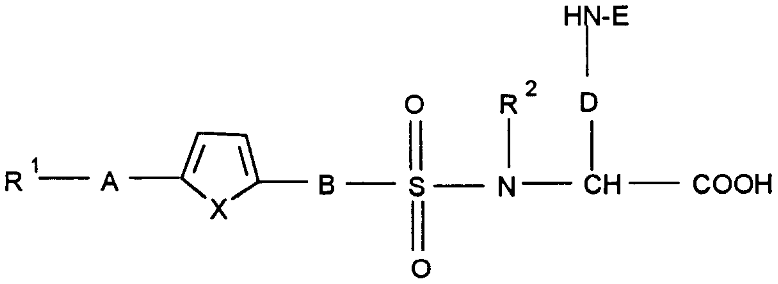
c) reacting the protected diaminocarboxylic acids of the formula VII,



$$R^{2}-\overset{H}{N}-\overset{\begin{array}{c}HN\text{-}E\\|\\D\\|\end{array}}{CH}-COOH$$

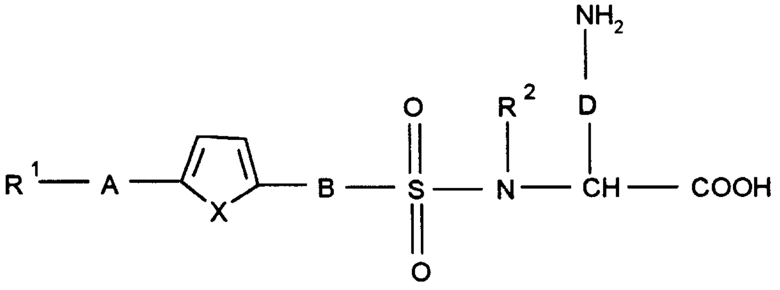
(VII)

in which R^2 and D have the abovementioned meanings and E is a protective group of the amino function, with a sulfonic acid derivative of formula IV to give a compound of the formula VIII



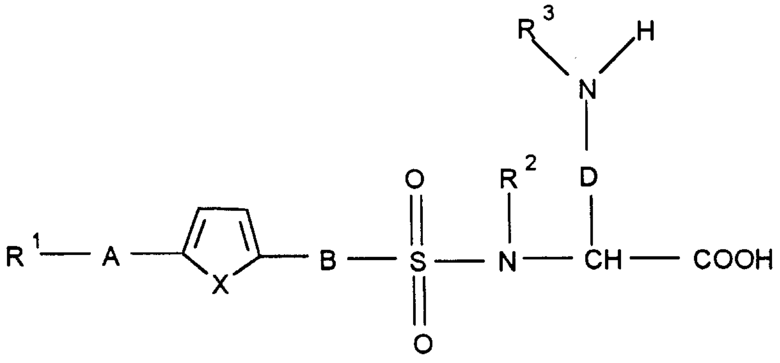
(VIII)

then converting the compound of the formula VIII, with removal of the protective group E with the aid of suitable cleavage agents, into a compound of the formula I,



(I)

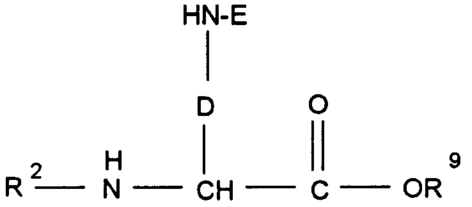
in which R^1, R^2, A, B, D and X have the abovementioned meaning and R^3 and G are a hydrogen atom, and reacting this compound of the formula I if appropriate with the aid of R^3-Y, in which R^3 and Y have the meanings indicated above, in the presence of a base to give a compound of the formula I,



(I)

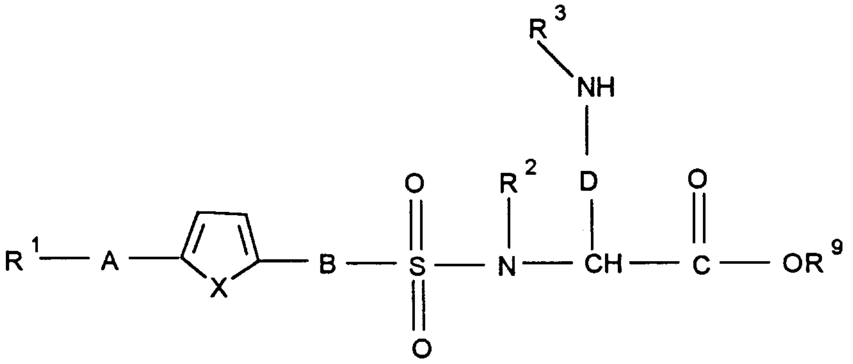
in which R^1, R^2, R^3, A, B and X have the abovementioned meanings and G is a hydrogen atom,

d) as starting compounds, converting protected diamino acid esters of the formula IX, ,



$$R^2-\overset{H}{N}-\underset{}{\overset{\overset{HN-E}{|}}{\underset{}{\overset{D}{\underset{}{|}}}}}CH-\overset{O}{\overset{\|}{C}}-OR^9 \quad (IX)$$

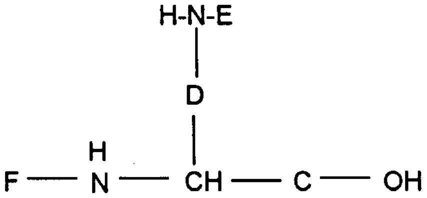
in which R^2, R^9 , D and E have the abovementioned meaning, in the same manner as described in process variant c), into the esters of the formula X,



(X)

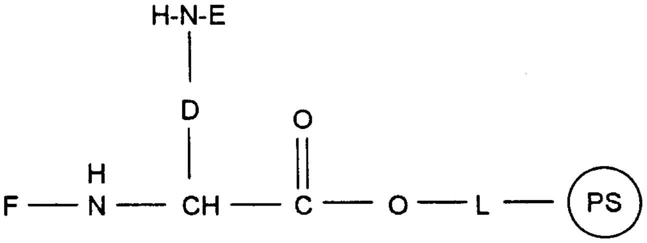
which are optionally converted into the corresponding compounds of the formula I according to process variant b), or

e) coupling a diaminocarboxylic acid of the formula XI,



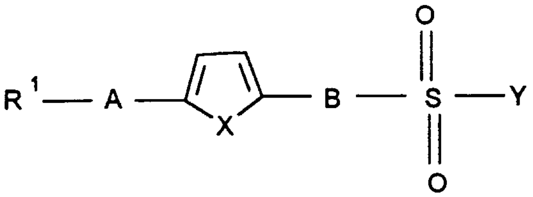
$$F-\overset{H}{N}-\overset{\overset{H-N-E}{|}}{\overset{D}{\overset{|}{CH}}}-C-OH \quad (XI)$$

in which D is defined as in formula I and E and F are N-amino protective groups which are different from one another, by its carboxyl group via an intermediate chain L to a polymeric resin of the formula PS, a compound of the formula XII



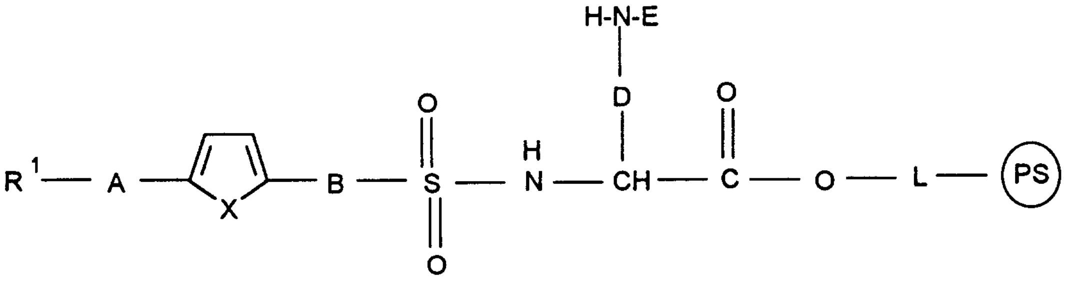
$$F-\overset{H}{N}-\overset{\overset{H-N-E}{|}}{\overset{D}{\overset{|}{CH}}}-\overset{O}{\overset{\|}{C}}-O-L-\boxed{PS} \quad (XII)$$

resulting, which, after selective removal of the protective group F, is reacted with a sulfonic acid derivative of the formula IV



(IV)

where R^1, A, B and Y have the abovementioned meanings, in the presence of a base or, if appropriate, of a dehydrating agent to give a compound of the formula XIII

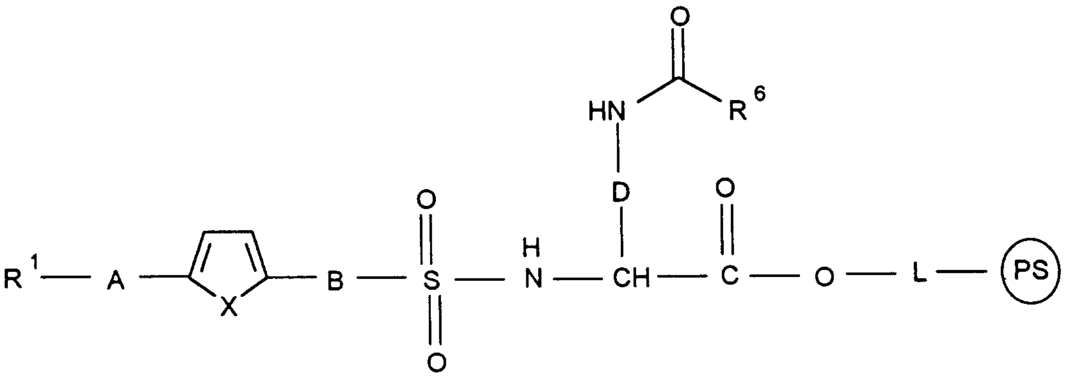


(XIII)

and reacting the compound of the formula XIII, after removal of the protective group E, with a carboxylic acid derivative of the formula XIV

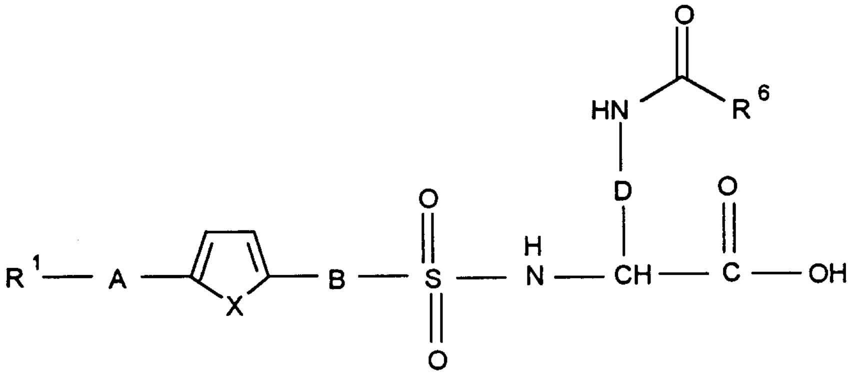
R^6-C(O)-Y (XIV)

in which R^6 and Y have the abovementioned meaning, in the presence of a base or of a dehydrating agent, to give a compound of the formula XV



(XV)

and converting this, after removal from the support material, into a compound of the formula I,



(I)

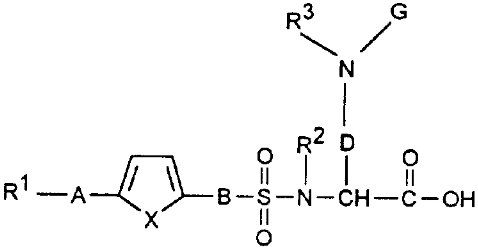
in which R^1, R^6, A, B, D and X have the abovementioned meaning.

5. A pharmaceutical, which comprises an efficacious content of at least one compound of the formula I as claimed in one or more of claims 1 to 3, together with a pharmaceutically suitable and physiologically tolerable excipient, additive and/or other active compounds and auxiliaries.

6. The use of at least one compound of the formula I as claimed in one or more of claims 1 to 3 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.

7. The use as claimed in claim 6, 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 athritides, arthropathies, myalgias and disorders of the bone metabolism, ulceration, atherosclerosis and stenoses, but also for the treatment of inflammation, carcinomatous disorders, formation of tumor metastases, cachexia, anorexia and septic shock.

8. 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 3 into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, other suitable active compounds, additives or auxiliaries.



(I)