



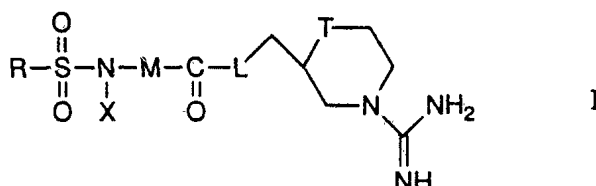
AU9179490

**(12) PATENT ABRIDGMENT (11) Document No. AU-B-79490/91**  
**(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 650458**

- (54) Title  
**GUANIDINES**
- (51)<sup>5</sup> International Patent Classification(s)  

<b>C07D 211/22</b>	<b>A61K 031/47</b>	<b>A61K 031/55</b>	<b>C07D 211/26</b>
<b>C07D 265/30</b>	<b>C07D 401/12</b>	<b>C07D 401/14</b>	<b>C07D 409/12</b>
<b>C07D 409/14</b>	<b>C07D 413/12</b>	<b>A61K 031/445</b>	<b>A61K 031/535</b>
- (21) Application No. : **79490/91** (22) Application Date : **01.07.91**
- (30) Priority Data
- |                |                 |                       |
|----------------|-----------------|-----------------------|
| (31) Number    | (32) Date       | (33) Country          |
| <b>2250/90</b> | <b>05.07.90</b> | <b>CH SWITZERLAND</b> |
| <b>1315/91</b> | <b>02.05.91</b> | <b>CH SWITZERLAND</b> |
- (43) Publication Date : **09.01.92**
- (44) Publication Date of Accepted Application : **23.06.94**
- (71) Applicant(s)  
**F. HOFFMANN-LA ROCHE AG**
- (72) Inventor(s)  
**JEAN ACKERMANN; DAVID BANNER; KLAUS GUBERNATOR; PAUL HADVARY; KURT HILPERT; KLAUS MULLER; LUDVIK LABLER; GERARD SCHMID; THOMAS B. TSCHOPP; HANS PETER WESSEL; BEAT WIRZ**
- (74) Attorney or Agent  
**SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001**
- (56) Prior Art Documents  
**AU 22379/88 C07D 211/22 211/46**
- (57) Claim

1. A guanidine of the formula



wherein

R is aryl, heteroraryl or heterocyclyl,

T is CH<sub>2</sub> or O,

L is NH or O and

-N(X)-M- is a -N(SO<sub>2</sub>-R<sup>0</sup>)-CH<sub>2</sub>- group or an isoquinolylene group optionally substituted in the phenyl ring and

R<sup>0</sup> has the same significance as R or

X is H, -CH<sub>2</sub>COOH, -CH<sub>2</sub>COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>CO-(tetra- to heptamethyleneimino) or optionally N-mono- or N-di-C<sub>1-4</sub>-alkylated -CH<sub>2</sub>CONH<sub>2</sub> and

M is a R'-(CH<sub>2</sub>)<sub>1-2</sub>CH=, R'-COCH<sub>2</sub>CH=, R''-COCH<sub>2</sub>CH=, R'-(CO)<sub>1-2</sub>NHCH<sub>2</sub>CH=, benzyl-OCONHCH<sub>2</sub>CH=,

-CH<sub>2</sub>[R'-(CO)<sub>1-2</sub>NH]CH-, -CH<sub>2</sub>(benzyl-OCONH)CH- or  
-CH(CO-Q)CH<sub>2</sub>- group,

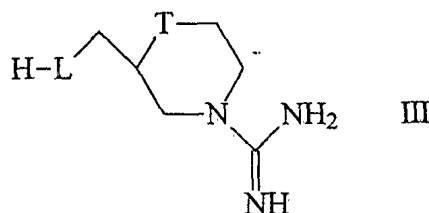
R' is aryl, heteroaryl, cycloalkyl or heterocyclyl,

R'' is tetra- to heptamethyleneimino optionally carrying up  
to 2 substituents from the group oxo, -COO-C<sub>1-4</sub>-alkyl,  
-(CH<sub>2</sub>)<sub>0-1</sub>OH, -(CH<sub>2</sub>)<sub>0-1</sub>OCO-C<sub>1-4</sub>-alkyl and optionally  
mono- or di-C<sub>1-4</sub>-alkylated carbamoyl and

Q is benzylamino or a tetra- to heptamethyleneimino group  
optionally interrupted by an O or S-atom and optionally  
substituted by up to 2 substituents from the group C<sub>1-4</sub>-  
alkyl, COOH, -COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>OH and -CH<sub>2</sub>O-benzyl,  
as well as hydrates or solvates and physiologically usable salts  
thereof.

31. A compound of formulae V in accordance with claim 30.

33. A compound of the formula:



where L is NH or O and T is CH<sub>2</sub> or O.

38. A method for the treatment or prophylaxis of illness caused by thrombin  
induced platelet aggregation or the clotting of fibrinogen in blood plasma in a mammal  
requiring said treatment or prophylaxis, which method comprises administering to said  
mammal an effective amount of at least one compound according to any one of claims 1  
to 29 or 35, or of a composition according to claim 36 or claim 37.

650458

S & F Ref: 183408

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

Name and Address  
of Applicant:

F.Hoffmann-La Roche AG  
124 Grenzacherstrasse  
CH-4002, Basel  
SWITZERLAND

Actual Inventor(s):

Jean Ackermann, David Banner, Klaus Gubernator, Paul  
Hadvary, Kurt Hilpert, Klaus Muller, Ludvik Labler,  
Gerard Schmid, Thomas B. Tschopp, Hans Peter Wessel and  
Beat Wirz

Address for Service:

Spruson & Ferguson, Patent Attorneys  
Level 33 St Martins Tower, 31 Market Street  
Sydney, New South Wales, 2000, Australia

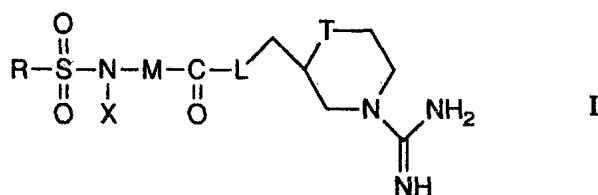
Invention Title:

Guanidines

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

5

The invention is concerned with novel guanidines of the formula



10 wherein

R is aryl, heteroraryl or heterocyclyl,

T is CH<sub>2</sub> or O,

L is NH or O and

-N(X)-M- is a -N(SO<sub>2</sub>-R<sup>0</sup>)-CH<sub>2</sub>- group or an isoquinolylylene group optionally substituted in the phenyl ring and

R<sup>0</sup> has the same significance as R or

X is H, -CH<sub>2</sub>COOH, -CH<sub>2</sub>COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>CO-(tetra- to heptamethyleneimino) or optionally N-mono- or N-di-C<sub>1-4</sub>-alkylated -CH<sub>2</sub>CONH<sub>2</sub> and

M is a R'-(CH<sub>2</sub>)<sub>1-2</sub>CH=, R'-COCH<sub>2</sub>CH=, R''-COCH<sub>2</sub>CH=, R'-(CO)<sub>1-2</sub>NHCH<sub>2</sub>CH=, benzyl-OCONHCH<sub>2</sub>CH=, -CH<sub>2</sub>[R'-(CO)<sub>1-2</sub>NH]CH-, -CH<sub>2</sub>(benzyl-OCONH)CH- or -CH(CO-Q)CH<sub>2</sub>- group,

R' is aryl, heteroaryl, cycloalkyl or heterocyclyl,

R'' is tetra- to heptamethyleneimino optionally carrying up to 2 substituents from the group oxo, -COO-C<sub>1-4</sub>-alkyl, -(CH<sub>2</sub>)<sub>0-1</sub>OH, -(CH<sub>2</sub>)<sub>0-1</sub>OCO-C<sub>1-4</sub>-alkyl and optionally mono- or di-C<sub>1-4</sub>-alkylated carbamoyl and

Q is benzylamino or a tetra- to heptamethyleneimino group optionally interrupted by an O or S-atom and optionally substituted by up to 2 substituents from the group C<sub>1-4</sub>-alkyl, COOH, -COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>OH and -CH<sub>2</sub>O-benzyl, as well as hydrates or solvates and physiologically usable salts thereof.

Further, the invention is concerned with a process for the manufacture of the above compounds, pharmaceutical preparations which contain such compounds as well as the use of these  
 5 compounds in the manufacture of pharmaceutical preparations.

Examples of physiologically usable salts of the guanidines of formula I are salts with physiologically acceptable mineral acids such as hydrochloric acid, sulphuric acid, sulphurous acid or  
 10 phosphoric acid; or with organic acids such as methanesulphonic acid, p-toluenesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The guanidines of formula I having a free carboxy group can also form salts with physiologically acceptable bases.  
 15 Examples of such salts are alkali metal, alkaline earth metal, ammonium and alkylammonium salts such as the Na, K, Ca or tetramethylammonium salt. The guanidines of formula I can also be present in the form of zwitterions.

20 The guanidines of formula I can be solvated, especially hydrated. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties or an initially anhydrous compound of formula I.

25 The guanidines of formula I contain at least two asymmetric C atoms and can therefore be present as mixtures of diastereomers or as the optically pure compound.

30 In the scope of the present invention C<sub>1-4</sub>-alkyl denotes straight-chain (C<sub>1-4</sub>-n-alkyl) or branched groups such as methyl, ethyl, propyl, isopropyl, isopropyl, butyl, isobutyl and t-butyl.

35 Aryl denotes groups such as phenyl, naphthyl and anthryl, optionally with 1 to 4 substituents such as halogen, NO<sub>2</sub>, NH<sub>2</sub>, CN, OH, CH<sub>3</sub>, isopropyl, t-butyl, phenyl, phenylsulphonyl, OCH<sub>3</sub>, benzyloxy, formamido, COOH, COO-C<sub>1-4</sub>-n-alkyl or optionally mono- or di-C<sub>1-4</sub>-alkylated amino.

Further possible substituents on a phenyl group are -NHSO<sub>2</sub>-Ar or -NHCO-Ar (wherein Ar is phenyl with up to 3 substituents such as halogen, NO<sub>2</sub>, CF<sub>3</sub>, COOH and C<sub>1-4</sub>-alkyl, e.g. CH<sub>3</sub>, -NHCOCH<sub>2</sub>CH<sub>2</sub>COO(H, C<sub>1-4</sub>-alkyl or benzyl), acetamido, -NHCOCH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -NHCOO(H or C<sub>1-4</sub>-alkyl), -NHCOCOO (H or C<sub>1-4</sub>-alkyl), -NHCH<sub>2</sub>COO-ethyl, -NHCOCOC<sub>6</sub>H<sub>5</sub> and tetra- to heptamethyleneiminocarbonyl.

Cyclohexyl and decalyl are examples of cycloalkyl groups. Heteroaryl groups consist of one or 2 rings and contain 3 to 9 C atoms and 1 or 2 hetero atoms. Examples thereof are imidazolyl, thienyl, benzothienyl, quinolyl and indolyl. They can be substituted, e.g. by CH<sub>3</sub>, halogen, -CH<sub>2</sub>COOH or 1-methyl-5-trifluoromethylpyrazolyl.

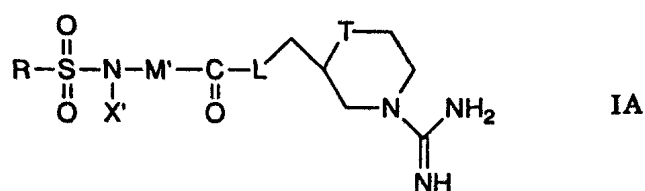
Heterocyclyl denotes groups containing 1 or 2 rings, 4 to 7 C atoms and 1 or 2 hetero atoms, such as tetrahydroquinolyl, azepinyl, piperidinyl, pyrrolidinyl, benzodiazepinyl, benzoxazolyl and benzopyrrolidinyl, optionally with 1 or 2 substituents such as methyl, halogen, oxo, COOH or COOCH<sub>3</sub>.

Piperidino, hexahydroazepino and heptahydroazocino are examples of tetra- to heptamethyleneimino groups. Acetoxy, acetoxymethyl, carbomethoxy, caromethoxy, carbethoxy, diethyl-carbamoyl, butyryloxymethyl and isobutyryloxymethyl are examples of substituents on such a group R".

Carboxyhexahydrooxazepino and hexahydrothiazepino are examples of tetra- to heptamethyleneimino groups which are interrupted by an O or S atom and which are optionally substituted.

Cl, NO<sub>2</sub> NH<sub>2</sub> and OH come into consideration e.g. as a substituent on the phenyl ring in an isoquinolyne group -N(X)-M.

Examples of compounds of formula I are those of the formula



wherein

5 -N(X')-M'- is an isoquinolylene group optionally substituted in the phenyl ring or

X' is H, -CH<sub>2</sub>COOH, -CH<sub>2</sub>COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>CO- (tetra- to heptamethyleneimino) or optionally N-mono- or N-di-C<sub>1-4</sub>-alkylated -CH<sub>2</sub>CONH<sub>2</sub> and

10 M' is a R'-(CH<sub>2</sub>)<sub>1-2</sub>CH=, R'-COCH<sub>2</sub>CH= or -CH(CO-Q')CH<sub>2</sub>- group,

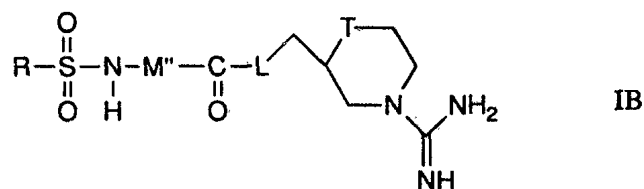
Q' is benzylamino, morpholino or tetra- to heptamethyleneimino and

R,R',L and T have the same significances as above,

15 as well as hydrates or solvates and physiological usable salts thereof.

Preferred among the compounds IA are those in which X' is H and R,M',L and T have the same significances as above.

Preferred among the compounds I are those of the formula



wherein

M'' is a R''-COCH<sub>2</sub>CH=, R'-(CO)<sub>1-2</sub>NHCH<sub>2</sub>CH=, benzyl-OCONHCH<sub>2</sub>CH=, -CH<sub>2</sub>[R'-(CO)<sub>1-2</sub>NH]CH-, -CH<sub>2</sub>(benzyl-OCONH)CH- or -CH(CO-Q'')CH<sub>2</sub>- group,

30 Q'' is a tetra- to heptamethyleneimino group optionally interrupted by an O or S atom and optionally substituted

by up to 2 substituents from the group C<sub>1-4</sub>-alkyl, COOH, -COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>OH and -CH<sub>2</sub>O-benzyl and R,R',R'',L and T have the same significances as given above.

5 Naphthyl, hydroxynaphthyl, 4-biphenyl, 2-anthryl, iodo-phenyl, nitrophenyl, benzyloxyphenyl, dimethoxyphenyl, 4-methoxy-2,3,6-trimethylphenyl, 2,4,6-triisopropylphenyl, carboxyphenyl, methoxycarbonylphenyl, benzyloxynaphthyl, phenylsulphonylphenyl, hexahydroazepinoylphenyl and t-  
10 butylphenyl are examples of aryl groups R.

3-Methyl-8-quinolyl, 5-(1-methyl-5-trifluoromethyl-pyrazol-3-yl)-2-thienyl and benzothienyl are examples of heteroaryl groups R.

15 3-Methyl-1,2,3,4-tetrahydro-8-quinolyl is an example of the heterocyclyl group R.

20 N-Dimethylaminonaphthylsulphonyl-aminomethylene is an example of a sulphonamide group -N(SO<sub>2</sub>-R<sup>0</sup>)-CH<sub>2</sub>- as a meaning of -N(X)-M-.

Preferred compounds of formula I are, further, those in which X is H or -CH<sub>2</sub>COOH.

25 When M signifies R'-(CH<sub>2</sub>)<sub>1-2</sub>CH= examples of these groups are 3-indolylethylidene, 2,3-dioxo-1-indolinylethylidene, phen-ethylidene, 1,4-dioxo-5H-2,5-benzodiazepin-5-ylethylidene, (fluoro, chloro, iodo, cyano, nitro, amino, carboxy, C<sub>1-4</sub>-alkoxy-carbonyl or hydroxy)-phenethylidene, cyclohexylpropylidene, decalylethylidene, imidazolylethylidene, thienylethylidene, (methyl, bromo, fluoro or carboxymethyl)-3-indolylethylidene, naphthylethylidene, (ethoxycarbonylcarbonylamino, methoxycar-  
30 bonylethylcarbonylamino, benzyloxycarbonylethylcarbonylamino, ethoxycarbonylamino, benzoylcarbonylamino, carboxybenzoyl-amino, methoxyethoxyacetamido, acetamido, carboxycarbonyl-amino, carboxypropionylamino, tolylsulphonamido, iodophenyl-sulphonamido, carboxyphenylsulphonamido or ethoxycarbonyl-



methylamino)phenethylidene, oxobenzoxazolinethylidene or 5-bromo- or 5-methyl-2,3-dioxo-1-indolinylethylidene.

When M signifies (R' or R'')COCH<sub>2</sub>CH= examples of these groups are hexahydroazepinoylethylidene, (methoxycarbonyl or carboxy)-pyrrolidinoylethylidene, 3,4-dihydro-2(1H)-isoquinolinoylethylidene, (nitro, amino, iodo or formamido)benzoylethylidene, morpholinoethylidene, heptahydroazocinoylethylidene, (ethoxycarbonyl, acetoxymethyl, dimethylcarbamoyl, isobutyryloxymethyl or butyryloxymethyl)piperidinoylethylidene, 3-methoxycarbonyl-4-oxopiperidinoylethylidene or 4-acetoxy-3-ethoxycarbonylpiperidinoylethylidene.

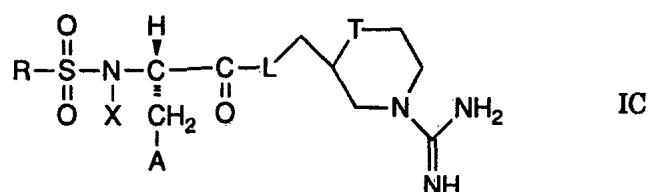
When M signifies R'-(CO)<sub>1-2</sub>NHCH<sub>2</sub>CH= examples of these groups are benzoylcarboxamidoethylidene, thienoylcarboxamidoethylidene, benzoylamidoethylidene or benzyloxycarboxamidoethylidene.

When M signifies -CH<sub>2</sub>[R'-(CO)<sub>1-2</sub>NH]CH- examples of these groups are 2-(carboxybenzoylamido)ethylene, 2-(benzyloxybenzoylamido)ethylene, 2-(2-piperidinecarboxamido)ethylene, 2-(hydroxybenzoylamido)ethylene and 2-(aminobenzoylamido)ethylene.

When M signifies -CH(CO-Q)CH<sub>2</sub>- examples of these groups are 1-(benzylaminocarbonyl)ethylene, 1-(hexahydroazepinoyl)ethylene, 1-(morpholinoyl)ethylene, 1-(heptahydroazocinoyl)ethylene, 1-[2-(benzyloxymethylmorpholinoyl)]ethylene, 1-[2-(hydroxymethylmorpholinoyl)]ethylene, 1-(2-ethoxycarbonyl-4-methylpiperidinoyl)ethylene, 1-(2-carboxy-4-methylpiperidinoyl)ethylene and 1-(3-carboxyhexahydro-1,4-oxazepinoyl)ethylene.

In the above formulae R is preferably aryl, especially naphthyl or nitro- or iodophenyl, L is preferably NH and the asymmetric C atom in the piperidine or morpholine ring is preferably in the (S)-configuration.

Preferred compounds of formula I are, further, those of the formula



5

wherein A is aryl, aroyl or heterocyclyl, especially phenyl, nitrophenyl, indolyl, 2,3-dioxo-1-indolinyll or aminobenzoyl.

The following are examples of preferred compounds:

10

(R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-α-(2-naphthylsulphonamido)-2,3-dioxo-1-indolinepropionamide,

(R)-N-[(RS)-1-amidino-3-piperidinylmethyl]-α-(2-naphthylsulphonamido)-o-nitrohydrocinnamamide,

15

(R)-N-[(RS)-1-amidino-3-piperidinylmethyl]-α-(o-nitrobenzenesulphonamido)indole-3-propionamide,

(R)-N-[(S)-1-amidino-3-piperidinylmethyl]-α-(p-iodobenzenesulphonamido)indole-3-propionamide,

20

(R)-N-[(S)-1-amidino-3-piperidinylmethyl]-α-(p-iodobenzenesulphonamido)-p-nitrohydrocinnamamide,

(R)-N-[(RS)-1-amidino-3-piperidinylmethyl]-3-(o-amino-benzoyl)-(2-naphthylsulphonamido)propionamide,

N-[(R)-α-[(S)-1-amidino-3-piperidinyl]methylcarbamoyl]-phenethyl]-N-(2-naphthylsulphonyl)glycine,

25

(R)-N-[(S)-1-amidino-3-piperidinylmethyl]-1,2,3,4-tetrahydro-2-(2-naphthylsulphonyl)-3-isoquinolinecarboxamide,

(S)-N-[(RS)-1-amidino-3-piperidinylmethyl]hexahydro-β-(2-naphthylsulphonamido)-γ-oxo-1H-1-azepinebutyramide,

30

(R)-N-[(S)-1-amidino-3-piperidinylmethyl]-α-(2-naphthylsulphonamido)-2,3-dioxo-1-indolinepropionamide,

4'-[(R)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]oxanilic acid,

(S)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]hexahydro-β-2-naphthylsulphonamido-γ-oxo-1(2H)-azocinebutyramide,

(2RS,4R)-1-[N<sup>4</sup>-[[[(S)-1-amidino-3-piperidiny]methyl]-N<sup>2</sup>-(2-naphthylsulphonyl)-L-asparaginy]-4-methyl-2-piperidine-carboxylic acid,

4'-[(R)-2-[[[(S)-1-amidino-3-piperidiny]methyl]carbamoyl]-  
5 2-(2-naphthylsulphonamido)ethyl]succinanilidic acid.

The above compounds can be manufactured by

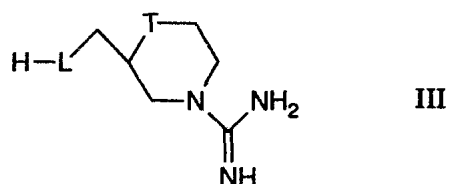
a) reacting an acid of the formula

10



with intermediary protection of a carboxy group present in the group X, R or M with an amine or alcohol of the formula

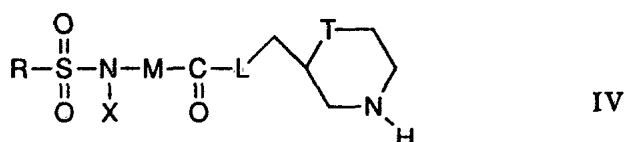
15



or a salt thereof, or

20

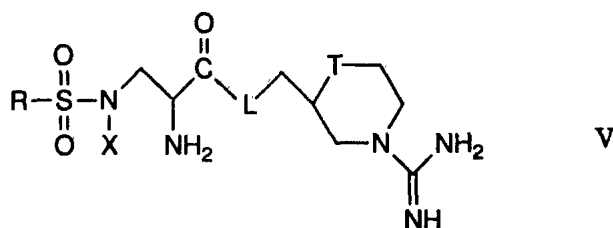
b) reacting a compound of the formula



with an amidinating reagent, or

25

c) reacting an amine of the formula



with an acid of the formula  $R'-COOH$  or a functional derivative thereof, and

d) if desired, functionally modifying a reactive group present  
5 in the group M in a compound of formula I, and

e) if desired, converting a compound of formula I into a  
physiologically acceptable salt or converting a salt of a compound  
of formula I into the free acid or base.

10

Conveniently, the acid II in a solvent such as dimethyl-  
formamide (DMF) is reacted at room temperature in the presence  
of a base such as 4-ethylmorpholine or ethyldiisopropylamine  
with a salt of a compound of formula III, e.g. a trifluoroacetate,  
15 bisulphite, nitrate, hydrochloride or hydroiodide, and with  
benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexa-  
fluorophosphate. A carboxy group protected e.g. as the t-butyl  
ester, which is present in group X, R or M, is thereby liberated.

20

In process variant b) the compound IV in a solvent such as  
DMF can be reacted in the presence of a base such as triethyl-  
amine with formamidinesulphonic acid or 3,5-dimethyl-1-pyra-  
zoly-formamidinium nitrate, conveniently at a temperature up to  
50°C.

25

According to process variant c) the amine V can be reacted  
with an acid  $R'-COOH$  or a functional derivative, e.g. an acid  
anhydride, in a solvent such as DMF in the presence of a base such  
as 4-ethylmorpholine at an elevated temperature, e.g. up to 50 or  
30 80°C.

The following can be mentioned as functional modifications  
in variant d):

35 1. The reduction of a nitroaryl group present in the group M to  
the aminoaryl group using Pd/C in a solvent such as ethanol;

2. the saponification of an ester group such as ethoxycarbonyl, e.g. in ethanol or methanol using a base such as aqueous sodium hydroxide;

5 3. the saponification of an ester group such as benzyloxy-carbonyl, e.g. in ethanol using Pd/C;

4. the cleavage of a benzyl ether, e.g. in ethanol using Pd/C in the presence of an acid such as hydrochloric acid or acetic acid.

10

The N-sulphonated amino acids II can be prepared by reacting a corresponding reactive sulphonic acid derivative such as the sulphonyl chloride  $R-SO_2Cl$  with the corresponding free amino acid  $HN(X)-M-COOH$  in the presence of a base such as an alkali metal hydroxide in a solvent such as an ether, e.g. diethyl ether or dioxan, and water.

In a variant, an acid II can be prepared by oxidizing the corresponding alcohol

20



e.g. in a solvent such as acetone with an oxidizing agent such as Jones reagent. At the same time a heterocyclic radical  $R'$ , such as 2-oxo-1-indolyl, present in the group M of the alcohol VI is oxidized to 2,3-dioxo-1-indolyl.

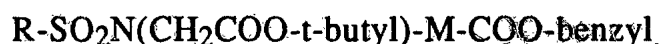
An alcohol VI can be prepared by reacting the corresponding  $\alpha$ -amino alcohol  $HN(X)-M-CH_2OH$  in the presence of aqueous sodium hydroxide and sodium bicarbonate with the sulphonyl chloride  $R-SO_2Cl$  in dioxan.

An amino alcohol  $HN(X)-M-CH_2OH$  in which M is e.g. a group  $-CH(CH_2-R')$  can be prepared by cleaving a corresponding oxazolidine which is protected at the N atom and which is substituted in the 4-position by  $-CH_2-R'$ , e.g. t-butyl (R)-2,2-dimethyl-4-( $CH_2-R'$ )-3-oxazolidinecarboxylate, with hydrochloric acid in methanol.

The above oxazolidine can be prepared in a manner known per se, e.g. when R' is a heterocyclyl radical attached via a N atom, such as 2-oxo-1-indoliny, by reacting the corresponding cyclic  
 5 amine H-R' with t-butyl (S)-2,2-dimethyl-4-(p-tolylsulphonyloxymethyl)-3-oxazolidinecarboxylate in the presence of a suspension of sodium hydride in DMF.

For the preparation of an amino acid II in which R is a  
 10 hydroxyaryl radical, the corresponding sulphonyl chloride R-SO<sub>2</sub>Cl in which the OH group is present in protected form, e.g. as the acetoxy group, can firstly be reacted in acetone with the amino acid HN(X)-M-COOH in the presence of aqueous sodium hydroxide and then the protecting group, e.g. acetyl, can be cleaved off with  
 15 a solution of sodium hydroxide in water and methanol.

For the manufacture of a guanidine of formula in which X is -CH<sub>2</sub>COOH, the sulphonyl chloride R-SO<sub>2</sub>Cl can firstly be reacted with a salt, e.g. the p-toluenesulphonate, of an ester H<sub>2</sub>N-M-COO-benzyl in a solvent such as methylene chloride in the presence of  
 20 a base such as triethylamine. The resulting sulphonamide R-SO<sub>2</sub>NH-M-COOC-benzyl is then reacted with t-butyl bromoacetate in a solvent such as THF at about -80°C in the presence of butyllithium. Thereafter, the benzyl group is cleaved off selectively, e.g. by catalytic hydrogenation with Pd/C in ethanol, from  
 25 the resulting diester



30 As described above, in the reaction of the resulting acid with a compound of formula III the carboxy group in the side-chain, which is protected as the t-butyl ester, is liberated.

The acid starting materials R-SO<sub>2</sub>NHCH(CO-Q)-CH<sub>2</sub>COOH can be  
 35 prepared by

a) reacting an aspartic acid derivative, e.g.



with an amine H-Q corresponding to the group Q' in a solvent such as DMF in the presence of benzotriazol-1-yloxy-tris(dimethyl-  
5 amino)phosphonium hexafluorophosphate,

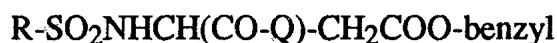
b) reacting the resulting amide



10

in a solvent such as ethyl acetate with an acid such as hydrochloric acid and then in dioxan with sodium hydroxide, sodium bicarbonate and a sulphonyl chloride R-SO<sub>2</sub>Cl and

15 c) cleaving off the benzyl group in the resulting sulphonamide

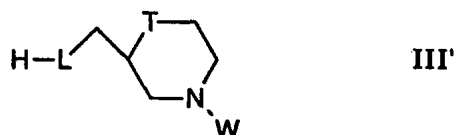


in a solvent such as methanol using sodium hydroxide solution.

20

The compounds III, IV and V are novel and as such are objects of the invention. The piperidine derivatives of formula III can be prepared as described in Examples 1, 2 and 3 hereinafter from 3-picolylamine where L = NH or from 3-hydroxymethyl-  
25 piperidine where L = O. Aminomethylmorpholine derivatives of formula III are obtained by reacting 2-aminomethyl-4-benzylmorpholine (J. Med. Chem. 33, 1990, 1406-1413) with di-t-butyl dicarbonate in dioxan, hydrogenating the resulting Boc-protected amine in ethanol in the presence of Pd/C to 2-(t-butoxycarbonyl-  
30 aminomethyl)morpholine and amidinating the latter. Hydroxymethylmorpholine derivatives of formula III can be prepared by amidinating 2-hydroxymethylmorpholine.

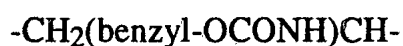
The compounds of formula IV are prepared by reacting the  
35 corresponding acid II with the compound of the formula



wherein W is a protecting group such as Boc or Z,  
e.g. as described above for the reaction of II with III, followed by  
5 the cleavage of the protecting group, e.g. using trifluoroacetic acid  
in methylene chloride, p-toluenesulphonic acid in acetonitrile or a  
solution of hydrogen chloride in ethyl acetate.

Alcohols of formula III' can be prepared as described in  
10 Example 3a) by introducing the protecting group at the N atom of  
3-hydroxymethylpiperidine or as described in Example 19a) to c)  
starting from benzyloxymethyloxirane via 2-benzyloxymethyl-  
morpholine and the e.g. Boc-protected 2-  
benzyloxymethylmorpholine. The resulting alcohol can be  
15 converted into the corresponding amine III' as described in  
Examples 6a) to d) and 19d) and e).

The amines V can be prepared by leaving off the  
benzyloxycarbonyl group in the corresponding compound I in  
20 which e.g. M is the group



e.g. in ethanol using Pd/C in the presence of hydrochloric acid.  
25

The guanidines of formula I, their solvates and their salts  
inhibit not only platelet aggregation induced by thrombin, but also  
the thrombin-induced clotting of fibrinogen in blood plasma. The  
said compounds influence not only the platelet-induced, but also  
30 the plasmatic blood clotting. They therefore prevent especially  
the formation of hyaline thrombi and of platelet-rich thrombi and  
can be used in the control or prevention of illnesses such as  
thrombosis, stroke, cardiac infarct, inflammation and arterio-  
sclerosis. Further, these compounds have an effect on tumour  
35 cells and prevent the formation of metastases. Accordingly, they  
can also be used as antitumour agents.



A differential inhibition of thrombin and other serine proteases by the above compounds is desirable in order to obtain compounds having as high a specificity as possible and at the same time to avoid possible side-effects. Alongside other tested serine proteases the ratio of the inhibition of trypsin to the inhibition of thrombin was taken as the general measurement for the specificity of a compound (q in the Table hereinafter), because trypsin as the most unspecific serine protease can be readily inhibited by the widest variety of inhibitors. In order for the inhibition of thrombin and trypsin to be directly comparable in spite of the use of different substrates, the inhibition constant  $K_i$  independent of substrate and enzyme concentration was determined as the measurement of the inhibition.

Specific chromogenic peptide substrates can be used to determine the inhibition of the catalytic activity of the above proteases. The inhibition of the amidolytic activity of thrombin and trypsin by the above guanidines was determined as described hereinafter.

The measurements were carried out on microtiter plates at room temperature. For this, in each well of the plate 150  $\mu$ l of buffer (50 mM Tris, 100 mM NaCl, 0.1% polyethylene glycol; pH 7.8) were mixed with 50  $\mu$ l of the inhibitor dissolved in DMSO and diluted in the buffer, and 25  $\mu$ l of human thrombin (0.5 nM final conc.) were added. After incubation for 10 minutes the reaction was started by the addition of chromogenic substrate S-2238 (H-D-Phe-Pip-Arg-paranitroaniline from Kabivitrum; 10 or 50  $\mu$ M final conc.) and the hydrolysis of the substrate was followed spectrophotometrically on a kinetic microtiter plate reader for 5 minutes. After graphical presentation of the inhibition curves the  $K_i$  values were determined according to the method described in Biochem. J. 55, 1955, 170-171. The inhibition of trypsin was effected analogously, but using the substrate S-2251 (H-D-Val-Leu-Lys-paranitroaniline) in 200 and 750  $\mu$ M final concentration.

The results will be evident from the following Table:

Product of Example	8	9	13a	14i	17b
K <sub>i</sub> (nM) Thrombin	8.55	135	20.8	25	20.7
K <sub>i</sub> (nM) Trypsin	20075	168700	29200	38000	6300
q	2350	1250	1400	1520	304

Product of Example	17c	17f	17j	18f
K <sub>i</sub> (nM) Thrombin	58	41.3	26.1	16
K <sub>i</sub> (nM) Trypsin	10000	18300	14800	18850
q	172	455	565	1180

The guanidines of formula I have a low toxicity. Thus, the products of Example 8, 13a, 14i and 18f have an LD<sub>50</sub> of 30-50 mg/kg in mice upon intravenous administration.

As mentioned earlier, medicaments containing a guanidine of formula I, a solvate or salt thereof are likewise objects of the present invention, as is a process for the manufacture of such medicaments which comprises bringing one or more of the said compounds and, where desired, one or more other therapeutically valuable substances into a galenical dosage form. The medicaments can be administered enterally, e.g. orally in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions, or rectally, e.g. in the form of suppositories, or as a spray. The administration can, however, also be effected parenterally, e.g. in the form of injection solutions.

For the manufacture of tablets, coated tablets, dragees and hard gelatine capsules the active substance can be mixed with pharmaceutically inert, inorganic or organic excipients. Lactose, maize starch or derivatives thereof, talc, stearic acid or its salts can be used e.g. as such excipients for tablets, coated tablets, dragees and hard gelatine capsules. Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols; depending on the nature of the active substance no excipients are, however, usually required in the case of soft gelatine capsules. Suitable excipients for the manufacture of

solutions and syrups are e.g. water, polyols, saccharose, invert sugar and glucose, suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol and vegetable oils and suitable excipients for suppositories are natural or hardened oils, waxes, fats, semi-liquid or liquid polyols. The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, coating agents or antioxidants.

10

For the control or prevention of the illnesses mentioned above the dosage of the active substance can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral or parenteral administration a dosage of about 0.1 to 20 mg/kg, preferably of about 0.5 to 4 mg/kg, per day should be appropriate for adults, although the upper limit just given can also be exceeded when this is shown to be indicated.

20

### Example 1

a) A solution of 66.6 g of di-t-butyl dicarbonate in 200 ml of dioxan is added to a solution of 30 g of 3-picolylamine in 300 ml of dioxan so that the temperature does not exceed 25°C. The reaction mixture is stirred at room temperature for 3 hours and evaporated. After filtration over silica gel with ethyl acetate there are obtained 55.5 g of 3-t-butyloxycarbonyl-picolylamine.

b) 45.5 g of 3-t-butyloxycarbonyl-picolylamine are dissolved in 220 ml of methanol and catalytically hydrogenated with 4.6 g of ruthenium-on-aluminium (5%) at 60°C under 100 bar or hydrogen. After filtration of the catalyst and evaporation of the solvent there are obtained 46 g of rac-3-t-butyloxycarbonyl-aminomethyl-piperidine.

35

c) 38.8 g of the product from b) are dissolved in 900 ml of DMF and treated with 74.5 ml of triethylamine. After the addition of 26.5 g of formamidinesulphonic acid the reaction mixture is

stirred for 15 hours and subsequently filtered. The mother liquor is evaporated and the residue is taken up in water and extracted with ethyl acetate. The aqueous phase is evaporated and the product is evaporated azeotropically with ethanol, toluene and dichloro-ethane. The residue is suspended in ether and filtered. There are obtained 44.0 g of rac-3-t-butoxycarbonylamino-methyl-1-amidinopiperidine hemisulphite, MS: 257 ( $M^{+}+1$ ), 201, 157, 126, 96.

d) 27.8 g of the product from c) are dissolved in 70 ml of methylene chloride, treated with 70 ml of trifluoroacetic acid at 0°C and stirred for 1 hour. The reaction mixture is evaporated and the residue is evaporated azeotropically with toluene and ethanol. There are obtained 27.6 g of rac-3-aminomethyl-1-amidinopiperidine sulphite, MS: 156 ( $M^{+}$ ), 126 ( $M^{+}-CH_2NH_2$ ), 69, 45.

### Example 2

A solution of 5.3 g of rac-3-hydroxymethylpiperidine in 100 ml of DMF is treated with 19 ml of triethylamine. After the addition of 6.8 g of formamidinesulphonic acid the reaction mixture is stirred for 15 hours. The suspension is filtered and the precipitate is washed with ether and dried. There are obtained 10.3 g of rac-3-hydroxymethyl-1-amidinopiperidine hemisulphite, MS: 158 ( $M+1$ ), 143, 116, 102; m.p. 100°C.

### Example 3

a) A solution of 211.2 g of di-t-butyl dicarbonate in 500 ml of dioxan is added to a solution of 92.9 g of rac-3-hydroxymethylpiperidine in 1500 ml of dioxan so that the temperature does not exceed 25°C. The reaction mixture is stirred at room temperature for 15 hours and evaporated. The residue is suspended in 800 ml of hexane and filtered. There are obtained 120.7 g of rac-N-t-butyloxycarbonyl-3-hydroxymethylpiperidine, m.p. 78°C.

b) A solution of 100 g of the product from a) in 4000 ml of methylene chloride is treated with 56.2 ml of pyridine and cooled to 0°C. 58.3 ml of butyryl chloride are added dropwise thereto so that the temperature does not exceed 10°C. The reaction mixture is subsequently stirred at room temperature for 15 hours. The suspension is filtered, the filtrate is evaporated and the residue is taken up in ethyl acetate. The organic phase is washed with aqueous 10% CuSO<sub>4</sub> solution, dried and evaporated. The residue is filtered through silica gel and eluted with hexane/ethyl acetate (8:2). There are obtained 119.7 g of t-butyl rac-3-(butyroxymethyl)-1-piperidinecarboxylate.

c) 116.6 g of the product from b) are emulsified in 2 l of 0.1M sodium chloride solution and 80 ml of sodium phosphate buffer, pH 7.0. The pH is adjusted to 7.0 with 1.0N sodium hydroxide solution and the reaction is started by the addition of 1.00 g of lipoprotein lipase produced from *Pseudomonas fluorescens* (Lipase P-30, Amano) in 10 ml of 0.1M sodium chloride solution. The pH is maintained at 7.0 by the addition of 2.0N sodium hydroxide solution while stirring. After 14 hours the reaction is terminated by the addition of 500 ml of methylene chloride, the reaction mixture is extracted with methylene chloride and the organic phase is dried and evaporated. Chromatography of the residue over silica gel with hexane/ethyl acetate gives 36.6 g of t-butyl [S]-3-hydroxymethyl-1-piperidinecarboxylate, m.p. 89-90°C,  $[\alpha]_{365}^{25} = +53.5^{\circ}$  (c = 1.0, EtOH).

d) The 65.7 g of ester fraction from c) are emulsified in 1.15 l of 0.1M sodium chloride solution and 45 ml of 0.1M sodium phosphate buffer (pH 7.0) and treated with 0.50 g of Lipase P-30 in 5 ml of 0.1M sodium chloride solution. The pH is maintained at 7.0 by the addition of 2.0N sodium hydroxide solution while stirring. After 40 hours the reaction is terminated by the addition of 400 ml of methylene chloride, the reaction mixture is extracted with methylene chloride and the organic phase is dried and evaporated. Chromatography of the residue over silica gel with hexane/ethyl acetate gives 49.5 g of t-butyl [R]-3-(butyryloxymethyl)-1-piperidinecarboxylate. This is dissolved in 250 ml

of ethanol, treated with 88 ml of 2N sodium hydroxide solution, stirred overnight and then evaporated. The residue is taken up in 200 ml of methylene chloride and washed with water, the aqueous phase is extracted with methylene chloride and the organic phase is dried and concentrated. Chromatography of the residue over silica gel with hexane/ethyl acetate gives 33.7 g of t-butyl [R]-3-hydroxymethyl-1-piperidinecarboxylate,  $[\alpha]_{365}^{25} = -60.7^\circ$  ( $c = 1.0$ , EtOH).

- 10 e) A solution of 5.0 g of the product from d) in 20 ml of methylene chloride is cooled to  $0^\circ\text{C}$  and treated with 15 ml of trifluoroacetic acid. After 2 hours the reaction mixture is evaporated and the residue is taken up in water and treated with sodium bicarbonate to pH 7.5. This aqueous phase is evaporated and the crystal mass is suspended in 100 ml of methylene chloride/ethanol (9:1). The salts are filtered off and the filtrate is evaporated. The residue is dissolved in 30 ml of DMF and treated with 9.7 ml of triethylamine. After the addition of 3.5 g of formamidinesulphonic acid the reaction mixture is stirred for 15 hours. The precipitate is filtered off and the solvent is evaporated. The residue is purified by reverse phase chromatography over silylated silica gel RP-18 with water. There are obtained 2.6 g of (R)-3-hydroxymethyl-1-amidinopiperidine hemisulphate, FAB-MS: 158 (M+1).

#### Example 4

(S)-3-Hydroxymethyl-1-amidinopiperidine hemisulphate, FAB-MS: 158 (M+1), is manufactured from t-butyl [S]-3-hydroxymethyl-1-piperidinecarboxylate analogously to Example 3e).

#### Example 5

- 35 A solution of 1.5 g of N-(2-naphthylsulphonyl)-D-tryptophan in 30 ml of DMF is treated with 1.5 ml of ethylmorpholine. After the addition of 0.7 g of rac-3-aminomethyl-1-amidinopiperidine sulphite (Example 1) and 1.7 g of benzotriazol-1-yloxy-tris(di-methylamino)phosphonium

hexafluorophosphate the reaction mixture is stirred for 15 hours. The solvent is evaporated and the residue is taken up in 50 ml of water and extracted with 100 ml of ethyl acetate. The ethyl acetate phase is washed with water, dried and evaporated. The crude material is purified on a RP-18 column with water/acetonitrile (0-30%). There is obtained 0.8 g of (R)-N-[(RS)-1-amidino-3-piperidinylmethyl]- $\alpha$ (2-naphthylsulphonamido)indole-3-propionamide bisulphite, FAB-MS: 533 (M+H)<sup>+</sup>.

### Example 6

a) A solution of 5.0 g of t-butyl (S)-3-hydroxymethyl-1-piperidinecarboxylate (Example 3c) in 100 ml of pyridine is treated with 5.4 g of p-chlorosulphonyl chloride. The reaction mixture is stirred for 15 hours, evaporated, taken up in 200 ml of ethyl acetate and washed with water and aqueous 10% CuSO<sub>4</sub> solution. The organic phase is dried and evaporated. The residue is filtered over silica gel and eluted with hexane/ethyl acetate (8/2). There are obtained 6.5 g of t-butyl (S)-3-(p-chlorophenylsulphonyloxymethyl)-1-piperidinecarboxylate.

b) A solution of the product from a) in 50 ml of DMF is treated with 3.25 g of sodium azide. The reaction mixture is stirred at 50°C for 15 hours and evaporated. The residue is taken up in water and ether and washed with water. The ether phase is dried and evaporated. There are obtained 4.0 g of t-butyl (S)-3-azidomethyl-1-piperidinecarboxylate.

c) A solution of the product from b) in 100 ml of ethanol is hydrogenated in the presence of 0.6 g of platinum oxide under 1 bar of hydrogen. Then, the reaction mixture is filtered over silica gel and eluted with methanol. There are obtained 3.4 g of t-butyl (R)-3-aminomethyl-1-piperidinecarboxylate,  $[\alpha]_D^{25} = +23.0^\circ$  (c = 0.4, EtOH).

d) Using an identical process, from (R)-3-hydroxymethyl-1-piperidinecarboxylate there is obtained t-butyl (S)-3-amino-methyl-1-piperidinecarboxylate,  $[\alpha]_D^{25} = -17.7^\circ$  (c = 0.6 EtOH).

5 e) A solution of 1.5 g of N-(2-naphthylsulphonyl)-D-tryptophan in 50 ml of DMF is treated with 0.8 ml of ethyldiisopropylamine. After the addition of 1.0 g of the product from d) and 1.7 g of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexa-fluorophosphate the  
10 reaction mixture is stirred for 15 hours. The solvent is evaporated and the residue is taken up in water and extracted with ethyl acetate. The ethyl acetate phase is washed with water, dried and evaporated. Chromatography over silica gel with ethyl acetate gives 2.3 g of (R)[(S)-1-(t-butoxycarbonyl)-3-piperidinylmethyl]- $\alpha$ -naphthylsulphonamidoindole-3-propion-  
15 amide.

f) A solution of the product from e) in 10 ml of methylene chloride is treated at  $0^\circ\text{C}$  with 3 ml of trifluoroacetic acid. The  
20 reaction mixture is stirred at  $0^\circ\text{C}$  for 1 hour, evaporated and the residue is azeotroped with ethylene chloride. The residue is taken up in water and ethyl acetate, adjusted to pH 9 with 10% sodium carbonate and extracted. The organic phase is dried and  
25 evaporated. There are obtained 2.5 g of (R)- $\alpha$ -naphthylsulphon-amido-N-[(S)-3-piperidinylmethyl]-indole-3-propionamide.

g) A solution of the product from f) in 50 ml of DMF is treated with 1.7 ml of triethylamine. After the addition of 0.7 g of formamidinesulphonic acid the reaction mixture is stirred for  
30 15 hours. The solvent is evaporated and the residue is taken up in ethyl acetate and methanol. The organic phase is washed with water, dried and evaporated. Purification of the product on a RP-18 column with water/acetonitrile gives 1.85 g of (R)-N-[(S)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-  
35 indole-3-propionamide bisulphite, FAB-MS: 533 (M+H)<sup>+</sup>.

### Example 7



a) A solution of 1.0 g of N-2-naphthylsulphonyl-(D)-tryptophan in 20 ml of DMF is treated with 0.5 ml of ethyldiisopropylamine. After the addition of 0.6 g of t-butyl (S)-3-hydroxymethyl-1-piperidinecarboxylate (Example 3c) and 1.1 g of benzotriazol-1-yloxy-tris(dimethylamino)phosphoniumhexafluorophosphate the reaction mixture is stirred for 15 hours. The solvent is evaporated and the residue is taken up in water and extracted with ethyl acetate. The ethyl acetate phase is washed with water, dried and evaporated. Chromatography over silica gel with ethyl acetate gives 1.0 g of N-(2-naphthylsulphonyl)-D-tryptophan (S)-1-t-butyloxycarbonyl-3-piperidinylmethyl ester.

b) A solution of the product from a) in 10 ml of acetonitrile is treated with 0.9 g of p-toluenesulphonic acid. The reaction mixture is stirred for 15 hours. After evaporation the residue is taken up in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic phase is dried and evaporated. Purification over a RP column with water/acetonitrile give 0.47 g of N-(2-naphthylsulphonyl)-D-tryptophan (S)-3-piperidinylmethyl ester.

c) A solution of the product from b) in 20 ml of DMF is treated with 0.4 ml of triethylamine. After the addition of 0.2 g of formamidinesulphonic acid the reaction mixture is stirred for 15 hours. The DMF is evaporated and the residue is taken up in ethyl acetate and washed with water. The organic phase is dried and evaporated. Purification on a RP column with water/acetonitrile gives 0.27 g of N-(2-naphthylsulphonyl)-D-tryptophan (S)-1-amidino-3-piperidinylmethyl ester bisulphite, FAB-MS: 534 (M+1).

### Example 8

a) A solution of 10.7 g of t-butyl (R)-4-hydroxymethyl-2,2-dimethyl-3-oxazolidinecarboxylate (J. Org. Chem. 52, 1987, 2361-64), in 107 ml of pyridine is treated with 9.7 g of p-toluenesulphonyl chloride. The reaction mixture is stirred for

17 hours, then taken up in ethyl acetate and washed with water. After drying and evaporation the residue is purified over silica gel with hexane/ethyl acetate (3:1). There are obtained 15.1 g of t-butyl (S)-2,2-dimethyl-4-(p-tolylsulphonyloxymethyl)-3-oxazolidinecarboxylate.

b) 4.6 g of 2-indolinone are added to a suspension of 0.82 g of sodium hydride in 50 ml of DMF and the mixture is stirred for 90 minutes. Then, 6.6 g of the product from a) in 60 ml of DMF are added thereto and the reaction mixture is stirred at 50°C overnight. After evaporation of the solvent the residue is taken up in ethyl acetate and washed with water. After drying and evaporation of the solvent the residue is purified over silica gel with ethyl acetate/hexane (1:4). There are obtained 2.5 g of t-butyl (R)-2,2-dimethyl-4-(2-oxo-1-indolinylmethyl)-3-oxazolidinecarboxylate.

c) A solution of 2.5 g of the product from b) in 30 ml of methanol is treated with 36 ml of 2N hydrochloric acid and stirred overnight. After evaporation of the solvent the residue is azeotroped with toluene. 1.56 g of the resulting 1-[(R)-2-amino-3-hydroxypropyl]-2-indolinone are dissolved in 2 equivalents of 1N sodium hydroxide solution. Thereto there are added 0.8 g of sodium bicarbonate in 8.1 ml of water and subsequently a solution of 1.46 g of 2-naphthylsulphonyl chloride in 28 ml of dioxan and the mixture is stirred overnight. The reaction mixture is poured into 200 ml of aqueous 5% potassium hydrogen sulphate/10% potassium sulphate and extracted with ethyl acetate. After washing the organic phase with water and drying the solvent is distilled off. The residue is purified over silica gel with methyl-ene chloride/methanol (98/2). There are obtained 1.9 g of N-[(R)-2-hydroxy-1-(2-oxo-1-indolinylmethyl)ethyl]-2-naphthylsulph-onamide.

d) A solution of 1.82 of the product from c) in 70 ml of acetone is treated at 0°C with 17.4 ml of Jones reagent and the mixture is stirred for 4 hours. The reaction mixture is poured on to ice and extracted with ethyl acetate. After washing the organic phase

with water, drying and evaporation the product is purified over silica gel with methylene chloride/methanol (19:1) and 1% acetic acid. There are obtained 1.5 g of N-(2-naphthylsulphonyl)-3-(2,3-dioxo-1-indoliny)-D-alanine.

5

e) Analogously to Example 5, from the product of d) there is obtained (R)-N-[(RS)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido-2,3-dioxo-1-indolinepropionamide acetate (epimers 1:1), FAB-MS: 671 (M+H)+.

10

### Example 9

a) 20 g of 2-naphthylsulphonyl chloride in 150 ml of ether are added to a solution of 7.3 g of (R)-phenylalanine in 120 ml of 1N sodium hydroxide solution. The reaction mixture is stirred for 15 hours and decanted. The aqueous phase is separated, washed with ether, acidified to pH 3 with HCl and extracted with ethyl acetate. The organic phase is dried and evaporated. The separated crystals are suspended in ether and filtered off. There are obtained 14.4 g of N-(2-naphthylsulphonyl)-3-phenyl-D-alanine, m.p. 146°C.

b) The following N-sulphonated amino acids are prepared using an identical process:

N-(2-Naphthylsulphonyl)-3-(p-chlorophenyl)-D-alanine,  
m.p. 154°C

N-(2-naphthylsulphonyl)-3-(p-cyanophenyl)-D-alanine, m.p.  
182°C

N-(2-naphthylsulphonyl)-3-(p-nitrophenyl)-D-alanine, m.p.  
218°C

N-(2-naphthylsulphonyl)-3-benzyl-D-alanine, m.p. 138°C

N-(2-naphthylsulphonyl)-D-tryptophan, m.p. 167°C

N-(2-biphenylsulphonyl)-D-tryptophan, m.p. 227-230°C

N-(2-anthrylsulphonyl)-D-tryptophan, m.p. 210°C

N-(4-nitrophenylsulphonyl)-D-tryptophan, MS: M+ 389

N-(2-nitrophenylsulphonyl)-D-tryptophan, m.p. 70-80°C

N-(3-nitrophenylsulphonyl)-D-tryptophan, m.p. 80-84°C

35

N-(4-benzyloxyphenylsulphonyl)-D-tryptophan, m.p. 193°C

N-(3,4-dimethoxyphenylsulphonyl)-D-tryptophan, m.p.  
182-184°C

5 N-(2,3,6-trimethyl-4-methoxyphenylsulphonyl)-D-trypto-  
phan, MS:  $M^+$  416

N-(2,4,6-triisopropylphenylsulphonyl)-D-tryptophan, MS:  
 $M^+$  470

10 N-(2-naphthylsulphonyl)-5-methyltryptophan, m.p. 192°C  
(R)-2-(2-naphthylsulphonyl)-1,2,3,4-tetrahydro-3-iso-  
quinolinecarboxylic acid, m/e 322, 191, 176, 150, 127.

c) Analogously to Example 5, from the product of a) there is  
obtained (R)-N-[(RS)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(2-  
naphthylsulphonamido)hydrocinnamide bisulphite (epimers 1:1),  
15 FAB-MS: 494 ( $M+H$ ) $^+$ .

#### Example 10

a) 1.1 g of sodium hydride dispersion (60%) are suspended in  
50 ml of DMF. 5.23 g of 4-methyl-3H-1,4-benzodiazepine-2,5(1H,  
4H)-dione are added thereto so that the temperature does not  
exceed 35°C and the mixture is stirred at room temperature for  
90 minutes. Subsequently, a solution of 5.3 g of t-butyl (S)-2,2-  
dimethyl-4-(p-tolylsulphonyloxymethyl)-3-oxazolidinecarboxylate  
25 (Example 6a) in 50 ml of DMF is added thereto and the mixture is  
stirred at 50°C overnight. The reaction mixture is evaporated and  
the residue is taken up in ethyl acetate, washed with water and  
dried. After evaporation of the solvent the residue is purified  
over silica gel with ethyl acetate/hexane (1:1). There are obtained  
30 1.85 g of t-butyl (R)-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-  
1,4-benzodiazepin-1-ylmethyl)-2,2-dimethyl-3-  
oxazolidinecarboxylate.

b) A solution of the product from a) in 37 ml of methanol is  
35 treated with 23 ml of 2N hydrochloric acid. After stirring over-  
night the reaction mixture is evaporated. 1.37 g of the resulting  
1-[(R)-2-amino-3-hydroxypropyl]-3,4-dihydro-4-methyl-2H-1,4-  
benzodiazepine-2,5(1H)-dione are dissolved in 15 ml of pyridine

and treated with 2.08 g of 2-naphthylsulphonyl chloride. After 3 hours the reaction mixture is poured into 2N hydrochloric acid and extracted with ethyl acetate. The extracts are washed with water, dried and the solvent is evaporated. The residue is purified over silica gel with methylene chloride/methanol (97:3). 0.5 g of N-[(R)-1-hydroxymethyl-2-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-benzodiazepin-1-ylmethyl)ethyl]-2-naphthylsulphonamide is isolated.

c) A solution of 0.4 g of the product from b) in 12 ml of acetone is treated at 0°C with 3 ml of Jones reagent. After 3 hours at room temperature the reaction mixture is poured on to ice and extracted with ethyl acetate. After washing with water and drying there is obtained, after evaporation, 0.4 g of N-(2-naphthylsulphonyl)-3-(2,3,4,5-tetrahydro-4-methyl-2,5-dioxo-1H-1,4-benzodiazepin-1-yl)-D-alanine.

d) Analogously to Example 5, from the product of c) there is obtained (R)-N-[(RS)-1-amidino-3-piperidinylmethyl]-1,2,3,4-tetrahydro-2-methyl- $\alpha$ -(2-naphthylsulphonamido)-1,4-dioxo-5H-2,5-benzodiazepine-5-propionamide (epimers 1:1), FAB-MS: 606 (M+H)<sup>+</sup>.

### Example 11

a) A solution of 1.25 g of 6-acetoxynaphthyl-2-sulphonyl chloride (Monatsh. 49, 1928, 96) in 4.4 ml of acetone is added dropwise to a solution of 0.9 g of D-tryptophan in 4.8 ml of 1N NaOH and 4.8 ml of acetone and the pH is maintained at 9 by the addition of 1N NaOH. Then, the acetone is evaporated, the resulting suspension is acidified with 1N HCl and the product is extracted with ethyl acetate. The product is chromatographed on silica gel with ethyl acetate/acetone (1:1). The main fraction is taken up in 8.8 ml of a methanolic solution of 0.5N NaOH and stirred for 17 hours. The solution is evaporated, treated with water and 1N HCl and extracted with ethyl acetate. Purification on silica gel with ethyl acetate/acetone (3:2) gives 0.54 g of N-(6-

hydroxy-2-naphthylsulphonyl)-D-tryptophan, MS:  $M^+$  410,  $m/e$  207, 130.

- b) Analogously to Example 5 from the product of a) there is  
 5 obtained (R)-N-[(RS)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(6-hydroxy-2-naphthylsulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 549 ( $M+H$ ) $^+$ .

### Example 12

10

The following compounds are manufactured analogously to Examples 5 and 9:

- a) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-p-fluoro- $\alpha$ -(2-naphthylsulphonamido)hydrocinnamamide bisulphite (epimers  
 15 1:1), FAB-MS: 512 ( $M+H$ ) $^+$ .
- b) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-p-chloro- $\alpha$ -(2-naphthylsulphonamido)hydrocinnamamide bisulphite (epimers  
 20 1:1), FAB-MS: 528 ( $M+H$ ) $^+$ .
- c) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-p-cyano- $\alpha$ -(2-naphthylsulphonamido)hydrocinnamamide bisulphite (epimers  
 25 1:1), FAB-MS: 519 ( $M+H$ ) $^+$ .
- d) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-p-nitrohydrocinnamamide bisulphite  
 (epimers 1:1), FAB-MS: 539 ( $M+H$ ) $^+$ .
- e) (R)-p-Amino-N-[(RS)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)hydrocinnamamide bisulphite (epimers  
 30 1:1), FAB-MS: 509 ( $M+H$ ) $^+$ .
- f) (R)-N-[(RS)-1-amidino-3-piperidinylmethyl]-3-(p-hydroxy-phenyl)-2-(2-naphthylsulphonamido)propionamide bisulphite  
 35 (epimers 1:1), FAB-MS: 510 ( $M+H$ ) $^+$ .

### Example 13

The following compounds are manufactured analogously to Examples 5 and 9:

- 5 a) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-o-nitrohydrocinnamamide bisulphite (epimers 1:1), FAB-MS: 539 (M+H)<sup>+</sup>.
- b) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)cyclohexanepropionamide bisulphite (epimers 1:1), FAB-MS: 500 (M+H)<sup>+</sup>.
- 10 c) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-2-(2-naphthylsulphonamido)-4-phenylbutyramide bisulphite (epimers 1:1), FAB-MS: 508 (M+H)<sup>+</sup>.
- 15 d) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)cyclohexanebutyramide bisulphite (epimers 1:1), FAB-MS: 514 (M+H)<sup>+</sup>.
- 20 e) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-1-naphthylpropionamide bisulphite, FAB-MS: 586 (M+H)<sup>+</sup>.
- 25 f) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-2-naphthylpropionamide bisulphite (epimers 1:1), FAB-MS: 544 (M+H)<sup>+</sup>.
- 30 g) ( $\alpha$ R,2S,4aR and/or S,8aR and/or S)-N-[(RS)-1-amidino-3-piperidinylmethyl]decahydro- $\alpha$ -(2-naphthylsulphonamido)-2-naphthylpropionamide bisulphite (mixture of diastereomers), FAB-MS: 554 (M+H).
- h) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-4-imidazolepropionamide bisulphite (epimers 1:1), FAB-MS: 484 (M+H)<sup>+</sup>.
- 35

i) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-2-thienylpropionamide bisulphite (epimers 1:1), FAB-MS: 500 (M+H)<sup>+</sup>.

5

Example 14

The following compounds are manufactured analogously to Examples 5 and 11:

10 a) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(3-methyl-8-quinolinesulphonamido)indole-3-propionamide bisulphite (epimers 1:1), FAB-MS: 548 (M+H)<sup>+</sup>.

15 b) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -[(RS)-3-methyl-1,2,3,4-tetrahydro-8-quinolinesulphonamido]indole-3-propionamide bisulphite, (epimers 1:1), FAB-MS: 552 (M+H)<sup>+</sup>.

20 c) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(4-biphenylsulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 559 (M+H)<sup>+</sup>.

d) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-anthrylsulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 583 (M+H)<sup>+</sup>.

25 e) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -[5-(1-methyl-5-trifluoromethylpyrazol-3-yl)-2-thienylsulphonamido]indole-3-propionamide bisulphite (epimers 1:1), FAB-MS: 637 (M+H)<sup>+</sup>.

30 f) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(p-iodobenzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 609 (M+H)<sup>+</sup>.

35 g) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(o-iodobenzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 608 (M+H)<sup>+</sup>.



h) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(p-nitro-benzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 528 (M+H)<sup>+</sup>.

5 i) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(o-nitro-benzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 528 (M+H)<sup>+</sup>.

10 j) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(m-nitro-benzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 528 (M+H)<sup>+</sup>.

15 k) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(p-benzyl-oxybenzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 589 (M+H)<sup>+</sup>.

20 l) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(3,4-dimethoxybenzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 543 (M+H)<sup>+</sup>.

m) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(4-methoxy-2,3,6-trimethylbenzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 555 (M+H)<sup>+</sup>.

25 n) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2,4,6-triisopropylbenzenesulphonamido)indole-3-propionamide hydrochloride (epimers 1:1), FAB-MS: 609 (M+H)<sup>+</sup>.

### Example 15

30 The following compounds are manufactured analogously to Example 5:

35 a) (RS)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-5-methyl- $\alpha$ -(2-naphthylsulphonamido)indole-3-propionamide bisulphite, FAB-MS: 547 (M+H)<sup>+</sup>.

b) (RS)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-5-fluoro- $\alpha$ -(2-naphthylsulphonamido)indole-3-propionamide bisulphite, FAB-MS: 551 (M+H)<sup>+</sup>.

- 5 c) 3-[(R)-2-[(RS)-1-Amidino-3-piperidinylmethylcarbamoyl]-2-(2-naphthylsulphonamido)ethyl]indole-1-acetic acid bisulphite (epimers 1:1), FAB-MS: 591 (M+H)<sup>+</sup>.

### Example 16

10

Analogously to Example 6 and, respectively, Example 7 there are obtained:

- 15 a) (R)-N-[(R)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)indole-3-propionamide bisulphite, FAB-MS: 533 (M+H)<sup>+</sup>, and, respectively,

- 20 b) N-(2-naphthylsulphonyl)-D-tryptophan (R)-1-amidino-3-piperidinylmethyl ester p-toluenesulphonate (1:1), FAB-MS: 534 (M+H)<sup>+</sup>.

### Example 17

25 The following compounds are obtained analogously to Examples 6 and 7:

- a) (R)-N-[(R)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(p-iodobenzenesulphonamido)indole-3-propionamide p-toluenesulphonate (1:1), FAB-MS: 609 (M+H)<sup>+</sup>.

- 30 b) (R)-N-[(S)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(p-iodobenzenesulphonamido)indole-3-propionamide p-toluenesulphonate (1:1), FAB-MS: 609 (M+H)<sup>+</sup>.

- 35 c) N-(p-Iodophenylsulphonyl)-D-tryptophan (R)-1-amidino-3-piperidinylmethyl ester p-toluenesulphonate (1:1), FAB-MS: 609 (M+H)<sup>+</sup>.

d) N-(p-Iodophenylsulphonyl)-D-tryptophan (S)-1-amidino-3-piperidinylmethyl ester p-toluenesulphonate (1:1), FAB-MS: 610 (M+H)<sup>+</sup>.

5 e) (R)-N-[(R)-1-Amidino-3-piperidinylmethyl]-α-(p-iodobenzenesulphonamido)-2-naphthylpropionamide p-toluenesulphonate (1:1), FAB-MS: 620 (M+H)<sup>+</sup>.

10 f) (R)-N-[(S)-1-Amidino-3-piperidinylmethyl]-α-(p-iodobenzenesulphonamido)-2-naphthylpropionamide p-toluenesulphonate (1:1), FAB-MS: 620 (M+H)<sup>+</sup>.

15 g) N-(p-Iodophenylsulphonyl)-3-(2-naphthyl)-D-alanine (R)-1-amidino-3-piperidinylmethyl ester p-toluenesulphonate (1:1), FAB-MS: 621 (M+H)<sup>+</sup>.

20 h) N-(p-Iodophenylsulphonyl)-3-(2-naphthyl)-D-alanine (S)-1-amidino-3-piperidinylmethyl ester p-toluenesulphonate (1:1), FAB-MS: 621 (M+H)<sup>+</sup>.

i) (R)-N-[(R)-1-Amidino-3-piperidinylmethyl]-α-(p-iodobenzenesulphonamido)-p-nitrohydrocinnamamide bisulphite (2:1), FAB-MS: 615 (M+H)<sup>+</sup>.

25 j) (R)-N-[(S)-1-Amidino-3-piperidinylmethyl]-α-(p-iodobenzenesulphonamido)-p-nitrohydrocinnamamide p-toluenesulphonate (1:1), FAB-MS: 615 (M+H)<sup>+</sup>.

30 k) N-(p-Iodophenylsulphonyl)-3-(p-nitrophenyl)-D-alanine (R)-1-amidino-3-piperidinylmethyl ester p-toluenesulphonate (1:1), FAB-MS: 616 (M+H)<sup>+</sup>.

35 l) N-(p-Iodophenylsulphonyl)-3-(p-nitrophenyl)-D-alanine (S)-1-amidino-3-piperidinylmethyl ester p-toluenesulphonate (1:1), FAB-MS: 616 (M+H)<sup>+</sup>.

### Example 18

The following compounds are manufactured analogously to Example 5:

- 5 a) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]hexahydro- $\alpha$ -2-naphthylsulphonamido- $\gamma$ -oxo-1H-azepine-1-butyramide bisulphite (epimers 1:1), FAB-MS: 543 (M+H)<sup>+</sup>.
- 10 b) 1-[(R)-23-[(RS)-1-Amidino-3-piperidinylmethylcarbamoyl]-3-(2-naphthylsulphonamido)propionyl]-L-proline methyl ester (epimers 1:1), FAB-MS: 573 (M+H)<sup>+</sup>.
- 15 c) 1-[(R)-3-[(RS)-1-Amidino-3-piperidinylmethylcarbamoyl]-3-(2-naphthylsulphonamido)propionyl]-L-proline (epimers 1:1), FAB-MS: 559 (M+H)<sup>+</sup>.
- 20 d) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-3,4-dihydro- $\alpha$ -(2-naphthylsulphonamido)- $\gamma$ -oxo-2(1H)-isoquinolinebutyramide (epimers 1:1), FAB-MS: 577 (M+H)<sup>+</sup>.
- e) (RS)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-2-(2-naphthylsulphonamido)-3-(o-nitrobenzoyl)propionamide bisulphite, FAB-MS: 567 (M+H)<sup>+</sup>.
- 25 f) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-3-(o-amino-benzoyl)-2-(naphthylsulphonamido)propionamide (epimers 1:1), FAB-MS: 537 (M+H)<sup>+</sup>.
- g) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-3-anthranilo-yl-2-(p-iodobenzenesulphonamido)propionamide trifluoroacetate (epimers 1:1), FAB-MS: 613 (M+H)<sup>+</sup>.
- 30 h) (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]-3-(o-formamidobenzoyl)- $\alpha$ -(2-naphthylsulphonamido)propionamide acetate (epimers 1:1), FAB-MS: 565 (M+H)<sup>+</sup>.

35

### Example 19

a) 199 g of 2-aminoethyl hydrogen sulphate are added to 164 ml of 70% sodium hydroxide solution, the solution is heated to 50°C and added dropwise to a solution of (RS)-benzyloxymethyloxirane in 280 ml of methanol. After 1 hour at 50°C a further 280 ml of 70% sodium hydroxide solution are added thereto and the solution is stirred overnight. Then, the reaction mixture is poured on to ice and extracted with toluene. The organic phase is washed with water, dried and evaporated. After distillation there are obtained 26.8 g of rac-2-benzyloxymethyl-morpholine, MS:  $M^+ - 91 = 116$  (benzyl).

b) A solution of 31.0 g of di-t-butyl dicarbonate in 287 ml of dioxan is added 26.8 g of the product from a) in 287 ml of dioxan and the reaction mixture is stirred overnight. After evaporation of the solvent and chromatography of the residue on silica gel with ethyl acetate/hexane there are obtained 15 g of t-butyl rac-2-benzyloxymethyl-4-morpholinecarboxylate, MS:  $M^+ - 56 = 251$  (isobutylene).

c) A solution of 15 g of the product from b) in 300 ml of ethanol is hydrogenated in the presence of 1.5 g of Pd/C under normal conditions and, after filtration and evaporation of the solvent, there is obtained quantitatively t-butyl rac-2-hydroxymethyl-4-morpholinecarboxylate, MS:  $M^+ = 217$ .

d) A solution of 8.8 g of the product from c) in 44 ml of pyridine is treated with 9.4 g of p-chlorobenzenesulphonyl chloride. After stirring for 5 hours the reaction mixture is evaporated, the residue is taken up in ethyl acetate and washed with 10% copper sulphate solution. After drying the organic phase, evaporation of the solvent and chromatography of the residue on silica gel with ethyl acetate/hexane there are obtained 14.7 g of t-butyl rac-2-(p-chlorophenylsulphonyloxymethyl)-4-morpholinecarboxylate, MS: 392 ( $M+H$ )<sup>+</sup>.

e) 7.3 g of sodium azide are added to a solution of 14.7 g of the product from d) in 91 ml of DMF. After stirring at 50°C for 24 hours the reaction mixture is poured on to ice and extracted

with ether. The organic phase is washed with water, dried and evaporated. 8.1 g of t-butyl rac-2-azidomethyl-4-morpholine-carboxylate are obtained.

- 5 f) A solution of 8.1 g of the product from e) in 92 ml of ethanol is hydrogenated in the presence of 0.8 g of platinum oxide for 4 hours under normal conditions and 6.5 g of t-butyl rac-2-aminomethyl-4-morpholinecarboxylate, (MS:  $M+H^+$  -56 = 159 (isobutylene) are isolated.

10

g) A solution of 3.0 g of N-(2-naphthylsulphonyl)-D-tryptophan (Example 9) in 35 ml of DMF is treated with 1.2 ml of 4-ethyl-morpholine and with 3.4 g of benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate. A  
 15 solution of 2.0 g of the product from f) in 2 ml of DMF is added thereto and the solution is stirred overnight. Then, the solvent is distilled off and the residue is taken up in ethyl acetate and washed with water. After drying, evaporation of the solvent and chroma- tography of the residue on silica gel with ethyl acetate  
 20 there are obtained 4.5 g of t-butyl (RS)-2-N-(2-naphthylsulphonyl)-D-tryptophylaminomethyl-4-morpholinecarboxylate, MS:  $(M+H)^+ -56 = 537$  (isobutylene).

- h) A solution of 2 g of the product from g) in 20 ml of ethyl  
 25 acetate is treated with 20 ml of a 4 molar solution of HCl in ethyl acetate. After stirring the solution is evaporated to dryness. The residue is dissolved in 20 ml of DMF, treated with 1.4 ml of triethylamine and 0.5 g of formamidinesulphonic acid and stirred at room temperature for 17 hours. Then, the solvent is  
 30 evaporated, the residue is taken up in 50 ml of ethyl acetate and 10 ml of methanol and this solution is washed with water. After drying the organic phase, evaporation of the solvent and chromatography of the residue on a RP column (alkylsilylated silica gel) with water/acetonitrile there is obtained 0.1 g of (R)-N-  
 35 [(RS)-4-amidino-2-morpholinylmethyl]- $\alpha$ -(2-naphthylsulphon-amido)indole-3-propionamide bisulphite, MS: 535  $(M+H)^+$ .

### Example 20

Analogously to Example 19g) and h), from t-butyl rac-2-hydroxymethyl-4-morpholinecarboxylate (Example 19c) and N-(2-naphthylsulphonyl)-D-tryptophan there is obtained N-(2-naphthylsulphonyl)-D-tryptophan (RS)-4-amidino-2-morpholinylmethyl ester bisulphite, MS: 536 (M+H)<sup>+</sup>.

### Example 21

Analogously to Example 19 there are obtained

a) (R)-N-[(RS)-4-amidino-2-morpholinylmethyl]- $\alpha$ -(2-naphthylsulphonyl)-p-nitrohydrocinnamamide bisulphite, MS: 541 (M+H)<sup>+</sup>

b) (R)-N-[(RS)-4-amidino-2-morpholinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-2-thienylpropionamide bisulphite, MS: 502 (M+H)<sup>+</sup>

c) (R)-N-[(RS)-4-amidino-2-morpholinylmethyl]-3-(o-amino-benzoyl)-2-(2-naphthylsulphonamido)propionamide bisulphite, MS: 539 (M+H)<sup>+</sup>.

### Example 22

a) A solution of 10 g of (D)-phenylalanine benzyl ester p-toluenesulphonate in 150 ml of methylene chloride is treated with 8.2 ml of triethylamine and cooled to 0°C. 5.8 g of 2-naphthylsulphonyl chloride are added thereto and the mixture is stirred at room temperature for 12 hours. The reaction mixture is evaporated, the residue is taken up in 200 ml of ethyl acetate, the precipitated triethylammonium chloride salt is filtered off under suction and the mother liquor is washed with water. After evaporation of the organic phase and crystallization from hexane there are obtained 9.7 g of N-(2-naphthylsulphonyl)-3-phenyl-D-alanine benzyl ester, m.p. 107°C.

b) A solution of 3 g of the product from a) in 40 ml of THF is treated at  $-80^{\circ}\text{C}$  with 5 ml of 1.6M butyllithium in hexane and then with 1.2 ml of t-butyl bromoacetate. After stirring at room temperature for 2 hours the reaction mixture is taken up in 200 ml of ethyl acetate, washed with water and the organic phase is evaporated. The product is purified over silica gel with hexane/ethyl acetate (9:1). There are obtained 1.35 g of N-(t-butoxycarbonylmethyl)-N-(2-naphthylsulphonyl)-3-phenyl-D-alanine benzyl ester, NMR ( $\text{CDCl}_3$ ) 1.45 (s, 9H, t-butyl).

c) A solution of 1.35 g of the product from b) in 50 ml of ethanol is hydrogenated in the presence of 0.3 g of Pd/C. After evaporating the reaction mixture and azeotroping with toluene there is obtained 0.95 g of N-(t-butoxycarbonylmethyl)-N-(2-naphthylsulphonyl)-3-phenyl-D-alanine.

d) Analogously to Example 5 there is obtained N-[(R)- $\alpha$ -[(S)-1-amidino-3-piperidinyl]methylcarbonyl]phenethyl]-N-(2-naphthylsulphonyl)glycine, FAB-MS: 552 ( $\text{M}+\text{H}$ ) $^{+}$ .

### Example 23

a) 13.7 g of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate and 16.9 ml of benzylamine are added to a solution of 10.0 g of N-Boc-L-aspartic acid  $\beta$ -benzyl ester in 200 ml of DMF and the reaction mixture is stirred at room temperature overnight. Then, the solvent is evaporated and the residue is taken up in ethyl acetate and washed with water. After drying, evaporation and chromatography on silica gel with ethyl acetate/hexane (1:4) there are obtained 5.4 g of benzyl (S)-3-(1,1-dimethylethoxycarbonylamino)-4-benzylamino-4-oxo-butyrates.

b) A solution of 2.0 g of the product from a) in 10 ml of ethyl acetate is treated with 10 ml of a 4 molar solution of HCl in ethyl acetate. After stirring for 3 hours the mixture is evaporated and the residue is suspended in 30 ml of dioxan. 5 ml of 1N sodium hydroxide solution, 0.8 g of sodium bicarbonate, 20 ml of water and then a solution of 1.1 g of 2-naphthylsulphonyl chloride in 15



ml of dioxan are added thereto and the mixture is stirred at room temperature overnight. The reaction mixture is poured into 5% potassium hydrogen sulphate/10% potassium sulphate solution and extracted with ethyl acetate. After drying and evaporating the organic phase the residue is recrystallized from ethyl acetate/hexane. 1.8 g of (S)-2-benzylcarbamoyl-N-(2-naphthylsulphonyl)- $\beta$ -alanine benzyl ester are obtained.

c) A solution of 1.0 g of the product from b) in 20 ml of methanol is treated with 2 ml of 1N sodium hydroxide solution and stirred at room temperature overnight. The mixture is acidified, extracted with ethyl acetate and, after evaporation, the residue obtained is crystallized from methanol/methylene chloride/hexane. 0.3 g of (S)-2-benzylcarbamoyl-N-(2-naphthylsulphonyl)- $\beta$ -alanine is obtained.

d) Analogously to Example 5 there is obtained (S)-N-[(RS)-1-amidino-3-piperidinylmethyl]-3-benzylcarbamoyl-3-(2-naphthylsulphonamido)propionamide trifluoroacetate (epimers 1:1), FAB-MS: 551 (M+H)<sup>+</sup>.

#### Example 24

Analogously to Example 23, via (R)-2-benzylcarbamoyl-N-(2-naphthylsulphonyl)- $\beta$ -alanine there is obtained (R)-N-[(RS)-1-amidino-3-piperidinylmethyl]-3-benzylcarbamoyl-3-(2-naphthylsulphonamido)propionamide hydrochloride, FAB-MS: 551 (M+H)<sup>+</sup>.

#### Example 25

Analogously to Example 23, using hexamethyleneimine in place of benzylamine there is obtained (S)-N-[(RS)-1-amidino-3-piperidinylmethyl]hexahydro- $\beta$ -(2-naphthylsulphonamido)- $\gamma$ -oxo-1H-1-azepinebutyramide trifluoroacetate, FAB-MS: 543 (M+H)<sup>+</sup>.

#### Example 26

Analogously to Example 6 there is obtained (R)-N-[(S)-1-amidino-3-piperidinylmethyl]1,2,3,4-tetrahydro-2-(2-naphthylsulphonyl)-3-is-quinolinecarboxamide hydrochloride, FAB-MS: 506 (M+H)<sup>+</sup>.

5

#### Example 27

Analogously to Examples 5 and 9 there is obtained methyl o-[(R)-α-[(RS)-1-amidino-3-piperidinylmethylcarbamoyl]-p-nitrophenethylsulphamoyl]benzoate, FAB-MS: 547 (M+H)<sup>+</sup>.

10

#### Example 28

Analogously to Examples 5 and 9 there is obtained (RS)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]-5-bromo-α-2-naphthylsulphonamidoindole-3-propionamide sulphite, FAB-MS: 611 (M+H)<sup>+</sup>.

15

#### Example 29

The following compounds are manufactured analogously to Examples 6 and 9:

20

a) (R)-N-[[[(RS)-1-Amidino-3-piperidinyl]methyl]-p-iodo-α-2-naphthylsulphonamidohydrocinnamide p-toluenesulphonate, FAB-MS: 620 (M+H)<sup>+</sup>.

25

b) (R)-N-[[[(S)-1-Amidino-3-piperidinyl]methyl]-α-2-naphthylsulphonamido-p-nitrohydrocinnamide p-toluenesulphonate, FAB-MS: 539 (M+H)<sup>+</sup>.

30

#### Example 30

a) A solution of 30.1 g of t-butyl (R)-4-hydroxymethyl-2,2-dimethyl-3-oxazolidinecarboxylate t-butyl ester in 400 ml methylene chloride, cooled to 0°, is treated with 27.2 ml of triethylamine. After the addition of 12.1 ml of methanesulphonyl chloride at 0° the reaction mixture is stirred for 1 hour. The salts

35

are filtered off, the filtrate is evaporated and the product is recrystallized from hexane. There are obtained 32.7 g of t-butyl (S)-2,2-dimethyl-4-(methanesulphonyloxymethyl)-3-oxazolidinecarboxylate,  $H^1$ -NMR ( $CDCl_3$ ): 1.48, s, 9H, t-butyl; 3.04, s, 3H, mesyl.

b) A solution of 29.1 g of the product from a) in 200 ml of DMF is treated with 24.5 g of sodium azide. The suspension is heated to  $50^\circ$  and stirred for 24 hours. The salts are then filtered off and the filtrate is evaporated. The crude product is dissolved in 400 ml of ethyl acetate and washed with water. The organic phase is dried and evaporated. There are obtained 20.2 g of t-butyl (R)-2,2-dimethyl-4-(azidomethyl)-3-oxazolidinecarboxylate, IR ( $CHCl_3$ )  $2140\text{ cm}^{-1}$  (azide-band).

c) A solution of 20.2 g of the product from b) in 400 ml of dioxane is treated with 4 g of platinum oxide. The reaction mixture is hydrogenated at room temperature and normal pressure. After filtration and evaporation of the filtrate there are obtained 17.9 g of t-butyl (R)-2,2-dimethyl-4-(amino-methyl)-3-oxazolidinecarboxylate.

d) A solution of the product from c) in 300 ml of methylene chloride is treated at  $0^\circ$  with 19.9 ml of Hünig base (ethyldiisopropylamine) and 12.2 ml of benzyl chloroformate. After stirring the reaction mixture is evaporated and the crude product is dissolved in 400 ml of ethyl acetate and washed with 100 ml of water. The organic phase is dried and evaporated and the crude material is purified on silica gel with ethyl acetate/hexane (1:9). There are obtained 26.4 g of t-butyl (R)-2,2-dimethyl-4-(carbo-benzoxymethyl)-3-oxazolidinecarboxylate.

e) A solution of the product from d) in 300 ml of methanol is treated with 36.2 ml of 2N HCl. After 24 hours the solution is evaporated and the residue is dissolved in 400 ml of dioxan and treated with 72.43 ml of 1N NaOH. After the addition of 30.4 g of sodium bicarbonate the suspension is treated with a solution of 24.6 g of 2-naphthylsulphonyl chloride in 100 ml of dioxan. The

suspension is stirred for 15 hours, the reaction mixture is then filtered, evaporated, taken up in ethyl acetate, washed with water and dried. The organic phase is evaporated and the crude product is purified on silica gel with ethyl acetate/ hexane (3:7). There are obtained 25.85 g of benzyl [(R)-3-hydroxy-2-(2-naphthylsulphonamido)propyl]carbamidate, MS: 415 (M+H)<sup>+</sup>, 371 (-CO<sub>2</sub>), 347, 325, 281, 269, 225, 191, 135.

f) After the addition of 1 g of 10% Pd/C a solution of 5 g of the product from e) in 100 ml of ethanol is hydrogenated at room temperature under normal pressure for 24 hours. The catalyst is filtered off and washed with methanol. After evaporation there are obtained 2.8 g of N-[(R)-2-amino-1-hydroxymethyl]ethyl]-2-naphthylsulphonamide, MS: 281 (M+H)<sup>+</sup> 251, 250, 221, 191, 128, 127, 60.

g) A solution of 1.3 g of the product from f) in 500 ml of DMF is treated with 0.83 g of phenylglyoxalic acid and 0.9 ml of Hünig base. After the addition of 2.0 g of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate the reaction mixture is stirred for 5 hours. The solvent is evaporated and the crude product is purified on silica gel with hexane/ ethyl acetate (1:1). There are obtained 1.4 g of N-[(R)-3-hydroxy-2-(2-naphthylsulphonamido)propyl]-2-phenylglyoxylamide.

h) A solution of 0.42 g of the product from g) in 30 ml of acetone is treated at 0° with 3.5 ml of Jones reagent (2.67 mg of CrO<sub>3</sub> in sulphuric acid). The mixture is stirred for 1 hour, poured on to ice-water and extracted with ethyl acetate. The organic phase is dried and evaporated. There is obtained 0.44 g of (R)-2-(2-naphthylsulphonamido)-3-(2-phenylglyoxylamido)propionic acid, FAB-MS: 427 (M+1)<sup>+</sup>.

i) Analogously to Example 5, from the product of h) there is obtained (R)-N-[[[(S)-1-amidino-3-piperidinyl]methyl]-2-naphthylsulphonamido-3-(2-phenylglyoxylamido)propionamide p-toluenesulphonate. FAB-MS: 565 (M+H)<sup>+</sup>.

Example 31

Analogously to Examples 5 and 9 there are obtained

5

a) via N-[(6-benzyloxy-2-naphthyl)sulphonyl]-D-tryptophan,  
FAB-MS: 394 (M+H)+,

the (R)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -(6-  
benzyloxy-2-naphthylsulphonamido)indole-3-propionamide  
10 hydrochloride, F.B-MS: 639 (M+),

b) via N-(1-naphthylsulphonyl)-D-tryptophan, FAB-MS: 394  
(M+H)+,

the (R)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -(1-  
15 naphthylsulphonamido)indole-3-propionamide hydrochloride,  
FAB-MS: 533 (M+H)+,

c) via N-(2-naphthylsulphonyl)-3-(m-nitrophenyl)-DL-alanine,  
MS: 400 (M+),

the (RS)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -[2-  
20 naphthylsulphonamido]-m-nitrohydrocinnamamide  
hydrochloride, FAB-MS: 539 (M+H)+.

Example 32

25

a) 0.36 g of sodium hydrogen carbonate and a solution of  
0.50 g of methyl p-(chlorosulphonyl)benzoate in 10 ml of ether  
are added to a solution of 0.71 g of D-tryptophan in 4.8 ml of  
water and 2.13 ml of 1N NaOH. The resulting suspension is  
30 stirred for 22 hours. The sodium salt of N-[[p-(methoxy-  
carbonyl)phenyl]sulphonyl]-D-tryptophan is filtered off under  
suction and rinsed with water (0.52 g), MS: 400 (M-Na)+. 0.38 g  
of product as the free acid is isolated from the mother liquor after  
acidification with citric acid.

35

b) Analogously to Examples 5 and 11, from the acid from a)  
there is obtained methyl p-[[[(R)-1-[[[(RS)-1-amidino-3-

piperidiny]methyl]carbamoyl]-2-indol-3-ylethyl]sulphamoyl]-  
benzoate hydrochloride, FAB-MS: 541 (M+H)+.

3  
3  
3  
3  
3

3  
3  
3  
3

3  
3  
3

Example 33

Analogously to Example 31 there is obtained (RS)-N-[[[(S)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -2-naphthylsulphonamido-m-nitrohydrocinnamamide hydrochloride, FAB-M<sub>s</sub> 539 (M+H)<sup>+</sup>.

Example 34

A solution of 0.15 g of (RS)-N-[[[(S)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -2-naphthylsulphonamido-m-nitrohydrocinnamamide hydrochloride (Example 33) in 50 ml of ethanol is treated with 0.12 g of 10% Pd/C and hydrogenated at room temperature under normal pressure. The reaction solution is filtered and evaporated, and the residue is dissolved in methanol and treated with ether. The separated (RS)-N-[[[(S)-1-amidino-3-piperidinyl]methyl]-m-amino- $\alpha$ -2-naphthylsulphonamido-hydrocinnamamide hydrochloride is filtered off under suction and rinsed with ether; yield 0.12 g, FAB-MS: 509 (M+H)<sup>+</sup>.

Example 35

a) A solution of 50 g of N-(2-naphthylsulphonyl)-3-(p-nitrophenyl)-D-alanine (Example 9b) in 100 ml of DMF is treated with 45 ml of Raney-nickel and hydrogenated at room temperature and normal pressure. The reaction solution is filtered, then concentrated and poured into water. Separated 3-(p-aminophenyl)-N-(2-naphthylsulphonyl)-D-alanine is filtered off under suction, washed with water and dried. Yield 37.6 g, m.p. 211-212°. MS: 370 (M)<sup>+</sup>.

30

b) A suspension of 1.0 g of the product from a) in 15 ml of methylene chloride is treated with 1.13 ml of triethylamine. The resulting solution is cooled in an ice-bath and treated with a solution of 0.3 ml of monoethyl oxalyl chloride in 5 ml of methylene chloride. After a further 30 minutes in the ice-bath the solution is stirred at room temperature overnight. The reaction mixture is concentrated, the residue is dissolved in water and acidified with 10% citric acid and the separated product is

filtered off under suction. It is dissolved in ethyl acetate, washed with water and dried. After evaporation there is obtained 0.92 of oxalic acid ester amide which, analogously to Example 5, gives 0.87 g of ethyl 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-[(2-naphthylsulphonamido)ethyl]oxanilate hydrochloride, FAB-MS: 609 (M+H)<sup>+</sup>.

### Example 36

The following compounds are manufactured analogously to Example 35:

- a) methyl 4'-[(R)-[[[(RS)-1-amino-3-piperidinyl]methyl]carbamoyl]-2-[(2-naphthylsulphonamido)ethyl]succinanilate hydrochloride, FAB-MS: 623 (M+H)<sup>+</sup>,
- b) methyl 3'-[(RS)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]-succinanilate hydrochloride, FAB-MS: 623 (M+H)<sup>+</sup>,
- c) benzyl 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-[(2-naphthylsulphonamido)ethyl]succinanilate hydrochloride, FAB-MS: 699 (M+H)<sup>+</sup>,
- d) methyl 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-[(p-iodobenzenesulphonamido)ethyl]succinanilate hydrochloride, FAB-MS: 699 (M+H)<sup>+</sup>,
- e) ethyl 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]carbanilate hydrochloride, FAB-MS: 581 (M+H)<sup>+</sup>.

### Example 37

Analogously to Example 35 there is obtained N-(2-naphthylsulphonyl)-3-[p-(2-phenylglyoxylamido)phenyl]-D-alanine, MS: 502 (M<sup>+</sup>), which is converted analogously to Example 6e)-g) into (R)-N-[(S)-1-amidino-3-piperidinyl]methyl]-α-(2-



naphthylsulphonyl)-p-(2-phenylglyoxylamido)hydrocinnamamide hydrochloride, FAB-MS: 641 (M+H)<sup>+</sup>.

### Example 38

5

Analogously to Examples 35 and 42, via methyl p-[p-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]benzamido]benzoate hydrochloride, FAB-MS: 671 (M+H)<sup>+</sup>, there is obtained p-[p-[(R)-2-[[[(RS)-1-amidino-3-  
10 piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)-ethyl]benzamido]benzoic acid hydrochloride, FAB-MS: 657 (M+H)<sup>+</sup>.

### Example 39

15

Analogously to Example 35 there is obtained (R)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]-p-[2-(2-methoxyethoxy)acetamido]-α-2-naphthylsulphonamidohydrocinnamamide hydrochloride, FAB-MS: 625 (M+H)<sup>+</sup>.

20

### Example 40

Analogously to Example 35 there is obtained 4'-[(R)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]oxanilic acid hydrochloride, FAB-MS: 581 (M+H)<sup>+</sup>.

25

### Example 41

30

A solution of 0.7 g of 3-(p-aminophenyl)-N-(2-naphthylsulphonyl)-D-alanine (Example 35a) in 5 ml of pyridine is treated with 1 ml of acetic anhydride and left to stand at room temperature for 20 hours. After the addition of water and conc. HCl (ice-cooling) the separated product is filtered off under suction, dissolved in ethyl acetate, washed with water, dried and evaporated. The product is dissolved in 20 ml of methanolic 1N NaOH  
35 and left to stand. The solution is evaporated, the residue is dissolved in water, acidified with conc. HCl, the precipitated product is filtered off under suction, dissolved in ethyl acetate and washed with water. After evaporation the residue is reacted

analogously to Example 5 and gives 146 mg of (R)-p-acetamido-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -(2-naphthylsulphonamido)hydrocinnamamide hydrochloride, FAB-MS: 551 (M+H)<sup>+</sup>.

5

#### Example 42

A suspension of 150 mg of ethyl 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]oxanilate hydrochloride (Example 35) in 10 ml of  
 10 ethanolic 0.1N NaOH solution is dissolved at room temperature while stirring. The reaction solution is acidified with ethanolic 2.78N HCl, the separated NaCl is filtered off under suction and the filtrate is treated with ether. The separated hydrochloride is  
 15 decanted off and stirred with ether. The product is filtered off under suction. Yield: 60 mg of 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]-oxanilic acid hydrochloride, FAB-MS: 581 (M+H)<sup>+</sup>.

20

#### Example 43

A solution of 0.5 g of benzyl 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]-succinanilate hydrochloride  
 25 (Example 36c) in 20 ml of ethanol is treated with 0.5 g of 10% Pd/C and hydrogenated. The catalyst is filtered off, the filtrate is concentrated and the residue is treated with ether. The separated  
 30 product is decanted off, stirred with ether and finally filtered off under suction. Yield: 0.35 g of 4'-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]succinilidic acid hydrochloride, FAB-MS: 609 (M+H)<sup>+</sup>.

#### Example 44

35

A solution of 0.5 g of 3-(p-aminophenyl)-N-(2-naphthylsulphonyl)-D-alanine (Example 35a) in 1.35 ml of 1N NaOH and 7 ml of water is treated with 6 ml of dioxan and 0.34 g of

sodium hydrogen carbonate. 0.26 g of tosyl chloride is added while stirring. After stirring at room temperature for 24 hours the solution is concentrated, diluted with water and extracted with ether. The aqueous phase is treated with 6 ml of 2N HCl while cooling with ice and the separated product is filtered off under suction. The latter, without purification, is converted analogously to Example 5 into 0.39 g of (R)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -2-naphthylsulphonamido-p-(p-toluenesulphonamido)hydrocinnamamide hydrochloride, FAB-MS: 663 (M+H)<sup>+</sup>.

#### Example 45

Analogously to Example 44 there is obtained (R)-N-[[[(S)-1-amidino-3-piperidinyl]methyl]-p-(p-iodobenzenesulphonamido)- $\alpha$ -(2-naphthylsulphonamido)hydrocinnamamide hydrochloride, FAB-MS: 775 (M+H)<sup>+</sup>.

#### Example 46

Analogously to Example 44 via methyl p-[[p-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]phenyl]sulphamoyl]benzoate hydrochloride, FAB-MS: 707 (M+H)<sup>+</sup>, there is obtained p-[[p-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]phenyl]sulphamoyl]benzoic acid hydrochloride, FAB-MS: 693 (M+H)<sup>+</sup>.

#### Example 47

0.45 ml of a 50% solution of ethyl glyoxylate in toluene is added to a suspension of 0.37 g of 3-(p-aminophenyl)-N-(2-naphthylsulphonyl)-D-alanine (Example 35a) in 20 ml of dioxan. The resulting solution is treated with 0.3 g of 10% Pd/C and hydrogenated at room temperature and normal pressure for 6 hours. The catalyst is filtered off, the filtrate is evaporated and the residue is reacted as in Example 5. Yield: 89 mg of N-[p-[(R)-2-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-

naphthylsulphonamido)ethyl]phenyl]glycine ethyl ester hydrochloride, FAB-MS: 595 (M+H)<sup>+</sup>.

#### Example 48

5

Analogously to Example 26 there is obtained (R)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]-1,2,3,4-tetrahydro-2-(2-naphthylsulphonyl)-3-isoquinolinecarboxamide hydrochloride (epimers 1:1),  $[\alpha]_{589}^{25} = +76.8^{\circ}$  (MeOH, c = 0.5%), FAB-MS: 506 (M+H)<sup>+</sup>.

10

#### Example 49

Analogously to Example 5 there is obtained (RS)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]-3-(o-aminobenzoyl)-2-(2-naphthylsulphonamido)propionamide hemisulphite, FAB-MS: 537 (M+H)<sup>+</sup>.

15

#### Example 50

20

The following compounds are manufactured analogously to Example 23:

25

a) (S)-N-[[[(RS)-1-Amidino-3-piperidinyl]methyl]-β-2-naphthylsulphonamido-γ-oxo-4-morpholinebutyramide trifluoroacetate, FAB-MS: 531 (M+H)<sup>+</sup>.

30

b) (R)-N-[[[(RS)-1-Amidino-3-piperidinyl]methyl]hexahydro-β-2-naphthylsulphonamido-γ-oxo-1H-azepinebutyramide trifluoroacetate, FAB-MS: 543 (M+H)<sup>+</sup>

35

c) (S)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]hexahydro-β-2-naphthylsulphonamido-γ-oxo-1(2H)-azocinebutyramide hydrochloride, FAB-MS: 557 (M+H)<sup>+</sup>.

#### Example 51

a) 5 g of potassium diphenylsulphone-3-sulphonate in 50 ml of thionyl chloride are boiled under reflux overnight. The precipitated material is filtered off and, after drying, there are obtained 3.2 g of diphenylsulphone-3-sulphonyl chloride.

5

b) 6.7 ml of 1N sodium hydroxide solution and 2.82 g of sodium bicarbonate are added to a solution of 1.52 g of p-nitro-D-phenylalanine in 37 ml of dioxan. A solution of the product from a) in 119 ml of dioxan is added thereto and the mixture is stirred at room temperature overnight. Subsequently, the reaction mixture is poured on to ice and extracted with ethyl acetate. The organic phase is washed with water, dried and concentrated. There are thus obtained 1.75 g of 3-(p-nitro-phenyl)-N-[(m-phenylsulphonyl)phenyl]sulphonyl]-D-alanine.

15

c) From the above acid there is obtained analogously to Example 6e)-g) (R)-N-[(S)-1-amidino-3-piperidinyl]methyl]-p-nitro- $\alpha$ -[m-(phenylsulphonyl)benzenesulphonamido]hydrocinnamamide hemisulphite, FAB-MS: 629 (M+H)<sup>+</sup>.

20

### Example 52

a) 2.3 g of p-nitro-D-phenylalanine are suspended in 25 ml of dioxan and treated with 10 ml of 1N sodium hydroxide solution and 1.7 g of sodium bicarbonate. A solution of 2.6 g of methyl 2-chlorosulphonylbenzoate in 22 ml of dioxan is added dropwise thereto and the mixture is stirred at room temperature for 9 hours. The reaction mixture is poured into ice-cold 2N hydrochloric acid and extracted with ethyl acetate. The organic phase is washed with water, dried and evaporated. There are obtained 3.2 g of N-[[o-(methoxycarbonyl)phenyl]sulphonyl]-3-(p-nitrophenyl)-D-alanine.

35

b) The material obtained from a) is dissolved in 30 ml of DMF, treated with 5.3 ml of hexamethyleneimine and stirred at 80°C for 5 hours. The reaction mixture is evaporated, the residue is taken up in ethyl acetate and shaken once against 2N hydrochloric

acid and twice against water. After drying the organic phase, evaporation and chromatography of the residue on silica gel there is obtained 0.9 g of N-[[o-[(hexahydro-1H-azepin-1-yl)carbonyl]-phenyl]sulphonyl]-3-(p-nitrophenyl)-D-alanine.

5

- c) Analogously to Example 5, from the material obtained under b) there is obtained (R)-N-[[[(RS)-1-amidino-3-piperidinyl]-methyl]- $\alpha$ -[o-[(hexahydro-1H-azepin-1-yl)carbonyl]benzenesulphonamido]-p-nitrohydrocinnamamide hydrochloride, FAB-MS: 614 (M+H)<sup>+</sup>.

10

### Example 53

The following compounds are manufactured analogously to Example 52:

15

- a) (R)-N-[[[(RS)-1-Amidino-3-piperidinyl]methyl]- $\alpha$ -(p-t-butylbenzenesulphonamido)-p-nitrohydrocinnamamide acetate, FAB-MS: 545 (M+H)<sup>+</sup>.

20

- b) (R)-N-[[[(RS)-1-Amidino-3-piperidinyl]methyl]-p-nitro- $\alpha$ -(benzo[b]thiophensulphonamido)hydrocinnamamide hydrochloride, FAB-MS: 545 (M+H)<sup>+</sup>.

25

### Example 54

Analogously to Examples 90a) and 23 there is obtained ( $\beta$ S,2RS)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]-2-benzyloxy-methyl- $\beta$ -2-naphthylsulphonamido- $\gamma$ -oxo-4-morpholinebutyramide acetate, FAB-MS: 651 (M+H)<sup>+</sup>.

30

### Example 55

A solution of the product from Example 54 in ethanol/1N hydrochloric acid is hydrogenated in the presence of 10% Pd/C for 30 hours under normal conditions. There is obtained ( $\beta$ S,2RS)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]-2-hydroxymethyl- $\beta$ -2-

35

naphthylsulphonamido- $\gamma$ -oxo-4-morpholinebutyramide hydrochloride, FAB-MS: 561 (M+H)<sup>+</sup>.

### Example 56

5

A)a) A solution of 23.3 g of rac-2-(aminomethyl)-4-benzyl-morpholine in 250 ml of dioxan is treated with 27.1 g of di-t-butyl dicarbonate in 250 ml of dioxan and stirred at room temperature for 17 hours. Then, the solvent is evaporated and the residue is chromatographed on silica gel with methylene chloride/ethyl acetate (3:1). The product is recrystallized from methylene chloride/hexane and there are obtained 25.6 g of t-butyl rac-[(4-benzyl-2-morpholinyl)methyl]carbamate.

15

A)b) A solution of the product from a) in 500 ml of ethyl acetate and 50 ml of acetic acid is treated with 2.6 g of Pd/C and hydrogenated for 5 hours at room temperature under normal conditions. After filtration and evaporation the residue is dissolved in 230 ml of DMF, treated with 46 ml of triethylamine and 10.8 g of formamidinesulphonic acid and stirred at room temperature for 20 hours. Subsequently, the reaction mixture is evaporated and the residue is partitioned between ethyl acetate and water. After drying the organic phase and evaporation there is obtained t-butyl rac-[(4-amidino-2-morpholinyl)methyl]-carbamate hemisulphite.

25

A)c) 6.5 g of the material obtained under b) are suspended in 50 ml of methylene chloride and treated at 0° with 20 ml of TFA. After 7 hours at 0° the reaction mixture is evaporated and the residue is azeotroped with ethylene chloride and toluene. rac-2-(Aminomethyl)-4-morpholinecarboxamidine trifluoroacetate is isolated.

30

B) A solution of 0.8 g of (S)- $\beta$ -2-naphthylsulphonamido- $\gamma$ -oxo-4-morpholinebutyric acid, obtained analogously to Example 23a)-c), in 16 ml of DMF is treated with 0.76 ml of 4-ethyl-morpholine, 0.89 g of benzotriazol-1-yloxy-tris-(dimethyl-amino)phosphonium hexafluorophosphate and 1.16 g of the

35

material obtained under A)c) and the mixture is stirred at room temperature for 17 hours. Subsequently, the reaction mixture is treated with 1N hydrochloric acid and evaporated. After chromatography on a RP-18 column with water/acetonitrile there is obtained 0.5 g of (S)-N-[[[(RS)-4-amidino-2-morpholinyl]-methyl]- $\beta$ -2-naphthylsulphonamido- $\gamma$ -oxo-morpholinebutyramide hydrochloride, FAB-MS: 533 (M+H)<sup>+</sup>.

#### Example 57

10

Analogously to Example 56 there are obtained:

a) (S)-N-4-[[[(RS)-4-Amidino-2-morpholinyl]methyl]- $\beta$ -2-naphthylsulphonamido-hexahydro- $\gamma$ -oxo-1H-azepine-1-butylamide hydrochloride, FAB-MS: 545 (M+H)<sup>+</sup>.

15

b) (S)-N-4-[[[(RS)-4-Amidino-2-morpholinyl]methyl]hexahydro- $\beta$ -2-naphthylsulphonamido- $\gamma$ -oxo-1(2H)-azocine-1-butylamide hydrochloride, FAB-MS: 559 (M+H)<sup>+</sup>.

20

#### Example 58

Analogously to Example 8 there is obtained (R)-N-[[[(RS)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -(2-naphthylsulphonamido)-2-oxo-3-benzoxazolinepropionamide triacetate, FAB-MS: 551 (M+H)<sup>+</sup>.

25

#### Example 59

The following compounds are manufactured analogously to Examples 8 and 56:

30

a) (R)-N-[[[(RS)-4-Amidino-2-morpholinyl]methyl]- $\alpha$ -2-naphthylsulphonamido-2,3-dioxo-1-indolinepropionamide hydrochloride, FAB-MS: 565 (M+H)<sup>+</sup>.

35

b) (R)-N-[[[(RS)-4-Amidino-2-morpholinyl]methyl]- $\alpha$ -2-naphthylsulphonamido-2-oxo-3-benzoxazolinepropionamide hydrochloride, FAB-MS: 553 (M+H)<sup>+</sup>.



Example 60

A)a) 3.7 g of tetrabutylammonium hydrogen sulphate and  
 5 100 ml of 1N sodium hydroxide solution are added to a solution  
 of 10.0 g of t-butyl (S)-3-aminomethyl-1-piperidinecarboxylate  
 (Example 6d) in 400 ml of hexane and 100 ml of water. 9.3 ml  
 of benzyl chloroformate are added dropwise to this mixture and  
 the mixture obtained is stirred at room temperature for 3 hours.  
 10 Subsequently, the organic phase is separated, washed with  
 water, 10% citric acid, water and saturated sodium bicarbonate  
 solution, dried and evaporated. t-Butyl (S)-3-[(1-  
 (benzyloxy)formamido]-methyl]-1-piperidinecarboxylate is  
 obtained.

15 A)b) 11.3 g of the material obtained under a) are dissolved in  
 120 ml of ethyl acetate, treated at 40° with 120 ml of a 4 molar  
 solution of hydrochloric acid in ethyl acetate and stirred at room  
 temperature for 5 hours. Subsequently, the reaction solution is  
 20 concentrated, the residue is dissolved in 265 ml of DMF, treated  
 with 18 ml of triethylamine and 4.3 g of formamidinesulphonic  
 acid and stirred at room temperature for 17 hours. The solvent is  
 evaporated, the residue is treated with 1N hydrochloric acid, again  
 concentrated and chromatographed on a RP-18 column with  
 25 water/acetonitrile. There are thus isolated 5.4 g of benzyl [(S)-  
 1-amidino-3-piperidinyl]methyl]carbamate hydrochloride.

A)c) 6.6 g of the material obtained under b) are dissolved in  
 165 ml of ethanol and 165 ml of 1N hydrochloric acid, treated  
 30 with 1 g of Pd/C and hydrogenated under normal conditions for  
 2 hours. After filtration, evaporation and azeotropeing with  
 ethanol there are obtained 4.5 g of (S)-1-amidino-3-  
 (aminomethyl)piperidine dihydrochloride, m.p. 252-254°C, FAB-  
 MS: 156 (M<sup>+</sup>), [α]<sub>D</sub> -16.9° (c = 1.0, water).

35 B) A solution of 1.9 g of N-(2-naphthylsulphonyl)-3-(2,3-  
 dioxo-1-indoliny)-D-alanine in 30 ml of DMF is treated with  
 2.3 ml of 4-ethylmorpholine, 2.0 g of benzotriazol-1-yloxy-

tris(dimethylamino)phosphonium hexafluorophosphate and 1.0 g of the material obtained under A)c) and stirred at room temperature for 20 hours. The reaction mixture is concentrated, treated with 1N hydrochloric acid, again evaporated and the residue is chromatographed on silica gel with ethyl acetate/acetone/acetic acid/water (16:2:1:1). There is isolated 0.8 g of (R)-N-[(S)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-2,3-dioxo-1-indolinepropionamide acetate, FAB-MS: 563 (M+H)<sup>+</sup>.

### Example 61

The following compounds are obtained analogously to Examples 8 and 60:

a) (R)-N-[(S)-1-Amidino-3-piperidinyl]methyl]- $\alpha$ -2-naphthylsulphonamido-2-oxo-3-benzoxazolidinepropionamide hydrochloride, FAB-MS: 551 (M+H)<sup>+</sup>,

b) (R)-N-[(S)-1-amidino-3-piperidinyl]methyl]-5-bromo- $\alpha$ -2-naphthylsulphonamido-2,3-dioxo-1-indolinepropionamide tetraacetate, FAB-MS: 643 (M+H)<sup>+</sup>,

c) (R)-N-[(S)-1-amidino-3-piperidinyl]methyl]-5-methyl- $\alpha$ -2-naphthylsulphonamido-2,3-dioxo-1-indolinepropionamide acetate, FAB-MS: 577 (M+H)<sup>+</sup>,

d) (R)-N-[(S)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -[(p-iodophenyl)sulphonyl]-2,3-dioxo-1-indolinepropionamide hydrochloride, FAB-MS: 639 (M+H)<sup>+</sup>,

e) (R)-N-[(S)-1-amidino-3-piperidinyl]methyl]- $\alpha$ -(o-nitrobenzenesulphonamido)-2,3-dioxo-1-indolinepropionamide hydrochloride, FAB-MS: 558 (M+H)<sup>+</sup>.

### Example 62

- a) A solution of 21.4 g of 2-naphthylsulphonyl chloride in 200 ml of ether is added dropwise while stirring to a solution of 15 g of N- $\alpha$ -Z-L-2,3-diaminopropionic acid in 189 ml of 1N sodium hydroxide solution. The mixture is left to stir for a further 5 6 hours. Subsequently, the reaction mixture is poured into ice-cold 2N hydrochloric acid and extracted with ethyl acetate. The organic is washed with water, dried and evaporated. After chromatography of the residue on silica gel with methylene chloride/methanol/acetic acid (94:5:1) there are isolated 17.9 g of 10 N-[(benzyloxy)carbonyl]-3-(2-naphthylsulphonamido)-L-alanine.
- b) From the material obtained under a) there is manufactured analogously to Example 5 benzyl [(S)-1-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)-ethylcarbamate, FAB-MS: 567 (M+H)<sup>+</sup>. 15

#### Example 63

- a) A solution of 1.1 g of the product from Example 62b) in 20 22 ml of 1N hydrochloric acid and 11 ml of ethanol is treated with 0.2 g of Pd/C and hydrogenated under normal conditions for 5 hours. After filtration and evaporation there is obtained 0.96 g of (S)-[[[(RS)-1-amidino-3-piperidinyl]methyl]-2-amino-3-(2-naphthylsulphonamido)propionamide dihydrochloride, FAB-MS: 25 433 (M+H)<sup>+</sup>.
- b) A solution of 0.95 g of the material obtained under a) in 20 ml of DMF is treated with 0.24 ml of 4-ethylmorpholine and 0.3 g of phthalic anhydride and stirred at 50° for 6 hours. The 30 reaction mixture is evaporated and the residue is chromatographed over a RP-18 column with water/acetonitrile. There is obtained 0.3 g of o-[[[(S)-1-[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]carbamoyl]-benzoic acid, FAB-MS: 35 581 (M+H)<sup>+</sup>.

#### Example 64

A solution of 1.4 g of the product from Example 63a) in 28 ml of DMF is treated with 1.05 ml of 4-ethylmorpholine, 1.23 g of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate and 0.95 g of o-(benzyloxy)benzoic acid and stirred at room temperature overnight. The reaction mixture is evaporated and the residue is partitioned between ethyl acetate and water. The organic phases are dried and evaporated, and the residue is chromatographed on silica gel with ethyl acetate/acetone/acetic acid/water (16:2:1:1). There is isolated 0.2 g of (S)-2-N-[o-(benzyloxy)benzamido]-3-(2-naphthylsulphonamido)-N-[[[(RS)-1-amidino-3-piperidiny]methyl]propionamide acetate, FAB-MS: 643 (M+H)<sup>+</sup>.

#### Example 65

15

a) t-Butyl (R)-2-[[[(S)-1-[[[(RS)-1-amidino-3-piperidyl]-methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]carbamoyl]-1-piperidinecarboxylate trifluoroacetate, FAB-MS: 644 (M+H)<sup>+</sup>, is obtained analogously to Example 64 using t-butyl-(R)-2-piperidinecarboxylic acid in place of o-(benzyloxy)benzoic acid.

20

b) A solution of 300 mg of the product from a) in 5 ml of ethyl acetate is treated with 5 ml of a 4 molar hydrochloric solution in ethyl acetate. After stirring at room temperature for 3 hours the suspension is evaporated and there is isolated (R)-N-(S)-1-[[[(RS)-1-amidino-3-piperidiny]methyl]carbamoyl]-2-(2-naphthylsulphonamido)-2-piperidinecarboxamide dihydrochloride, FAB-MS: 544 (M+H)<sup>+</sup>.

25

30

#### Example 66

A solution of 120 mg of the product from Example 64 in 12 ml of acetic acid is treated with 50 mg of Pd/C and hydrogenated under normal conditions for 6 hours. After filtration and evaporation there are obtained 80 mg of (S)-N-[[[(RS)-1-amidino-3-piperidiny]methyl]-2-(2-hydroxybenzamido)-

35

3-(2-naphthylsulphonamido)propionamide acetate, FAB-MS: 553 (M+H)<sup>+</sup>.

### Example 67

5

a) The material obtained according to Example 62a) is reacted analogously to Example 6a)-e). There is obtained t-butyl (S)-3-[[[N-[(benzyloxy)carbonyl]-3-(2-naphthylsulphonamido)-L-alanyl]amino]methyl]-1-piperidinecarboxylate, FAB-MS: 525 (M+H)<sup>+</sup>Boc.

10

b) A solution of 3.0 g of the material obtained according to a) in 80 ml of ethyl acetate/acetic acid (1:1) is treated with 0.8 g of Pd/C and hydrogenated under normal conditions for 48 hours.

15

After filtration and evaporation the residue is dissolved in 25 ml of DMF, 1.6 ml of 4-ethylmorpholine and 0.81 g of isatoic anhydride are added thereto and the mixture is stirred at 80° for 16 hours. The solvent is evaporated and the residue is partitioned between ethyl acetate and water. The organic phase is washed with water, dried and evaporated, and the residue is chromatographed on silica gel with methylene chloride/ethyl acetate (3:1). There are isolated 1.3 g of t-butyl (S)-3-[[[N-anthraniloxy-3-(2-naphthylsulphonyl)-L-alanyl]amino]methyl]-1-piperidinecarboxylate FAB-MS: 610 (M+H)<sup>+</sup>.

20

25

c) From the material isolated according to b) there is obtained analogously to Example 6f-g) N-[(S)-1-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]-o-aminobenzamide hemisulphite, FAB-MS: 552 (M+H)<sup>+</sup>.

30

### Example 68

35

Analogously to Example 23a)-c) and Example 60B) using ethyl rac-trans-4-methyl-2-piperidinecarboxylate in place of benzylamine there is obtained ethyl (2RS,4R)-1-[(S)-3-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphon-

amido)propionyl]-4-methyl-2-piperidinecarboxylate acetate (epimers 1:1), FAB-MS: 615 (M+H)<sup>+</sup>.

#### Example 69

5

By treating the product from Example 68 with methanolic sodium hydroxide solution there is obtained (2RS,4R)-1-[N<sup>4</sup>-[[[(S)-1-amidino-3-piperidinyl]methyl]-N<sup>2</sup>-(2-naphthylsulphonyl)-L-asparaginy]-4-methyl-2-piperidinecarboxylic acid (epimers 1:1),  
10 FAB-MS: 587 (M+H)<sup>+</sup>.

#### Example 70

a) 22.4 ml of 2N NaOH are added dropwise at 10°C to a  
15 solution of 5 g of D-aspartic acid β-benzyl ester and 5.07 g of 2-naphthylsulphonyl chloride in 80 ml of dioxan cooled to 10°C. The reaction mixture is subsequently stirred at room temperature for 2 hours and then treated with 25 ml of 1N hydrochloric acid. After evaporation of the dioxan the residue is taken up in ethyl  
acetate and washed with water. After drying and evaporation of  
the ethyl acetate phase there are obtained 9.1 g of 4-benzyl 1-hydrogen N-(2-naphthylsulphonyl)-D-aspartate, R<sub>f</sub> = 0.53 (ethyl  
acetate/glacial acetic acid 0.97:0.03).

b) 3.72 ml of Hünig base, 9.67 g of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate and 4.68 g of t-butyl (S)-3-aminomethyl-1-piperidinecarboxylate are added in succession while stirring to the product from a) in 100 ml of DMF. The reaction mixture is stirred for 4 hours,  
subsequently taken up in ether and the ether phase is washed  
with water. After drying and evaporation of the ether phase the residue is chromatographed over silica gel with ether/hexane (9:1). There are obtained 9.1 g of benzyl (R)-3-[[[(S)-1-(t-butoxycarbonyl)-3-piperidinyl]methyl]carbonyl]-3-(2-naphthylsulphonamido)- propionate, R<sub>f</sub> = 0.35 (ether/hexane 9:1).  
35

c) 3.0 g of the product from b) are dissolved in 60 ml of methanol and, after the addition of 10% Pd/C, hydrogenated at

room temperature under normal pressure. After 8 hours the catalyst is filtered off and the methanol solution is concentrated. There are obtained 2.38 g of (R)-3-[[[(S)-1-(t-butoxycarbonyl)-3-piperidinyl]methyl]carbamoyl]-3-(2-naphthylsulphonamido)-propionic acid,  $R_f = 0.08$  (ethyl acetate).

d) 1 g of carboxylic acid from c) in 18 ml of methylene chloride is cooled to  $-23^{\circ}\text{C}$  and there are added thereto in succession 0.25 ml of N-methylmorpholine and 0.3 ml of isobutyl chloroformate. Then, the reaction mixture is stirred at  $-23^{\circ}$  and treated with 0.36 ml of ethyl piperidine-3-carboxylate. The reaction mixture is subsequently taken up in 100 ml of ether. The ether solution is washed with 1N hydrochloric acid and with water. After drying and evaporation of the ether phase the residue is chromatographed over silica gel with ethyl acetate/hexane (4:1). There are obtained 917 mg of ethyl (R,S)-1-[(R)-3-[[[(S)-1-(t-butoxycarbonyl)-3-piperidinyl]methyl]carbamoyl]-3-(2-naphthylsulphonamido)propionyl]-3-piperidinecarboxylate,  $R_f = 0.4$  (ethyl acetate/hexane 4:1).

e) 1.2 ml of trifluoroacetic acid are added while stirring to a solution of 400 mg of the product from d) in 9.5 ml of methylene chloride. The methylene chloride and the trifluoroacetic acid are subsequently evaporated at  $50^{\circ}\text{C}$ . The residue is dissolved in methanol and the methanol solution is treated with 0.42 ml of triethylamine and 150 mg of formamidinesulphonic acid. The reaction mixture is subsequently stirred at room temperature for 8 hours. A further 0.09 ml of triethylamine and 75 mg of formamidinesulphonic acid are added three times at intervals of 2 hours. The reaction mixture is concentrated, the residue is suspended in 20 ml of Takeda solution/ethyl acetate (1:1) (Takeda solution = ethyl acetate/acetone/water/glacial acetic acid 6:2:1:1) and filtered. The filtrate is concentrated and the residue is subsequently chromatographed over silica gel with Takeda solution/ethyl acetate (1:1). From the chromatography there are obtained 114 mg of ethyl (RS)-1-[(R)-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-3-(2-naphthylsulphonamido)-

propionyl]-3-piperidinecarboxylate acetate,  $R_f = 0.34$  MS (EI): 601 (M+H).

### Example 71

5

The following compounds are manufactured analogously to Example 70:

10 a) [(R)-1-[(S)-3-[(S)-1-Amidino-3-piperidinyl]methyl]-carbamoyl]-3-(2-naphthylsulphonamido)propionyl]-3-piperidinyl]methyl acetate,  $R_f = 0.61$  (Takeda solution), FAB-MS: 601 (M+1).

15 b) [(S)-1-[(S)-3-[(S)-1-Amidino-3-piperidinyl]methyl]-carbamoyl]-3-(2-naphthylsulphonamido)propionyl]-3-piperidinyl]methyl p-tosylate (1:1),  $R_f = 0.29$  (Takeda solution), FAB-MS: 601 (M+1).

20 c) Methyl (RS)-1-[(R)-3-[[[(S)-1-amidino-3-piperidinyl]-methyl]carbamoyl]-3-(2-naphthylsulphonamido)propionyl]-4-oxo-3-piperidinecarboxylate acetate (1:1),  $R_f = 0.27$  (Takeda solution), FAB-MS: 601 (M+1).

25 d) [(S)-1-[(R)-3-[(S)-1-Amidino-3-piperidinyl]methyl]-carbamoyl]-(2-naphthylsulphonamido)acetyl]-3-piperidinyl]-methyl acetate acetate,  $R_f = 0.29$  (Takeda solution), FAB-MS: 601 (M+1).

30 e) [(R)-1-[(R)-3-[(S)-1-Amidino-3-piperidinyl]methyl]-carbamoyl]-(2-naphthylsulphonamido)acetyl]-3-piperidinyl]-methyl acetate acetate,  $R_f = 0.35$  (Takeda solution), FAB-MS: 601 (M+1).

35 f) Diethyl (RS)-1-[(R)-[[[(S)-1-amidino-3-piperidinyl]methyl]-carbamoyl]-3-(2-naphthylsulphonamido)propionyl]-3-piperidine-carboxamide acetate,  $R_f = 0.3$  (Takeda solution), FAB-MS: 628 (M+1).



g) [(S)-1-[(S)-3-[[[(S)-1-Amidino-3-piperidinyl]methyl]-carbamoyl]-3-(2-naphthylsulphonamido)propionyl]-3-piperidinyl]methyl isobutyrate acetate,  $R_f = 0.43$  (Takeda solution), MS (EI): 629 (M+1).

5

h) [(S)-1-[(S)-3-[[[(S)-1-Amidino-3-piperidinyl]methyl]-carbamoyl]-3-(2-naphthylsulphonamido)propionyl]-3-piperidinyl]methyl butyrate acetate,  $R_f = 0.47$  (Takeda solution), FAB-MS: 629 (M+1).

10

i) Ethyl (3R,4R)-4-acetoxy-1-[(R)-3-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-3-(2-naphthylsulphonamido)-propionyl]-3-piperidine carboxylate acetate (1:1),  $R_f = 0.21$  (Takeda solution), FAB-MS: 659 (M+1).

15

j) Ethyl (3S,4S)-4-acetoxy-1-[(R)-3-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-3-(2-naphthylsulphonamido)-propionyl]-3-piperidinecarboxylate acetate (1:1),  $R_f = 0.24$  (Takeda solution), FAB-MS: 659 (M+1).

20

S-Aspartic acid  $\beta$ -benzyl ester is used in place of D-aspartic acid  $\beta$ -benzyl ester (Example 70a)) for the manufacture of the products a), b), g) and h).

25

The intermediates for the manufacture of the products a), b), d), e), i) and j) are synthesized according to the following method:

30

2.0 g of t-butyl (S)-3-hydroxymethyl-1-piperidine-carboxylate or t-butyl (R)-3-hydroxymethyl-1-piperidine-carboxylate are stirred for 30 minutes together with 0.88 ml of acetic anhydride, 26.3 mg of dimethylaminopyridine and 3.0 ml of pyridine. The reaction mixture is subsequently taken up in ether and the ether phase is washed with 20% citric acid, saturated sodium bicarbonate solution and water. After drying and evaporation of the ether phase the 2.44 g of product,  $R_f = 0.85$  (ether), are dissolved in 50 ml of methylene chloride and treated with 12 ml of trifluoroacetic acid. The reaction solution is

35

stirred for 30 minutes and subsequently concentrated to dryness. The (S)- or (R)-3-acetoxymethyl-1-piperidinecarboxylic acid trifluoroacetic acid salt,  $R_f = 0.14$  (Takeda solution), is used in d) with an equivalent amount of triethylamine.

5

The intermediates for the synthesis of the products of Examples g) and h) are prepared as follows:

170 mg of dimethylaminopyridine and 3.4 mg of pyridine  
 10 are added to 3.0 g of t-butyl (S)-3-hydroxymethyl-1-piperidine-  
 carboxylate. 1.66 ml of isobutyryl chloride are added dropwise  
 thereto. The reaction mixture is then concentrated. The residue is  
 taken up in ether and the ether phase is washed in succession  
 with 20 ml of citric acid, water, sodium bicarbonate solution and  
 15 water. After drying and evaporation of the ether phase there are  
 obtained 3.9 g of t-butyl (S)-3-isobutyroxymethyl-1-  
 piperidinecarboxylate,  $R_f = 0.87$  (ether). 3.09 g of this ester are  
 dissolved in 80 ml of methylene chloride and treated with 20 ml  
 of trifluoroacetic acid. After stirring for 30 minutes the solution  
 20 is concentrated. 30 ml of methanol are added to the residue and  
 saturated sodium bicarbonate solution is then added dropwise.  
 The aqueous phase is extracted with methylene chloride and the  
 methylene chloride extracts are dried and concentrated. There  
 are obtained 2.82 g of (S)-3-iso- butyroxymethyl-1-  
 25 piperidinecarboxylic acid trifluoroacetic acid salt,  $R_f = 0.4$  (Takeda  
 solution).

(S)-3-Butyroxymethyl-1-piperidinecarboxylic acid tri-  
 fluoroacetic acid salt,  $R_f = 0.4$  (Takeda solution) is obtained  
 30 according to the same method.

### Example 72

a) 14.4 ml of triethylamine are added dropwise to 6.91 g of  
 35 glycine t-butyl ester hydrochloride and 12.1 g of 2-naphthyl-  
 sulphonyl chloride in 70 ml of methylene chloride. The reaction  
 mixture is subsequently diluted with 200 ml of ether. The  
 organic phase is washed with 1N hydrochloric acid and with

water. After drying and evaporation the residue is suspended in ether and suction filtered. After drying the crystals there are obtained 11.57 g of N-(2-naphthylsulphonyl)-glycine t-butyl ester,  $R_f = 0.49$  (ether/hexane 2:1).

5

b) 1 g of the product from a), 923 mg of dansyl chloride, 0.48 mg of triethylamine and 418 mg of dimethylaminopyridine are stirred together in 10 ml of methylene chloride. The reaction mixture is taken up in 100 ml of ether and washed with 1N

10 hydrochloric acid and with water. After drying and evaporation there are obtained 1.67 g of N-[[5-(dimethylamino)-1-naphthyl]sulphonyl]-N-(2-naphthylsulphonyl)glycine,  $R_f = 0.33$  (methylene chloride/n-hexane 9:1).

15 c) Hydrochloric acid gas is conducted at 0 to 5°C through a solution of the product from b) in 17 ml of methylene chloride. After concentration of the reaction solution there are obtained 1.7 g of carboxylic acid,  $R_f = 0.72$  (ethyl acetate/glacial acetic acid 97:3). 844 mg of dicyclohexylcarbodiimide (DCC) are added to a  
 20 solution of this product in 17 ml of methylene chloride at room temperature. Then, 877 mg of t-butyl (S)-3-aminomethyl-1-piperidinecarboxylate dissolved in 3 ml of methylene chloride are added thereto. The reaction mixture is filtered, the filtrate is evaporated and the residue is chromatographed over silica gel  
 25 with methylene chloride/ether (9:1). There is obtained 0.82 g of t-butyl (S)-3-[[N-[[5-(dimethylamino)-1-naphthyl]sulphonyl]-N-(2-naphthylsulphonyl)glycyl]amino]methyl]-1-piperidinecarboxylate,  $R_f = 0.2$  (methylene chloride/ether 9:1). This 0.82 g is converted analogously to Example 70e) into 316 mg of N-[[[(S)-1-amidino-3-piperidinyl]methyl]-2-[[[5-(dimethylamino)-1-naphthyl]sulphonyl]-(2-naphthylsulphonyl)amino]acetamide  
 30 acetate,  $R_f = 0.46$  (Takeda solution). FAB-MS: 637 (M+1).

### Example 73

35

Analogously to Example 30, but using 2-thienylglyoxalic acid, benzoic acid and, respectively, benzylchloroformate in place of phenylglyoxalic acid (Example 30g) there are obtained:

a) (R)-N-[[[(S)-1-Amidino-3-piperidinyl]methyl]-2-(2-naphthylsulphonamido)-3-( $\alpha$ -oxo-2-thiophenacetamido)propionamide p-toluenesulphonate (1:1), FAB-MS: 571 (M+H)<sup>+</sup>,

5

b) N-[(R)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]benzamide p-toluenesulphonate (1:1), FAB-MS: 537 (M+H)<sup>+</sup>, bzw.

10 c) benzyl-[(R)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]carbamate acetate (1:1), FAB-MS: 567 (M+H)<sup>+</sup>.

#### Example 74

15

From the product of Example 27 by treatment with aqueous sodium hydroxide solution there is obtained o-[[[(R)- $\alpha$ -[[[(RS)-1-amidino-3-piperidinyl]methyl]carbamoyl]-p-nitrophenethyl]-sulphamoyl]benzoic acid, FAB-MS: 533 (M+H)<sup>+</sup>.

20

#### Example 75

Analogously to Examples 68 and 69 there is obtained (R)-4-[[[(S)-3-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)propionyl]hexahydro-1,4-oxazepine-3-carboxylic acid, FAB-MS: 589 (M+H)<sup>+</sup>.

25

#### Example 76

30 Analogously to Example 52 (but using 2-naphthylsulphonyl chloride) and Example 60 there is obtained p-[(RS)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)-ethyl]benzoic acid, FAB-MS: 538 (M+H)<sup>+</sup>.

35

#### Example 77

Analogously to Example 43 there is obtained 4'-[(R)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-

naphthylsulphonamido)ethyl]succinilidic acid, FAB-MS: 609  
(M+H)<sup>+</sup>.

A compound of formula I, a solvate or salt thereof can be  
5 used in a manner known per se as the active substance for the  
manufacture of pharmaceutical preparations, e.g. of tablets and  
capsules of the following composition:

### Example A

10

#### Per tablet

Active substance	200 mg
Microcrystalline cellulose	155 mg
15 Maize starch	25 mg
Talc	20 mg
Hydroxypropylmethyl cellulose	<u>20 mg</u>
	425 mg

20

### Example B

#### Per capsule

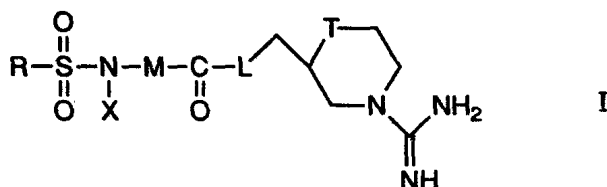
Active substance	100.0 mg
25 Maize starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	<u>0.5 mg</u>
	220.0 mg

30

Claims

The claims defining the invention are as follows:

1. A guanidine of the formula



5

wherein

R is aryl, heteroraryl or heterocyclyl,

T is CH<sub>2</sub> or O,

L is NH or O and

10 -N(X)-M- is a -N(SO<sub>2</sub>-R<sup>0</sup>)-CH<sub>2</sub>- group or an isoquinolylylene group optionally substituted in the phenyl ring and

R<sup>0</sup> has the same significance as R or

X is H, -CH<sub>2</sub>COOH, -CH<sub>2</sub>COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>CO-(tetra- to heptamethyleneimino) or optionally N-mono- or N-di-  
15 C<sub>1-4</sub>-alkylated -CH<sub>2</sub>CONH<sub>2</sub> and

M is a R'-(CH<sub>2</sub>)<sub>1-2</sub>CH=, R'-COCH<sub>2</sub>CH=, R''-COCH<sub>2</sub>CH=, R'-(CO)<sub>1-2</sub>NHCH<sub>2</sub>CH=, benzyl-OCONHCH<sub>2</sub>CH=, -CH<sub>2</sub>[R'-(CO)<sub>1-2</sub>NH]CH-, -CH<sub>2</sub>(benzyl-OCONH)CH- or -CH(CO-Q)CH<sub>2</sub>- group,

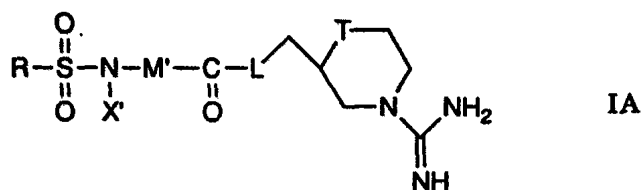
20 R' is aryl, heteroaryl, cycloalkyl or heterocyclyl,

R'' is tetra- to heptamethyleneimino optionally carrying up to 2 substituents from the group oxo, -COO-C<sub>1-4</sub>-alkyl, -(CH<sub>2</sub>)<sub>0-1</sub>OH, -(CH<sub>2</sub>)<sub>0-1</sub>OCO-C<sub>1-4</sub>-alkyl and optionally mono- or di-C<sub>1-4</sub>-alkylated carbamoyl and

25 Q is benzylamino or a tetra- to heptamethyleneimino group optionally interrupted by an O or S-atom and optionally substituted by up to 2 substituents from the group C<sub>1-4</sub>-alkyl, COOH, -COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>OH and -CH<sub>2</sub>O-benzyl, as well as hydrates or solvates and physiologically usable salts  
30 thereof.

2. A guanidine according to claim 1 and of the formula





wherein

5 -N(X')-M'- is an isoquinolylene group optionally substituted in the phenyl ring or

X' is H, -CH<sub>2</sub>COOH, -CH<sub>2</sub>COO-C<sub>1-4</sub>-alkyl, -CH<sub>2</sub>CO- (tetra- to heptamethyleneimino) or optionally N-mono- or N-di-C<sub>1-4</sub>-alkylated -CH<sub>2</sub>CONH<sub>2</sub> and

10 M' is a R'-(CH<sub>2</sub>)<sub>1-2</sub>CH=, R'-COCH<sub>2</sub>CH= or -CH(CO-Q')CH<sub>2</sub>- group,

Q' is benzylamino, morpholino or tetra- to heptamethyleneimino and

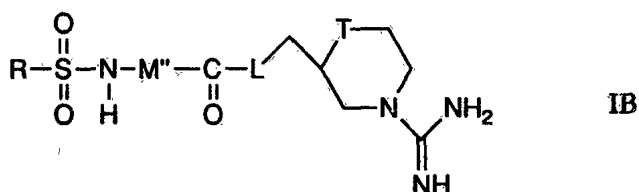
R,R',L and T have the same significances as in claim 1,

15 as well as hydrates or solvates and physiological usable salts thereof.

3. <sup>A guanidine</sup> ~~Compounds~~

according to claim 2, wherein X' is H and R, M', L and T have the same significances as in claim 2.

4. A guanidine according to claim 1 and of the formula



25 wherein

M'' is a R''-COCH<sub>2</sub>CH=, R'-(CO)<sub>1-2</sub>NHCH<sub>2</sub>CH=, benzyl-OCONHCH<sub>2</sub>CH=, -CH<sub>2</sub>[R'-(CO)<sub>1-2</sub>NH]CH-, -CH<sub>2</sub>(benzyl-OCONH)CH- or -CH(CO-Q'')CH<sub>2</sub>- group,

30 Q'' is a tetra- to heptamethyleneimino group optionally interrupted by an O or S atom and optionally substituted



by up to 2 substituents from the group  $C_{1-4}$ -alkyl,  $COOH$ ,  $-COO-C_{1-4}$ -alkyl,  $-CH_2OH$  and  $-CH_2O$ -benzyl and  $R, R', R'', L$  and  $T$  have the same significance as given in claim 1.

5 5. A guanidine according to claim 1, wherein  $R, L, T, M$  or  $-N(X)-M-$  and  $X$  have the same significances as in claim 1, but  $X$  is not  $H$ .

6. A guanidine according to claim 1, wherein  $R$  is aryl.

7. A guanidine according to claim 6, wherein the aryl is naphthyl, hydroxynaphthyl, 4-biphenyl, 2-anthryl, iodophenyl, nitrophenyl, benzyloxyphenyl, dimethoxyphenyl, 4-methoxy-2,3,6-trimethylphenyl, 2,4,6-triisopropylphenyl, 10 carboxyphenyl, methoxycarbonylphenyl, benzyloxyphenyl, phenylsulphonylphenyl, hexahydroazepinoylphenyl or *t*-butylphenyl.

8. A guanidine according to claim 1, wherein  $R$  is heteroaryl.

9. A guanidine according to claim 8, wherein the heteroaryl is 3-methyl-8-quinolyl, 5-(1-methyl-5-trifluoromethylpyrazol-3-yl)-2-thienyl or benzothienyl.

15 10. A guanidine according to claim 1 or claim 2, wherein  $R$  is heterocyclyl.

11. A guanidine according to claim 10, wherein the heterocyclyl is 3-methyl-1,2,3,5-tetrahydro-8-quinolyl.

12. A guanidine according to claim 1, wherein  $-N(X)-M-$  is isoquinolylene or  $N$ -dimethylaminonaphthylsulphonyl-amino-methylene.

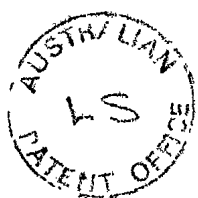
20 13. A guanidine according to claim 1 or claim 2, wherein  $X$  is  $H$  or  $-CH_2COOH$ .

14. A guanidine according to claim 1, wherein  $M$  is a  $R'-(CH_2)_{1-2}CH=$  group.

15. A guanidine according to claim 14, wherein the  $R'-(CH_2)_{1-2}CH=$  group is 3-indolylethylidene, 2,3-dioxo-1-indolinylethylidene, phenethylidene, 1,4-dioxo-5H-2,5-benzodiazepin-5-ylethylidene, (fluoro, chloro, iodo, cyano, nitro, amino, carboxy, 25  $C_{1-4}$ -alkoxycarbonyl or hydroxy)-phenethylidene, cyclohexylpropylidene, decalylethylidene, imidazolylethylidene, thienylethylidene, (methyl, bromo, fluoro or carboxymethyl)-3-indolylethylidene, naphthylethylidene, (ethoxycarbonylcarbonylamino, methoxycarbonyl ethylcarbonylamino, 30 benzyloxycarbonyl ethylcarbonylamino, ethoxycarbonylamino, benzoylcarbonylamino, carboxybenzoylamino, methoxyethoxyacetamido, acetamido, carboxycarbonylamino, carboxypropionylamino, tolylsulphonamido, iodophenylsulphonamido, carboxyphenylsulphonamido or ethoxycarbonylmethylamino)phenethylidene, oxobenzoxazolinethylidene or 5-bromo- or 5-methyl-2,3-dioxo-1-indolinyl-ethylidene.

35 16. A guanidine according to claim 1, wherein  $M$  is a  $(R' \text{ or } R'')COCH_2CH=$  group.

17. A guanidine according to claim 16, wherein the  $(R' \text{ or } R'')COCH_2CH=$  group is hexahydroazepinoylethylidene, (methoxycarbonyl or carboxy)-pyrrolidinoyl ethylidene, 3,4-dihydro-2(1H)-isoquinolinoyl ethylidene, (nitro, amino,





iodo or formamido)benzoylethylidene, morpholinoethylidene, heptahydroazocinoylethylidene, (ethoxycarbonyl, acetoxymethyl, dimethylcarbamoyl, isobutyryloxymethyl or butyryloxymethyl)piperidinoylethylidene, 3-methoxycarbonyl-4-oxopiperidinoylethylidene or 4-acetoxy-3-ethoxycarbonylpiperidinoylethylidene.

- 5 18. A guanidine according to claim 1, wherein M is benzyloxycarboxamidoethylidene or a  $R'-(CO)_{1-2}NHCH_2CH=$  group.

19. A guanidine according to claim 18, wherein the  $R'-(CO)_{1-2}NHCH_2CH=$  group is benzoylcarboxamidoethylidene, thienoylcarboxamidoethylidene, benzoylamidoethylidene.

- 10 20. A guanidine according to claim 1, wherein M is a  $-CH_2[R'-(CO)_{1-2}NH]CH-$  group.

21. A guanidine according to claim 20, wherein the  $-CH_2[R'-(CO)_{1-2}NH]CH-$  group is 2-(carboxybenzoylamido)ethylene, 2-(benzyloxybenzoylamido)-ethylene, 2-(2-piperidinecarboxamido)ethylene, 2-(hydroxybenzoylamido)ethylene or 2-  
15 (aminobenzoylamido)ethylene.

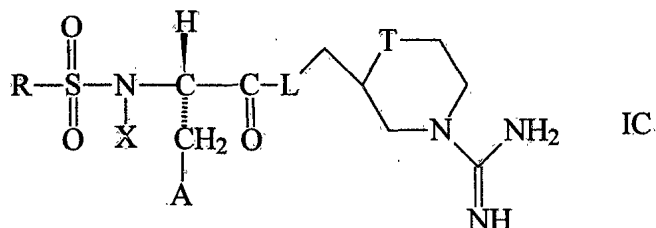
22. A guanidine according to claim 1, wherein M is a  $-CH(CO-Q)CH_2-$  group.

23. A guanidine according to claim 22, wherein the  $-CH(CO-Q)-CH_2-$  group is 1-(benzylaminocarbonyl)ethylene, 1-(hexahydroazepinoyl)ethylene, 1-(morpholinoyl)-ethylene, 1-(heptahydroazocinoyl)ethylene, 1-[2-(benzyloxymethyl-morpholinoyl)]-  
20 ethylene, 1-[2-(hydroxymethylmorpholinoyl)]ethylene, 1-(2-ethoxycarbonyl-4-methylpiperidinoyl)ethylene, 1-(2-carboxy-4-methylpiperidinoyl)-ethylene or 1-(3-carboxyhexahydro-1,4-oxazepinoyl)ethylene.

24. A guanidine according to claim 1, 2 or 6, wherein R is aryl.

- 25 25. A guanidine according to claim 24, wherein the aryl is naphthyl or nitro- or iodophenyl.

26. A guanidine according to claim 1, 15 or 16 and of the formula:



wherein A is aryl, aroyl or heterocyclyl.

27. A guanidine according to claim 26, wherein A is phenyl, nitrophenyl,  
30 indolyl, 2,3-dioxo-1-indolinyl or aminobenzoyl.

28. (R)-N-[(RS)-1-Amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-2,3-dioxo-1-indoline-3-propionamide,

(R)-N-[(RS)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-o-nitrohydrocinnamamide,



(R)-N-[(RS)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(o-nitro-benzenesulphonamido)-3-indole-3-propionamide,

(R)-N-[(S)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(p-iodo-benzenesulphonamido)-3-indole-3-propionamide,

5 (R)-N-[(S)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(p-iodo-benzenesulphonamido)-p-nitrohydrocinnamamide,

(R)-N-[(RS)-1-amidino-3-piperidinylmethyl]-3-(o-aminobenzoyl)- $\alpha$ -(2-naphthylsulphonamido)propionamide,

10 (N)-[(R)- $\alpha$ -[[(S)-1-amidino-3-piperidinyl]methylcarbamoyl]-phenethyl]-N-(2-naphthylsulphonyl)glycine,

(R)-N-[(S)-1-amidino-3-piperidinylmethyl]-1,2,3,4-tetrahydro-2-(2-naphthylsulphonyl)-3-isoquinolinecarboxamide,

(S)-N-[(RS)-1-amidino-3-piperidinylmethyl]hexahydro- $\beta$ -(2-naphthylsulphonamido)- $\gamma$ -oxo-(1H-1-azepine)butyramide,

15 (R)-N-[(S)-1-amidino-3-piperidinylmethyl]- $\alpha$ -(2-naphthylsulphonamido)-2,3-dioxo-1-indoline-3-propionamide,

4'-[(R)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]oxanilic acid,

20 (S)-N-[[[(RS)-1-amidino-3-piperidinyl]hexahydro- $\beta$ -(2-naphthylsulphonamido)- $\gamma$ -oxo-1-(2H)-azocinebutyramide,

(2RS,4R)-1-[N<sup>4</sup>-[[[(S)-1-amidino-3-piperidinyl]methyl]-N<sup>2</sup>-(2-naphthylsulphonyl)-L-asparaginy]-4-methyl-2-piperidine-carboxylic acid,

4'-[(R)-2-[[[(S)-1-amidino-3-piperidinyl]methyl]carbamoyl]-2-(2-naphthylsulphonamido)ethyl]succinilidic acid.

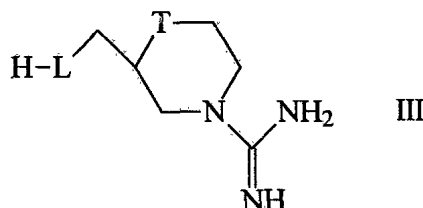
25 29. A guanidine according to claim 1, substantially as hereinbefore described with reference to the Examples.

30 30. A process for the manufacture of the compounds according to any one of claims 1 to 28, which process comprises

a) reacting an acid of the formula

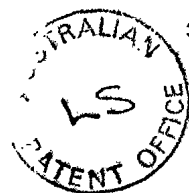


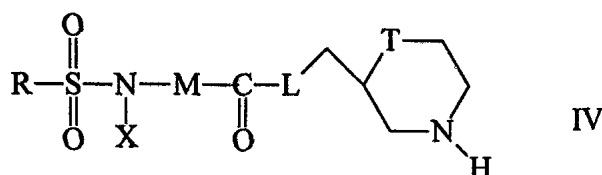
with intermediary protection of a carboxy group present in the group, X, R or M with an amine or alcohol of the formula



or a salt thereof, or

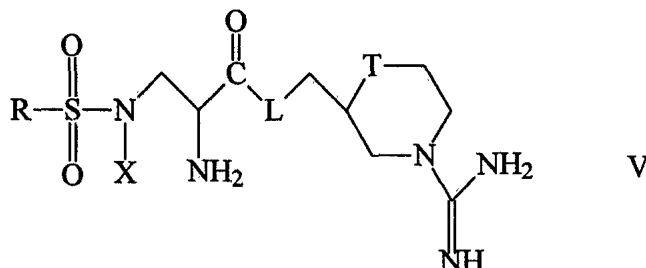
b) reacting a compound of the formula





with an amidinating reagent, or

c) reacting an amine of the formula



5 with an acid of the formula  $\text{R}'\text{-COOH}$  or a functional derivative thereof, and

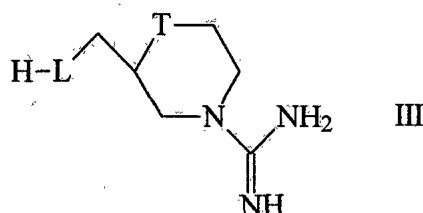
d) if desired, functionally modifying a reactive group present in the group M in a compound of formula I, and

e) if desired, converting a compound of formula I into a physiologically acceptable salt or converting a salt of a compound of formula I into the free acid or  
10 base.

31. A compound of formulae V in accordance with claim 30.

32. An amidino piperidine or amidino morpholine derivative, substantially as hereinbefore described with reference to the Examples.

33. A compound of the formula:



15

where L is NH or O and T is  $\text{CH}_2$  or O.

34. A process for the manufacture of a guanidine according to claim 1, substantially as hereinbefore described with reference to the Examples.

35. A guanidine prepared by the process of claim 34.

20 36. A pharmaceutical composition for the inhibition of platelet aggregation induced by thrombin and of the clotting of fibrinogen in a blood plasma, comprising an effective amount of a compound according to any one of claims 1 to 29 or 35 together with a pharmaceutically acceptable diluent, excipient, carrier and/or adjuvant.

37. A pharmaceutical composition, substantially as hereinbefore described with  
25 reference to Example A or Example B.

38. A method for the treatment or prophylaxis of illness caused by thrombin induced platelet aggregation or the clotting of fibrinogen in blood plasma in a mammal



requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 29 or 35, or of a composition according to claim 36 or claim 37.

39. A method according to claim 38, wherein said illness is thrombosis, stroke,  
5 cardiac infarct, inflammation or arteriosclerosis.

40. A method of inhibiting thrombin-induced platelet aggregation in a mammal requiring such inhibition, which method comprises administering to said mammal a platelet aggregating inhibiting amount of a compound according to any one of claims 1 to 29 or 35, or a composition according to claim 36 or claim 37.

10 41. A method of inhibiting the thrombin-induced clotting of fibrinogen in blood plasma in a mammal requiring such inhibition, which method comprises administering to said mammal a fibrinogen clotting inhibiting amount of a compound according to any one of claims 1 to 29 or 35 or a composition according to claim 36 or claim 37.

**Dated 11 January, 1994**

**F. Hoffmann-La Roche AG**

**Patent Attorneys for the Applicant/Nominated Person  
SPRUSON & FERGUSON**

82

82

