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Novel thrombin inhibitors

The present invention relates to novel carbo- and heterocyclic
5 amidines, the preparation thereof and the use thereof as thrombin
inhibitors.

Thrombin belongs to the group of serine proteases and plays a
central part in the blood coagulation cascade as terminal enzyme.
10 Both the intrinsic and the extrinsic coagulation cascade [sic]
lead via several amplification stages to the production of
thrombin from prothrombin. The thrombin-catalyzed cleavage of
fibrinogen to fibrin then initiates the coagulation of blood and
the aggregation of the platelets which in turn enhance, owing to
15 the binding of platelet factor 3 and coagulation factor XIII and
a whole series of highly active mediators, the formation of
thrombin.

The formation and action of thrombin are central events in the
20 production both of white, arterial and of red, venous thrombi and
therefore potentially effective points of attack for drugs.
Thrombin inhibitors are, in contrast to heparin, able to inhibit
completely, independently of cofactors, simultaneously the
actions of free thrombin and that bound to platelets. They are
25 able to prevent in the acute phase thromboembolic events after
percutaneous transluminal coronary angioplasty (PTCA) and lysis
and to act as anticoagulants in extracorporeal circulation
(heart-lung machine, hemodialysis). They can also be generally
used for the prophylaxis of thrombosis, for example after
30 surgical operations.

It is known that synthetic arginine derivatives influence the
enzymatic activity of thrombin by interacting with the active
serine residue of the protease thrombin. Peptides based on
35 Phe-Pro-Arg in which the N-terminal amino acid is in the D form
have proved to be particularly beneficial. D-Phe-Pro-Arg
isopropyl ester has been described as a competitive thrombin
inhibitor (C. Mattson et al., Folia Haematol, 109 (1983) 43-51).
40 Derivatization of the C-terminal arginine to the aldehyde leads
to an enhancement of the inhibitory effect. Thus, a large number
of arginals able to bind the hydroxyl group of the "active"
serine in the form of a hemiacetal have been described
(EP 185 390, 479 489, 526 877, 542 525; WO 93/15756, 93/18060).

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The thrombin-inhibitory activity of peptide ketones, fluorinated alkyl ketones and of keto esters, boric acid derivatives, phosphoric esters and α -keto carboxamides can likewise be explained by this interaction with serine (EP 118 280, 195 212, 5 362 002, 364 344, 410 411, 471 651, 589 741, 293 881, 503 203, 504 064, 530 167; WO 92/07869, 94/08941).

DE 31 08 810 and WO 93/11152 describe ω -aminoalkylguanidine dipeptides.

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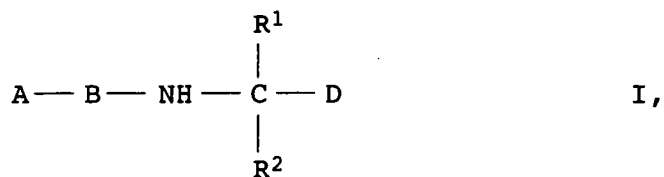
The diphenyl 4-amidinophenylglycinephosphonate peptides described by J. Oleksyszyn et al. in J. Med. Chem. 37 (1994) 226-231 are irreversible thrombin inhibitors with inadequate selectivity with respect to other serine proteases.

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WO 94/29336 and WO 95/23609 describe benzylamidines as thrombin inhibitors.

The invention relates to compounds of the formula I

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and the salts thereof with physiologically tolerated acids and the stereoisomers thereof, in which the substituents have the following meanings:

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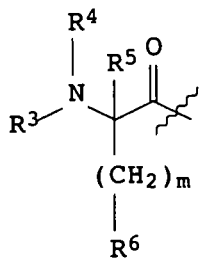
R^1 : H, C_{1-4} -alkyl;

R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic];

35 $\text{R}^{18}\text{O}-\text{CH}_2-$, $\text{R}^{18}-\text{CO}-$, $\text{R}^{18}-\text{O}-\text{CH}_2-\text{CO}-$, $\text{R}^{18}\text{O}-\text{CO}-\text{CO}-$, $\text{R}^{18}-\text{H}-\text{CO}-\text{CO}-$, where R^{18} is H, C_{1-4} -alkyl, phenyl- C_{1-4} -alkylene [sic] or phenyl, or $\text{CF}_3-\text{CO}-$, $\text{C}_2\text{F}_5-\text{CO}-$ or C_{1-4} -alkyl- $\text{O}-\text{CO}-$,

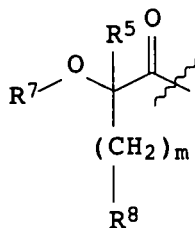
A:

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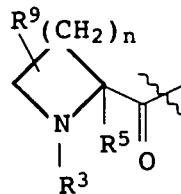


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IIa



IIb



IIc

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in which the substituents have the following meanings:

m: 0 or 1,

n: 1, 2, 3 or 4,

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R³: H, C₁₋₁₂-alkyl, aryl-C₁₋₄-alkylene [sic],
R¹⁹OOC-C₁₋₆-alkylene [sic] (R¹⁹ = H, C₁₋₄-alkyl, benzyl),
HO₃S-C₁₋₃-alkylene [sic], C₁₋₁₂-alkyl-CO-, aryl-CO-,
aryl-C₁₋₄-alkylene-CO- [sic], R¹⁹OOC-C₁₋₆-alkylene-CO-
[sic], HO₃S-C₁₋₃-alkylene-CO- [sic], C₁₋₇-alkyl-OOC-,
benzyl-OOC-, or

10

R²⁰R²¹N-CO- (R²⁰ and R²¹ are identical or different and
are H, C₁₋₆-alkyl, aryl, aryl-C₁₋₄-alkylene [sic],
R¹⁹OOC-C₁₋₄-alkylene [sic] and R¹⁹-NH-CO-C₁₋₄-alkylene
[sic], where R²⁰ and R²¹ may also together be a -(CH₂)₃₋₆-
group), or R¹⁹-O-

15

R⁴: H, C₁₋₁₂-alkyl, aryl-C₁₋₄-alkylene [sic] or R¹⁹OOC-C₁₋₄-al-
kylene [sic] (R¹⁹ = H, C₁₋₄-alkyl, benzyl),

20

R⁵: H, C₁₋₄-alkyl or benzyl,

R⁶: C₃₋₈-cycloalkyl, where the aliphatic rings can be
provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and
one or more methylene group(s) can be replaced by -O-,
-S- or N-C₁₋₄-alkyl,

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phenyl which can be substituted by up to 3 identical or
different radicals from the group of C₁₋₄-alkyl, CF₃-,
C₁₋₄-alkoxy, F- or Cl-,

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R²⁵R²⁶CH-, where R²⁵ is C₁₋₆-alkyl and R²⁶ is H or
C₁₋₆-alkyl,

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adamantyl, norbornyl-, 1-decalinyl-, 1-tetralinyl-,
2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which
can be monosubstituted on one or both aromatic rings,
diphenylmethyl which can be monosubstituted on one or
both rings, dicyclohexylmethyl, phenyl-C(CH₃)₂-,
phenyl-CH(CH₂-CH₂-OR¹⁹)-, C₁₋₄-alkyl-C≡C-, aryl-C≡C-,
(CH₃)₃Si-, R¹⁹-S-CH₂-,

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$R^{22}O-C(R^{23}R^{24})-$, where R^{22} is H, C_{1-4} -alkyl, phenyl, benzyl or C_{1-4} -alkyl-CO-, R^{23} is H, C_{1-4} -alkyl, HO- C_{1-3} -alkylene [sic], phenyl or benzyl and R^{24} is H, C_{1-4} -alkyl, HO- C_{1-3} -alkylene [sic], phenyl or benzyl,

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R^7 : H, C_{1-12} -alkyl, C_{1-20} -alkyl-CO-, $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene-CO- [sic], $R^{19}NH-CO-C_{1-4}$ -alkylene [sic], $R^{20}R^{21}N-CO-$, HO_3S-C_{1-4} -alkylene [sic], HO_3S-C_{1-4} -alkylene-CO- [sic], 5-(1H)-tetrazolyl- CH_2- or $(R^{19}O)_2OP-CH_2-$ or the acyl radical of a natural or unnatural bile acid,

10

R^8 : phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, C_{1-3} -alkyl, C_{1-3} -alkyl-O-, HO- or CF_3- ,

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C_{3-8} -cycloalkyl, where the aliphatic rings can be provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups, and one or more methylene group(s) can be replaced by -O-, -S- or N- C_{1-4} -alkyl,

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$R^{25}R^{26}CH-$ in which R^{25} is C_{1-6} -alkyl, C_{5-8} -cycloalkyl or phenyl, which can be substituted by 1 to 3 F, Cl, C_{1-3} -alkyl, C_{1-3} -alkyl-O-, HO- or CF_3 , and R^{26} is H or has one of the meanings stated for R^{25} ,

25

or $R^{22}O-CH_2-$, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, C_{1-4} -alkyl-C $\equiv$ C, aryl-C $\equiv$ C, $(CH_3)_3Si$ or dibenzosuberyl which can be monosubstituted on one or both aromatic rings,

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R^9 : H, C_{1-4} -alkyl, aryl or C_{5-6} -cycloalkyl (R^9 can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2)

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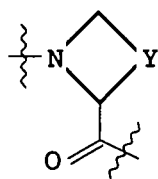
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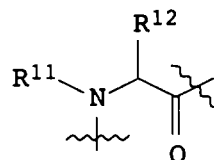
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B:

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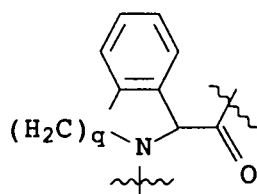


IIIa

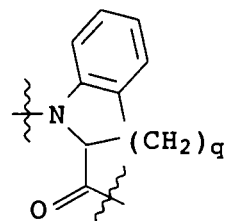


IIIb

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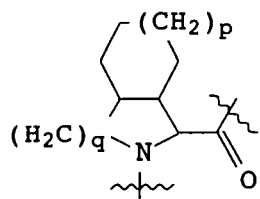
IIIc



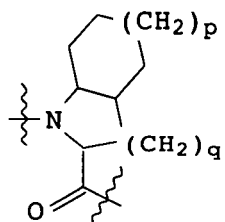
IIId

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IIIe

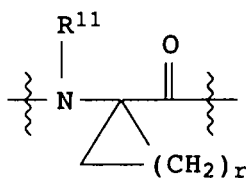


IIIf

or

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IIIg

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in which the substituents R^{10} , R^{11} and R^{12} , and p , q , r and Y , have the following meanings:

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- p : 0 or 1
 q : 1 or 2
 r : 1, 2, 3, 4 or 5

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Y a methylene group,
 an ethylene group in which the ring resulting
 therefrom can carry in position 4 a hydroxyl, oxo or
 C_{1-4} -alkoxy group,

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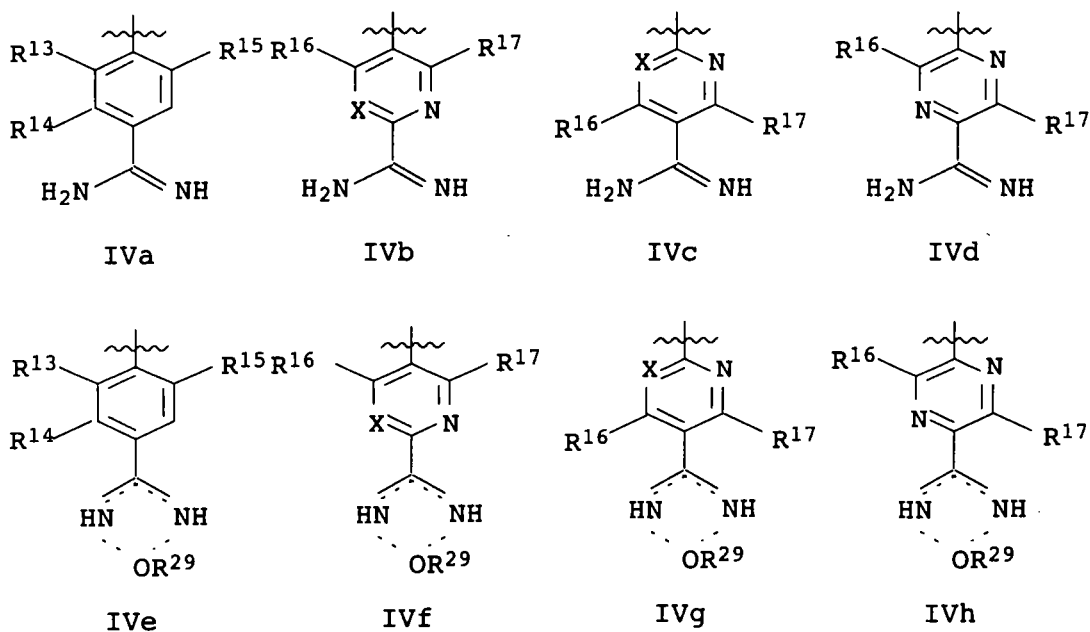
-CH₂-S-, -CH₂-SO-, -CH₂-O, -CH=CH- or a propylene group, in which the ring resulting therefrom can carry on the carbon in position 3 and/or 4 a C₁₋₄-alkyl group or in which a CH₂ group can be replaced by -O-, -S- or -SO-,

R¹⁰: H, C₁₋₄-alkyl or phenyl,

R¹¹: H, C₁₋₄-alkyl, C₃₋₈-cycloalkyl, phenyl or benzyl,

R¹²: H, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, phenyl or benzyl,

D:



in which the substituents have the following meanings:

R¹³, R¹⁴ and R¹⁵, which can be identical or different, are H, NO₂, F, Cl, Br, I, C₃₋₆-cycloalkyl, R³⁰-O-, R³⁰OOC-, R³⁰-NH-, R³⁰-CO-NH-, where R³⁰ is H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl, benzyl or phenyl, or

R¹³ and R¹⁴ together are the chains -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-, -O-CH₂-O- or -CH=CH-CH=CH-,

R¹⁶: H, F, Cl, C₁₋₄-alkyl, phenyl-C₁₋₂-alkylene [sic], phenyl, R³¹OOC- (R³¹ = H, C₁₋₄-alkyl, phenyl or benzyl), R³¹-NH-, R³¹-O- or R³¹OOC-CH₂-O-,

R¹⁷: H, F, Cl, C₁₋₄-alkyl, phenyl-C₁₋₂-alkylene [sic], phenyl, R³¹OOC-, R³¹-NH-, R³¹-O- or R³¹OOC-CH₂-O-,

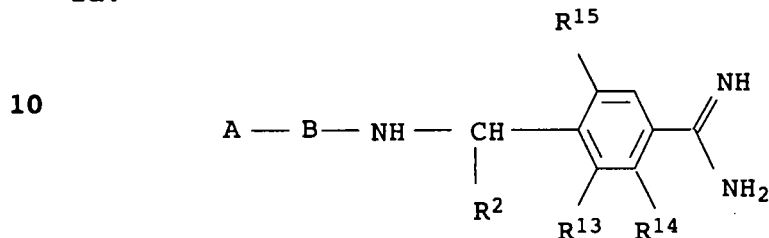
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R^{29} : H or C_{1-4} -alkyl, C_{1-4} -alkoxy, C_{1-4} -alkoxy-CO,

X: =CH- or =N-.

5 Preferred compounds are from the following groups Ia to Ii:

Ia:

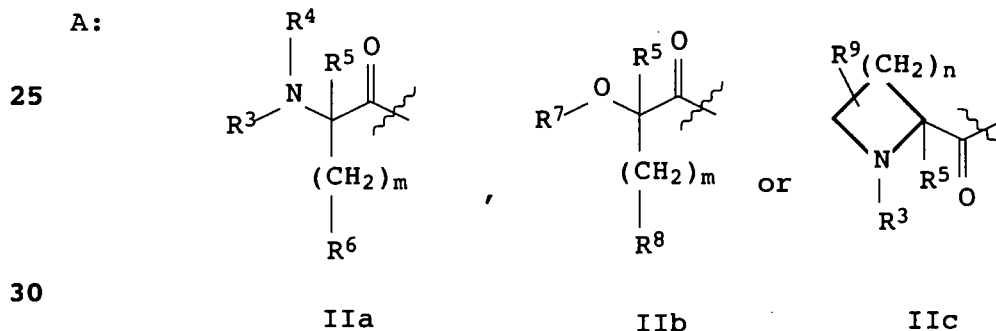


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In this, the substituents R and A and B have the following meanings:

20 R^2 : H, C_{1-4} -alkyl, phenyl and phenyl- C_{1-4} -alkylene [sic],
 $R^{18}O-CH_2-$, $R^{18}-CO-$, $R^{18}-O-CH_2-CO-$, $R^{18}O-CO-CO-$, $R^{18}-NH-CO-CO-$,
 where R^{18} is H or C_{1-4} -alkyl, CF_3-CO- or C_2F_5-CO- ,

A:



in which the substituents have the following meanings:

35 m: 0 or 1,

n: 2 or 3,

40 R^3 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkylene [sic], $R^{16}OOC-C_{1-6}$ -
 alkylene [sic] (R^{19} is H, C_{1-4} -alkyl, benzyl),
 HO_3S-C_{1-3} -alkylene [sic], C_{1-7} -alkyl- $OOC-$, benzyl- $OOC-$, or
 $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and
 are H, C_{1-6} -alkyl, aryl, aryl- C_{1-4} -alkylene [sic],
 $R^{19}OOC-C_{1-4}$ -alkylene [sic] or $R^{19}-NH-CO-C_{1-4}$ -alkylene [sic]
 45 or R^{20} and R^{21} together are $-(CH_2)_{3-6}$ group,

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R⁴: H, C₁₋₁₂-alkyl or aryl-C₁₋₄-alkylene [sic],

R⁵: H or C₁₋₄-alkyl,

5 R⁶: C₃₋₈-cycloalkyl, where the aliphatic rings can be provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and one or more methylene group(s) can be replaced by -O-, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetra-
 10 linyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted on one or both aromatic rings, diphenyl-methyl which can be monosubstituted on one or both rings, dicyclohexylmethyl, phenyl-C(CH₃)₂-, C₁₋₄-alkyl-C≡C-, R²²O-C(R²³R²⁴)-, where R²² is H or C₁₋₄-alkyl, and R²³ and R²⁴ are H, C₁₋₄-alkyl, HO-C₁₋₃-alkyl or phenyl,

15 phenyl which can be substituted by up to 3 identical or different radicals from the group of C₁₋₄-alkyl, CF₃, C₁₋₄-alkoxy, F or Cl,

20 R²⁵R²⁶CH-, where R²⁵ is C₁₋₆-alkyl, and R²⁶ is H or C₁₋₆-alkyl,

R⁷: H, C₁₋₁₂-alkyl, C₁₋₂₀-alkyl-CO-, R¹⁹OOC-C₁₋₄-alkylene [sic],
 25 R¹⁹OOC-C₁₋₄-alkylene [sic] -CO-, R²⁰R²¹N-CO-, HO₃S-C₁₋₄-alkylene [sic], or the acyl radical of a natural or unnatural bile acid,

R⁸: C₃₋₈-cycloalkyl, where the aliphatic rings can be provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and
 30 one or more methylene group(s) can be replaced by -O-, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetra-
 35 linyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted on one or both aromatic rings, diphenyl-methyl which can be monosubstituted on one or both rings, dicyclohexylmethyl, phenyl-C(CH₃)₂-, C₁₋₄-alkyl-C≡C-, R²²O-C(R²³R²⁴)-, where R²² is H or C₁₋₄-alkyl, and R²³ and R²⁴ are H, C₁₋₄-alkyl, HO-C₁₋₃-alkylene [sic] or phenyl,

40 phenyl which can be substituted by up to 3 identical or different radicals from the group of C₁₋₄-alkyl, CF₃, C₁₋₄-alkoxy, F or Cl,

R²⁵R²⁶CH-, where R²⁵ is C₁₋₆-alkyl, and R²⁶ is H or C₁₋₆-alkyl,

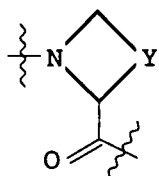
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R^9 : H, C_{1-4} -alkyl, phenyl or C_{5-6} -cycloalkyl (R^9 can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2),

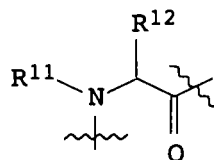
5 The structures IIa to IIc are preferably in the D configuration.

B:

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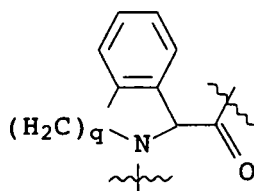


IIIa

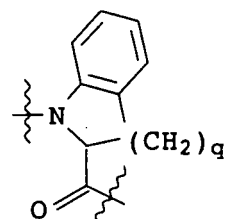


IIIb

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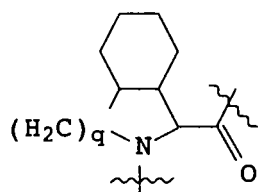


IIIc

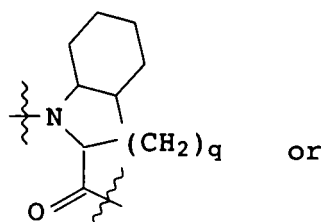


IIId

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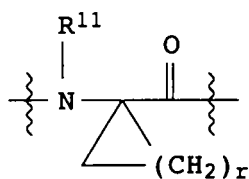


IIIe



IIIf

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IIIg

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q: 1 or 2

r: 3 or 4

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Y: a methylene group,

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an ethylene group in which the ring resulting therefrom can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group,

5 -CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group, in which the rings resulting therefrom can carry on the carbon in position 3 and/or 4 a C₁₋₄-alkyl group, or in which a -CH₂- group can be replaced by -O-,

R¹¹: H or C₃₋₆-cycloalkyl,

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R¹²: H, C₁₋₆-alkyl or C₅₋₆-cycloalkyl,

R¹³, R¹⁴ and R¹⁵, which are identical or different:

15 H, R³⁰-O- or R³⁰OOC-, where R³⁰ is H, C₁₋₆-alkyl and C₃₋₆-cycloalkyl, and R¹³ and R¹⁴ can together form the chains -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-, -O-CH₂-O- or -CH=CH-CH=CH-, where R¹³, R¹⁴ and R¹⁵ are not all hydrogen.

20 The structures IIIa to IIIf are preferably in the L configuration.

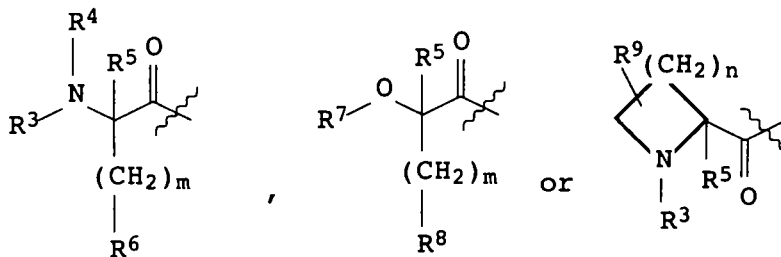
Particularly preferred compounds Ia are those in which the substituents R and A and B have the following meanings:

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R²: H,

A:

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IIa

IIb

IIc

in which the substituents have the following meanings:

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m: 0 or 1,

n: 2 or 3,

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R³: H, C₁₋₆-alkyl, benzyl, R¹⁹OOC-C₁₋₆-alkylene [sic] (R¹⁹ is H, C₁₋₄-alkyl, benzyl), HO₃S-C₁₋₃-alkylene [sic], or R²⁰R²¹N-CO- (R²⁰ and R²¹ are identical or different and

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are H, C₁₋₆-alkyl, or benzyl or R²⁰ and R²¹ together are a -(CH₂)₄₋₅- group),

R⁴: H,

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R⁵: H or CH₃-,

R⁶: C₅₋₈-cycloalkyl-, where the aliphatic rings can be substituted by up to 4 C₁₋₄-alkyl and/or CH₃O- groups and in which one methylene group can be replaced by -O-, or phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH₃- or CH₃O-, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxyethyl, adamantyl, norbornyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,

15

R⁷: H, C₁₋₆-alkyl-CO- or R¹⁹OOC-C₁₋₄-alkylene [sic],

R⁸: C₅₋₈-cycloalkyl-, where the aliphatic rings can be substituted by up to 4 C₁₋₄-alkyl and/or CH₃O- groups and in which one methylene group can be replaced by -O-, or phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH₃- or CH₃O-, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxyethyl, adamantyl, norbornyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,

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R⁹: H, C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2).

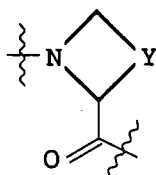
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The structures IIa to IIc are preferably in the D configuration.

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B:

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IIIa

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Y: a methylene group, an ethylene group, $-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{S}-$, $-\text{CH}_2-\text{O}-$ or a propylene group,

R^{13} : H, HO, $\text{CH}_3\text{O}-$, $\text{EtO}-$, $(\text{CH}_3)_2\text{CH}-\text{O}-$, Cl, Br or I,

5

R^{14} : H, HO, $\text{CH}_3\text{O}-$ or Cl,

R^{15} : H, HO, $\text{CH}_3\text{O}-$ or Cl,

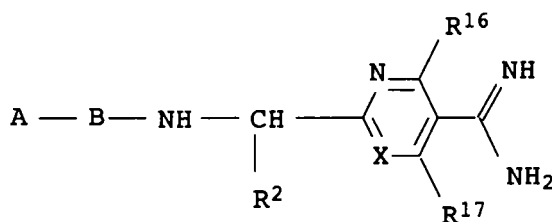
where R^{13} , R^{14} and R^{15} are not all H.

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The structure IIIa is preferably in the L configuration.

Ib:

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20 In this, the substituents R, the fragments A and B and X have the following meanings:

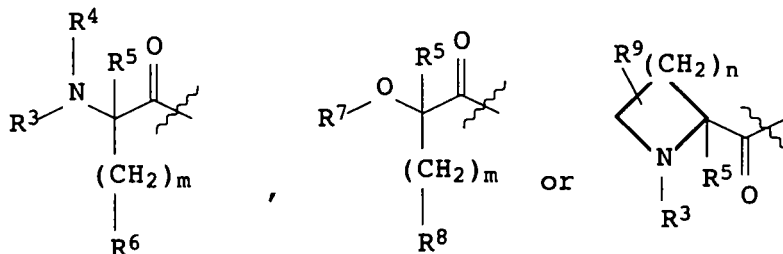
R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic], $\text{R}^{18}\text{O}-\text{CH}_2-$, $\text{R}^{18}-\text{CO}-$, $\text{R}^{18}-\text{O}-\text{CH}_2-\text{CO}-$, $\text{R}^{18}\text{O}-\text{CO}-\text{CO}-$, $\text{R}^{18}-\text{NH}-\text{CO}-\text{CO}-$, where R^{18}

25

is H and C_{1-4} -alkyl, or $\text{CF}_3-\text{CO}-$ and $\text{C}_2\text{F}_5-\text{CO}-$,

A:

30



35

IIa

IIb

IIc

in which the substituents have the following meanings:

m: 0 or 1,

40

n: 2 or 3,

R^3 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkylene [sic],

$\text{R}^{19}\text{OOC}-\text{C}_{1-6}$ -alkylene [sic] (R^{19} is preferably H,

45

C_{1-4} -alkyl, benzyl), $\text{HO}_3\text{S}-\text{C}_{1-3}$ -alkylene [sic],

C_{1-7} -alkyl-OOC-, benzyl-OOC- or $\text{R}^{20}\text{R}^{21}\text{N}-\text{CO}-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl, aryl,

13

aryl-C₁₋₄-alkylene [sic], R¹⁹OOC-C₁₋₄-alkylene [sic],
 R¹⁹-NH-CO-C₁₋₄-alkylene [sic] or R²⁰ and R²¹ together are a
 -(CH₂)₃₋₆- group),

- 5 R⁴: H, C₁₋₁₂-alkyl or aryl-C₁₋₄-alkylene [sic],
- R⁵: H or C₁₋₄-alkyl,
- 10 R⁶: C₃₋₈-cycloalkyl, where the aliphatic rings can be
 provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and
 one or more methylene group(s) can be replaced by -O-, or
 adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl,
 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which
 can be monosubstituted on one or both aromatic rings,
 15 diphenylmethyl which can be monosubstituted on one or
 both rings, dicyclohexylmethyl, phenyl-C(CH₃)₂-,
 C₁₋₄-alkyl-C≡C-, R²²O-C(R²³R²⁴)-, in which R²² is H or
 C₁₋₄-alkyl, and R²³ and R²⁴ are H, C₁₋₄-alkyl,
 HO-C₁₋₃-alkylene [sic] or phenyl,
 20 phenyl which can be substituted by up to 3 identical or
 different radicals from the group of C₁₋₄-alkyl, CF₃,
 C₁₋₄-alkoxy, F- or Cl-,
- 25 R²⁵R²⁶CH-, in which R²⁵ is C₁₋₆-alkyl, and R²⁶ is H or
 C₁₋₆-alkyl,
- 30 R⁷: H, C₁₋₁₂-alkyl, C₁₋₂₀-alkyl-CO-, R¹⁹OOC-C₁₋₄-alkylene [sic],
 R¹⁹OOC-C₁₋₄-alkylene-CO- [sic], R²⁰R²¹N-CO-,
 HO₃S-C₁₋₄-alkylene [sic], or the acyl radical of a natural
 or unnatural bile acid,
- 35 R⁸: C₃₋₈-cycloalkyl, where the aliphatic rings can be
 provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and
 one or more methylene group(s) can be replaced by -O-, or
 adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl,
 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which
 can be monosubstituted on one or both aromatic rings,
 diphenylmethyl which can be monosubstituted on one or
 40 both rings, dicyclohexylmethyl, phenyl-C(CH₃)₂-,
 C₁₋₄-alkyl-C≡C-, R²²O-C(R²³R²⁴)-, in which R²² is H or
 C₁₋₄-alkyl, and R²³ und R²⁴ are H, C₁₋₄-alkyl,
 HO-C₁₋₃-alkylene [sic] or phenyl,

14

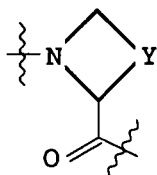
phenyl which can be substituted by up to 3 identical or different radicals from the group of C₁₋₄-alkyl, CF₃, C₁₋₄-alkoxy, F- or Cl-,

5 R²⁵R²⁶CH-, in which R²⁵ is C₁₋₆-alkyl, and R²⁶ is H or C₁₋₆-alkyl,

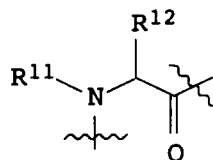
10 R⁹: H, C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2),

The structures IIa to IIc are preferably in the D configuration.

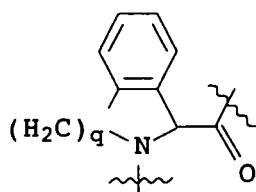
15 B:



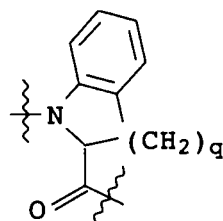
IIIa



IIIb



IIIc



IIId

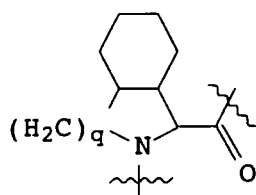
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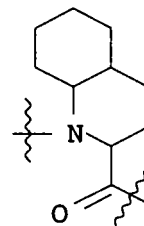
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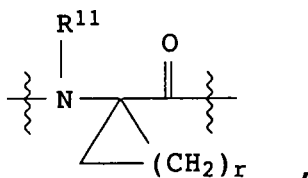
IIIIe



IIIIf

or

10



IIIIg

15

q: 1 or 2

20

r: 3 or 4

Y a methylene group,

25

an ethylene group in which the ring resulting therefrom can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group,

30

-CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group, in which the rings resulting therefrom can carry on the carbon in position 3 and/or 4 a C₁₋₄-alkyl group, or in which a -CH₂- group can be replaced by -O-,

R¹¹: H or C₃₋₆-cycloalkyl-,R¹²: H, C₁₋₆-alkyl or C₅₋₆-cycloalkyl,

35

R¹⁶: H, F, Cl, C₁₋₄-alkyl, R³¹OOC-, in which R³¹ is H or C₁₋₄-alkyl, R³¹-O-,

40

R¹⁷: H, F, Cl, C₁₋₄-alkyl, R³¹OOC- or R³¹-O-, where R³¹ is H or C₁₋₄-alkyl,

X: =CH- or =N-.

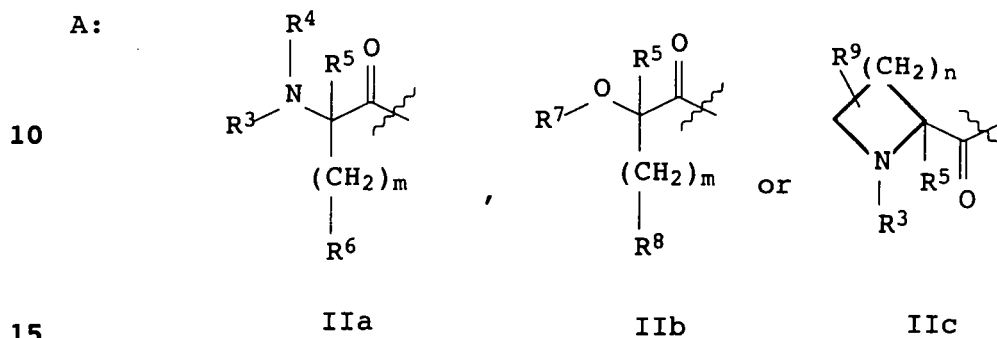
The structures IIIIa to IIIIf are preferably in the L configuration.

16

Particularly preferred compounds I are those in which the substituents R, the fragments A and B and X have the following meanings:

5 R^2 : H,

A:



in which the substituents have the following meanings:

20 m : 0 or 1,

n : 2 or 3,

25 R^3 : H, C_{1-6} -alkyl, benzyl, $R^{19}OOC-C_{1-6}$ -alkylene [sic] (R^{19} is H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic], or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl or benzyl or R^{20} and R^{21} together are a $-(CH_2)_{4-5}$ - group),

30 R^4 : H,

R^5 : H or CH_3 ,

35 R^6 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups, and in which one methylene group can be replaced by $-O-$, or phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH_3- or CH_3O- , diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxyethyl, adamantyl, norbornyl [sic], 1-decalinyl, 1-tetralinyl, 40 2-tetralinyl or $(CH_3)_3Si-$,

R^7 : H, C_{1-6} -alkyl-CO- or $R^{19}OOC-C_{1-4}$ -alkylene [sic],

45 R^8 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups, and in which one methylene group can be replaced by $-O-$, or

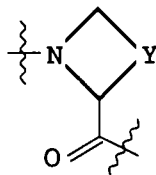
17

phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH₃- or CH₃O-, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxyethyl, adamantyl, norbornyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,

R⁹: H, C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with the formula IIc be a substituent on all ring positions apart from positions 1 and 2).

The structures IIa to IIc are preferably in the D configuration.

15 B:



IIIa

Y: a methylene group, an ethylene group
-CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group,

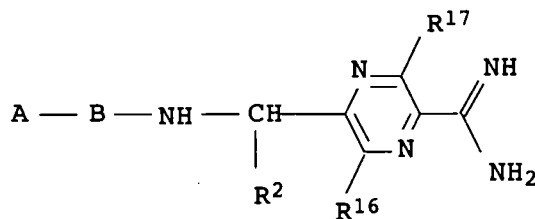
R¹⁶: H,

R¹⁷ H-,

X: =CH- or =N-.

The structure IIIa is preferably in the L configuration.

35 Ic:

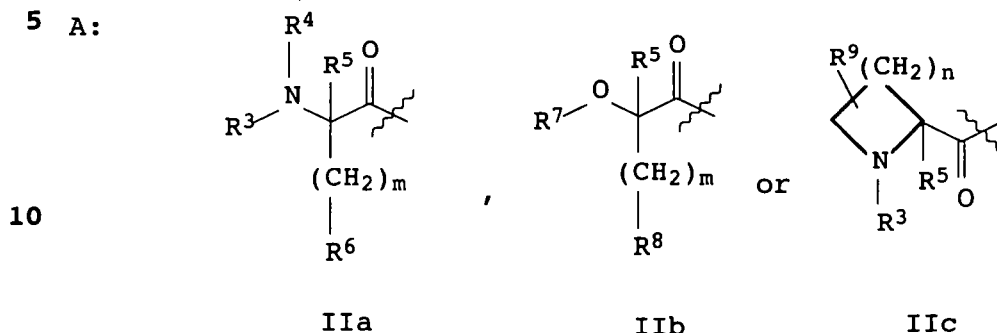


In this, the substituents R and the fragments A and B have the following meanings:

18

R^2 : H, C_{1-4} -alkyl, phenyl and phenyl- C_{1-4} -alkylene [sic],
 $R^{18}O-CH_2-$, $R^{18}-CO-$, $R^{18}-O-CH_2-CO-$, $R^{18}O-CO-CO-$, $R^{18}-NH-CO-CO-$,
 in which R^{18} is H and C_{1-4} -alkyl, CF_3-CO- or C_2F_5-CO- ,

5 A:

15 m : 0 or 1, n : 2 or 3,

20 R^3 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkylene [sic],
 $R^{19}OOC-C_{1-6}$ -alkylene [sic] (R^{19} is preferably H,
 C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic],
 C_{1-7} -alkyl- $OOC-$, benzyl- $OOC-$, or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21}
 are identical or different and are H, C_{1-6} -alkyl, aryl,
 aryl- C_{1-4} -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene [sic],
 25 $R^{19}-NH-CO-C_{1-4}$ -alkylene [sic] or R^{20} and R^{21} together are a
 $-(CH_2)_{3-6}$ - group),

 R^4 : H, C_{1-12} -alkyl or aryl- C_{1-4} -alkylene [sic],30 R^5 : H or C_{1-4} -alkyl,

35 R^6 : C_{3-8} -cycloalkyl, where the aliphatic rings can be
 provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups, and
 one or more methylene group(s) can be replaced by $-O-$, or
 adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl,
 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which
 can be monosubstituted on one or both aromatic rings,
 diphenylmethyl, which can be monosubstituted on one or
 both rings, dicyclohexylmethyl, phenyl- $C(CH_3)_2-$,
 40 C_{1-4} -alkyl- $C\equiv C-$, $R^{22}O-C(R^{23}R^{24})-$, in which R^{22} is H or
 C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl,
 $HO-C_{1-3}$ -alkylene [sic] or phenyl,

45 phenyl which can be substituted by up to 3 identical or
 different radicals from the group of C_{1-4} -alkyl, CF_3 ,
 C_{1-4} -alkoxy, F or Cl,

19

$R^{25}R^{26}CH-$, in which R^{25} is C_{1-6} -alkyl, and R^{26} is H or C_{1-6} -alkyl,

5 R^7 : H, C_{1-12} -alkyl, C_{1-20} -alkyl-CO-, $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene-CO- [sic], $R^{20}R^{21}N-CO-$, HO_3S-C_{1-4} -alkylene-CO- [sic], or the acyl radical of a natural or unnatural bile acid,

10 R^8 : C_{3-8} -cycloalkyl, where the aliphatic rings can be provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups, and one or more methylene group(s) can be replaced by -O-, -S- or N- C_{1-4} -alkyl, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted
15 on one or both aromatic rings, diphenylmethyl, which can be monosubstituted on one or both rings, dicyclohexylmethyl, phenyl- $C(CH_3)_2-$, C_{1-4} -alkyl- $C\equiv C-$, $R^{22}O-C(R^{23}R^{24})-$, in which R^{22} is H or C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl, $HO-C_{1-3}$ -alkylene [sic] or
20 phenyl,

phenyl which can be substituted by up to 3 identical or different radicals from the group of C_{1-4} -alkyl, CF_3 , C_{1-4} -alkoxy, F or Cl,

25 $R^{25}R^{26}CH-$, in which R^{25} is C_{1-6} -alkyl, and R^{26} is H or C_{1-6} -alkyl,

30 R^9 : H, C_{1-4} -alkyl, phenyl or C_{5-6} -cycloalkyl (R^9 can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2),

The structures IIa to IIc are preferably in the D configuration.

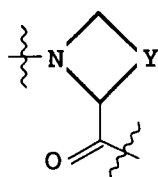
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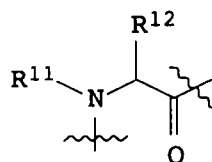
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B:

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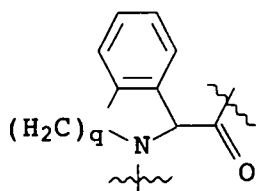


IIIIa

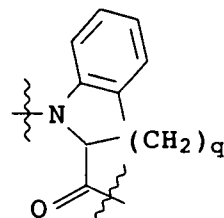


IIIIb

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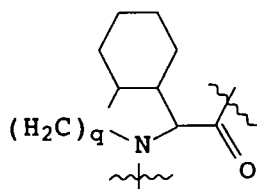


IIIIc

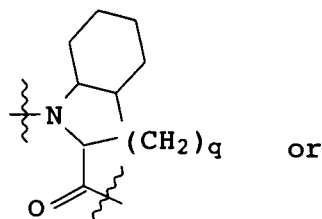


IIIIe

15



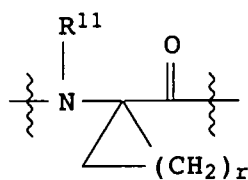
IIIIe



IIIIe

20

25



IIIIg

30

q: 1 or 2

35

r: 3 or 4

Y a methylene group,

40

an ethylene group in which the ring resulting therefrom
can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group,

45

-CH=CH-, -CH₂-S-, -CH₂-O-, or a propylene group, in which
the rings resulting therefrom can carry on the carbon in
position 3 and/or 4 a C₁₋₄-alkyl group, or in which a
-CH₂- group can be replaced by -O-,

21

R^{11} : H or C_{3-6} -cycloalkyl,

R^{12} : H, C_{1-6} -alkyl and C_{5-6} -cycloalkyl,

5 R^{16} : H, F, Cl, C_{1-4} -alkyl, R^{31} -OOC-, in which R^{31} is H- or C_{1-4} -alkyl, or R^{31} -O-,

R^{17} : H, F, Cl, C_{1-4} -alkyl, R^{31} -OOC-, R^{31} -O-, where R^{31} is H or C_{1-4} -alkyl.

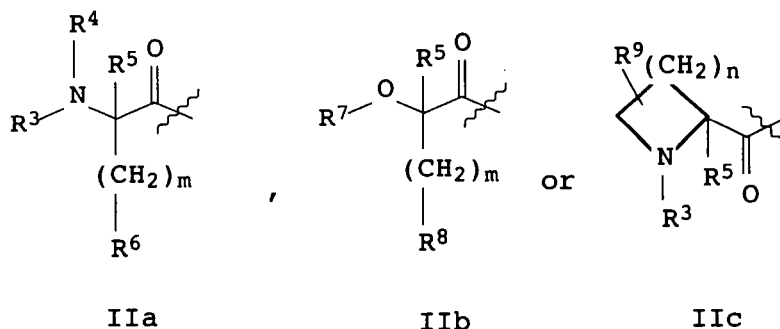
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The structures IIIa to IIIf are preferably in the L configuration.

Particularly preferred compounds Ic are those in which the substituents R and the fragments A and B have the following meanings:

R^2 : H-,

20 A:



25

30 m : 0 or 1,

n : 2 or 3,

35 R^3 : H, C_{1-6} -alkyl, benzyl, R^{19} OOC- C_{1-6} -alkylene [sic] (R^{19} is H, C_{1-4} -alkyl, benzyl), HO_3S - C_{1-3} -alkylene [sic], or $R^{20}R^{21}N$ -CO- (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl or benzyl or R^{20} and R^{21} together are a $-(CH_2)_{4-5}$ - group),

40 R^4 : H,

R^5 : H or CH_3 -,

45 R^6 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups, and in which one methylene group can be replaced by -O-, or phenyl which can be substituted by 1 to 3 identical or

22

different radicals from the group of F, Cl, CH₃ or CH₃O, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxymethyl, adamantyl, norbonyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,

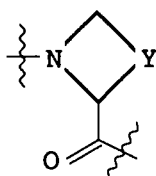
R⁷: H, C₁₋₆-alkyl or R¹⁹OOC-C₁₋₄-alkylene [sic],

R⁸: C₅₋₈-cycloalkyl, where the aliphatic rings can be substituted by up to 4 C₁₋₄-alkyl and/or CH₃O groups, and in which one methylene group can be replaced by -O-, or phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH₃ or CH₃O, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxymethyl, adamantyl, norbonyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,

R⁹: H, C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2).

The structures IIa to IIc are preferably in the D configuration.

B:



IIIa

Y: a methylene group, an ethylene group, -CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group,

R¹⁶: H,

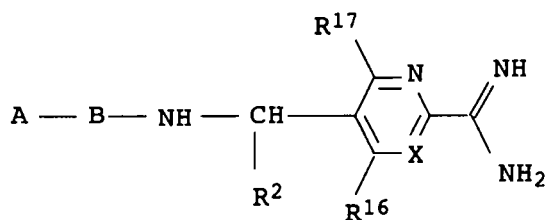
R¹⁷: H.

The structure IIIa is preferably in the L configuration.

23

Id:

5



In this, the substituents R, A, B and X have the following meanings:

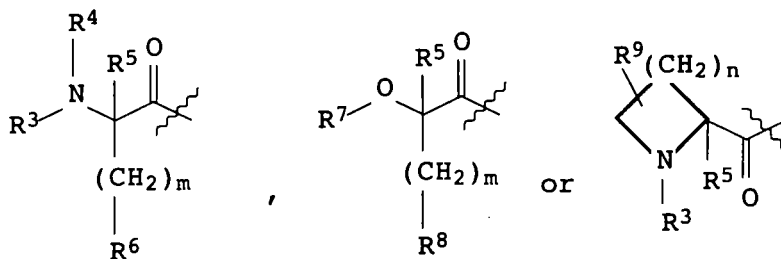
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R²: H, C₁₋₄-alkyl, phenyl and phenyl-C₁₋₄-alkylene [sic], R¹⁸O-CH₂-, R¹⁸-CO-, R¹⁸-O-CH₂-CO-, R¹⁸O-CO-CO-, R¹⁸-NH-CO-CO-, in which R¹⁸ is H and C₁₋₄-alkyl, or CF₃-CO- and C₂F₅-CO-,

15

A:

20



IIa

IIb

IIc

25

m: 0 or 1,

n: 2 or 3,

30

R³: H, C₁₋₁₂-alkyl, aryl-C₁₋₄-alkylene [sic], R¹⁹OOC-C₁₋₆-alkylene [sic] (R¹⁹ is preferably H, C₁₋₄-alkyl, benzyl), HO₃S-C₁₋₃-alkylene [sic], C₁₋₇-alkyl-OOC-, benzyl-OOC-, or R²⁰R²¹N-CO- (R²⁰ and R²¹ are identical or different and are H, C₁₋₆-alkyl, aryl, aryl-C₁₋₄-alkylene [sic], R¹⁹OOC-C₁₋₄-alkylene [sic], R¹⁹-NH-CO-C₁₋₄-alkylene [sic] or R²⁰ and R²¹ together are a -(CH₂)₃₋₆- group),

35

R⁴: H, C₁₋₁₂-alkyl or aryl-C₁₋₄-alkylene [sic],

40

R⁵: H or C₁₋₄-alkyl,

R⁶: C₃₋₈-cycloalkyl, where the aliphatic rings can be provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and one or more methylene group(s) can be replaced by -O-, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which

45

24

can be monosubstituted on one or both aromatic rings, diphenylmethyl which can be monosubstituted on one or both rings, dicyclohexylmethyl, phenyl- $C(CH_3)_2$ -, C_{1-4} -alkyl- $C\equiv C$ -, $R^{22}O-C(R^{23}R^{24})$ -, in which R^{22} is H or C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl, HO- C_{1-3} -alkylene [sic] or phenyl,

phenyl which can be substituted by up to 3 identical or different radicals from the group of C_{1-4} -alkyl, CF_3 , C_{1-4} -alkoxy, F or Cl,

$R^{25}R^{26}CH$ -, in which R^{25} is C_{1-6} -alkyl, and R^{26} is H or C_{1-6} -alkyl,

R^7 : H, C_{1-12} -alkyl, C_{1-20} -alkyl-CO-, $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene-CO- [sic], $R^{20}R^{21}N$ -CO-, HO_3S-C_{1-4} -alkylene-CO- [sic], or the acyl radical of a natural or unnatural bile acid,

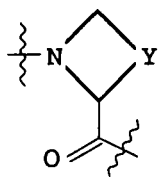
R^6 : C_{3-8} -cycloalkyl, where the aliphatic rings can be provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups, and one or more methylene group(s) can be replaced by -O-, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted on one or both aromatic rings, diphenylmethyl which can be monosubstituted on one or both rings, dicyclohexylmethyl, phenyl- $C(CH_3)_2$ -, C_{1-4} -alkyl- $C\equiv C$ -, $R^{22}O-C(R^{23}R^{24})$ -, in which R^{22} is H or C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl, HO- C_{1-3} -alkylene [sic] or phenyl,

R^9 : H, C_{1-4} -alkyl, phenyl or C_{5-6} -cycloalkyl (R^9 can in accordance with the formula IIc be a substituent on all ring positions apart from positions 1 and 2).

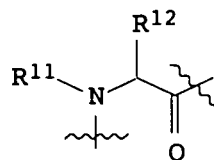
The structures IIa to IIc are preferably in the D configuration.

B:

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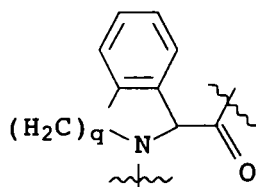


IIIa

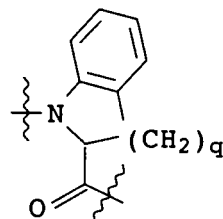


IIIb

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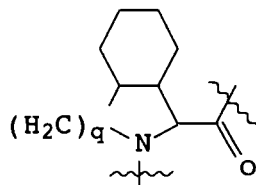


IIIc

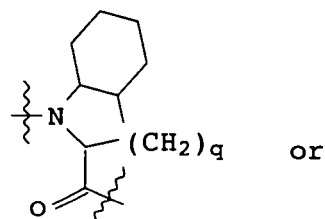


IIId

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IIIe

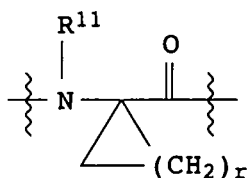


IIIf

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IIIg

35

q: 1 or 2

r: 3 or 4

40

Y a methylene group,

45

an ethylene group in which the ring resulting therefrom can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group, -CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group, in which the rings resulting therefrom can carry on the carbon in position 3 and/or 4 a C₁₋₄-alkyl group, or in which a CH₂ group can be replaced by -O-,

26

R^{11} : H or C_{3-6} -cycloalkyl,

R^{12} : H, C_{1-6} -alkyl or C_{5-6} -cycloalkyl,

5 R^{16} : H, F, Cl, C_{1-4} -alkyl, R^{31} -OOC-, in which R^{31} is H or C_{1-4} -alkyl, or R^{31} -O-,

R^{17} : H, F, Cl, C_{1-4} -alkyl, R^{31} -OOC- or R^{31} -O-, where R^{16} and R^{17} are not both H and not both F, and R^{31} is H or C_{1-4} -alkyl.

10

X: =CH- or =N-.

The structures IIIa to IIIf are preferably in the L configuration.

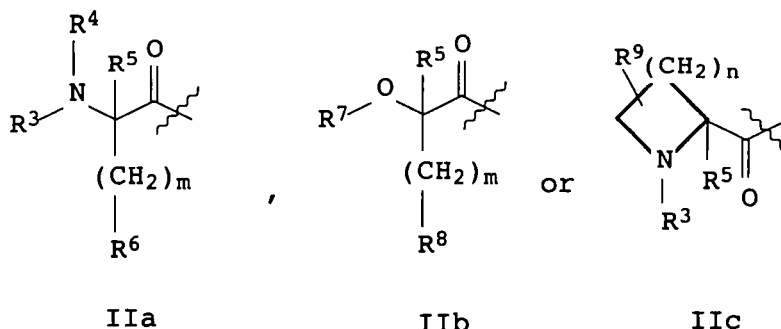
15

Particularly preferred compounds Id are those the substituents R, A, B and X have the following meanings:

R^2 : H

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A:



25

30

m: 0 or 1,

n: 2 or 3,

35 R^3 : H, C_{1-6} -alkyl, benzyl, R^{19} OOC- C_{1-6} -alkylene [sic] (R^{19} is H, C_{1-4} -alkyl, benzyl), HO_3S - C_{1-3} -alkylene [sic], or $R^{20}R^{21}N$ -CO- (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl or benzyl or R^{20} and R^{21} together are a $-(CH_2)_{4-5}$ - group),

40

R^4 : H,

R^5 : H or CH_3 ,

45 R^6 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups and in which one methylene group can be replaced by -O-, or

27

phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH₃ or CH₃O, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxymethyl, adamantyl, norbonyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,

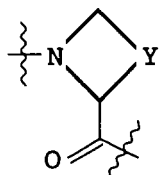
R⁷: H, C₁₋₆-alkyl-CO- or R¹⁹OOC-C₁₋₄-alkylene [sic],

R⁸: C₅₋₈-cycloalkyl, where the aliphatic rings can be substituted by up to 4 C₁₋₄-alkyl and/or CH₃O groups and in which one methylene group can be replaced by -O-, or phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH₃ or CH₃O, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxymethyl, adamantyl, norbonyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,

R⁹: H, C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with the formula IIc be a substituent on all ring positions apart from positions 1 and 2).

The structures IIa to IIc are preferably in the D configuration.

B:



IIIa

Y: a methylene group, an ethylene group -CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group,

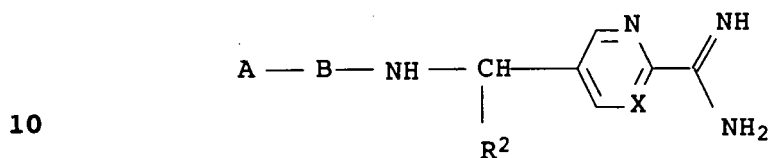
R¹⁶: H, Cl, C₁₋₄-alkyl or CH₃O,

R¹⁷: H, Cl, C₁₋₄-alkyl or CH₃O, where R¹⁶ and R¹⁷ are not both H,

X: =CH- or =N-.

The structure IIIa is preferably in the L configuration.

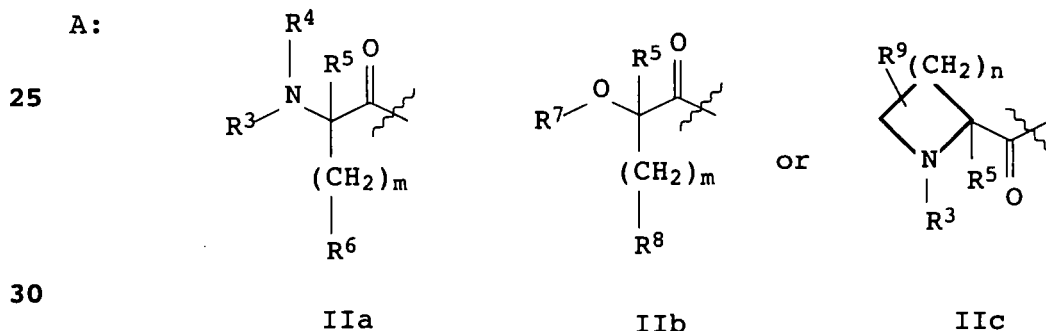
5 Ie:



15 In this, the substituents R, the fragments A and B and X have the following meanings:

a)

20 R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic], $R^{18}O-CH_2-$, $R^{18}-CO-$, $R^{18}-O-CH_2-CO-$, $R^{18}O-CO-CO-$, $R^{18}-NH-CO-CO-$, in which R^{18} is H or C_{1-4} -alkyl, or CF_3-CO- or C_2F_5-CO- ,



in which the substituents have the following meanings:

35 m: 0 or 1,

n: 2 or 3,

40 R^3 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkylene [sic], $R^{19}OOC-C_{1-6}$ -alkylene [sic] (R^{19} = H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic], C_{1-7} -alkyl- $OOC-$ or benzyl- $OOC-$, $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl, aryl, aryl- C_{1-4} -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene [sic] and $R^{19}-NH-CO-C_{1-4}$ -alkylene [sic], or R^{20} and R^{21} together are a $-(CH_2)_{3-6}$ - group),

45

R^4 : H, C_{1-12} -alkyl or aryl- C_{1-4} -alkylene [sic],

R⁵ H or C₁₋₄-alkyl,

5 R⁶: C₅₋₈-cycloalkyl, where the aliphatic rings are provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups and/or one or more CH₂ group(s) is(are) replaced by -O-, or phenyl which is substituted by 2 or 3 identical or different radicals from the group of C₁₋₄-alkyl, CF₃, C₁₋₄-alkoxy, F or Cl, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetra-
10 liny, 1-indanyl, 2-indanyl, diphenylmethyl, dicyclohexylmethyl, dibenzosuberyl, phenyl-C(CH₃)₂-, C₁₋₄-alkyl-C≡C-, Me₃Si, or

15 R²²O-C(R²³R²⁴)-, in which R²² is H or C₁₋₄-alkyl and R²³ and R²⁴ are H, C₁₋₄-alkyl or phenyl,

20 R⁷: H, C₁₋₁₂-alkyl, C₁₋₂₀-alkyl-CO-, R¹⁹OOC-C₁₋₄-alkylene [sic], R¹⁹OOC-C₁₋₄-alkylene-CO- [sic], R²⁰R²¹N-CO-, HO₃S-C₁₋₄-alkylene-CO- [sic], or the acyl radical of a natural or unnatural bile acid,

25 R⁸: C₅₋₈-cycloalkyl, where the aliphatic rings are provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups and/or one or more CH₂ group(s) is(are) replaced by -O-, or phenyl which is substituted by 2 or 3 identical or different radicals from the group of C₁₋₄-alkyl, CF₃, C₁₋₄-alkoxy, F or Cl, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetra-
30 liny, 1-indanyl, 2-indanyl, diphenylmethyl, dicyclohexylmethyl, dibenzosuberyl, phenyl-C(CH₃)₂-, C₁₋₄-alkyl-C≡C-, Me₃Si, or R²²O-C(R²³R²⁴)-,

35 R⁹: C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with the formula IIc be a substituent on all ring positions apart from position 1 and 2).

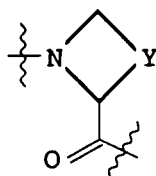
The structures IIa to IIc are preferably in the D configuration.

40

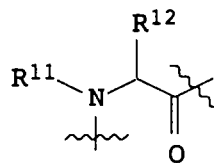
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B:

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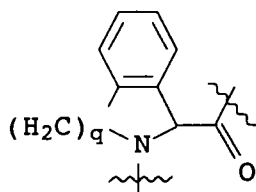


IIIIa

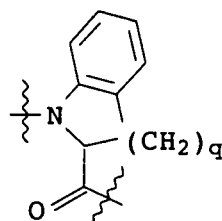


IIIIb

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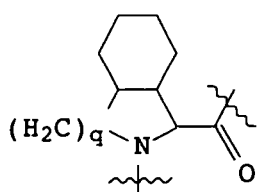
IIIIc



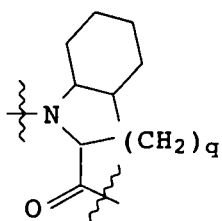
IIIIe

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IIIIe

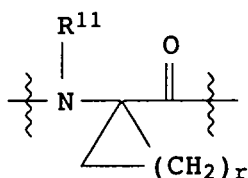


IIIIf

or

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IIIIg

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q: 1 or 2

r: 3 or 4

40

Y a methylene group,

an ethylene group in which the ring resulting therefrom
can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group,

45

31

-CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group, in which the rings resulting therefrom can carry on the carbon in position 3 and/or 4 a C₁₋₄-alkyl group, or in which one CH₂ group can be replaced by -O-,

5

R¹¹: H or C₃₋₆-cycloalkyl,

R¹²: H, C₁₋₆-alkyl or C₅₋₆-cycloalkyl,

10

X: =CH- or =N-.

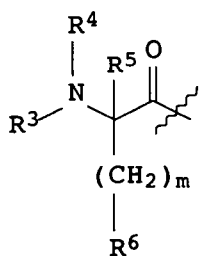
The structures IIIa to IIIf are preferably in the L configuration.

15 Particularly preferred compounds Ie listed under a) are those in which the substituents R, the fragments A and B and X have the following meanings:

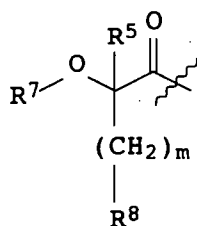
20 R²: H,

A:

25

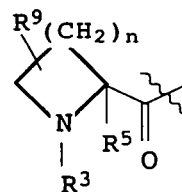


IIa



IIb

or



IIc

30 in which the substituents have the following meanings:

m: 0 or 1,

n: 2 or 3,

35

R³: H, C₁₋₆-alkyl, benzyl, R¹⁹OOC-C₁₋₆-alkylene [sic] (R¹⁹ = H, C₁₋₄-alkyl, benzyl), HO₃S-C₁₋₃-alkylene [sic], R²⁰R²¹N-CO- (R²⁰ and R²¹ are identical or different and are H, C₁₋₆-alkyl or benzyl, or R²⁰ and R²¹ together are a -(CH₂)₄₋₅- group),

40

R⁴: H,

R⁵ H or CH₃,

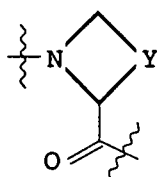
45

32

- R⁶: C₅₋₈-cycloalkyl, where the aliphatic rings are provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and/or one CH₂ group is replaced by -O-, or phenyl which is substituted by 2 or 3 identical or different radicals from the group of CH₃, CF₃, CH₃O, F or Cl, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, diphenylmethyl, dicyclohexylmethyl, Me₃Si or tert-butoxymethyl,
- R⁷: H, C₁₋₆-alkyl-CO- or R¹⁹OOC-C₁₋₄-alkylene [sic],
- R⁸: C₅₋₈-cycloalkyl, where the aliphatic rings are provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and/or one CH₂ group is replaced by -O-, or phenyl which is substituted by 2 or 3 identical or different radicals from the group of CH₃, CF₃, CH₃O, F or Cl, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, diphenylmethyl, dicyclohexylmethyl, Me₃Si or tert-butoxymethyl,
- R⁹: C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with the formula IIc be a substituent on all ring positions apart from positions 1 and 2).

The structures IIa to IIc are preferably in the D configuration.

30 B:



IIIa

- Y: a methylene group, an ethylene group, -CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group,
- X: =CH- or =N-.

The structure IIIa is preferably in the L configuration
or

33

in the compound Ie the substituents R, the fragments A and B and X have the following meanings:

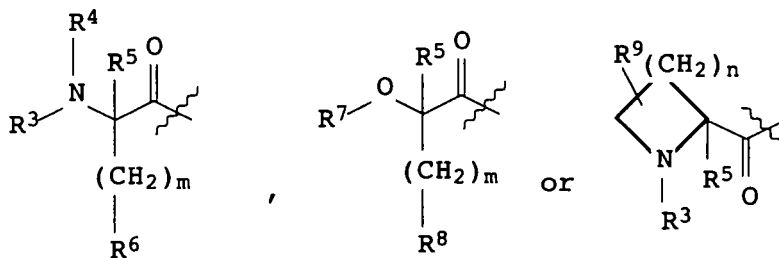
b)

5

R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic], $R^{18}O-CH_2-$, $R^{18}-CO-$, $R^{18}-O-CH_2-CO-$, $R^{18}O-CO-CO-$, $R^{18}-NH-CO-CO-$, in which R^{18} is H and C_{1-4} -alkyl, or CF_3-CO- and C_2F_5-CO- ,

10 A:

15



IIa

IIb

IIc

in which the substituents have the following meanings:

20

m : 0 or 1,

n : 2 or 3,

25

R^3 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkylene [sic], $R^{19}OOC-C_{1-6}$ -alkylene [sic] (R^{19} is preferably H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic], C_{1-7} -alkyl- $OOC-$, benzyl- $OOC-$, or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl, aryl, aryl- C_{1-4} -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}-NH-CO-C_{1-4}$ -alkylene [sic] or R^{20} and R^{21} together are a $-(CH_2)_{3-6}$ group),

30

R^4 : H, C_{1-12} -alkyl or aryl- C_{1-4} -alkylene [sic],

35

R^5 : H or C_{1-4} -alkyl,

R^6 : C_{3-8} -cycloalkyl which can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups and in which one methylene group can be replaced by $-O-$, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, phenyl- $C(CH_3)_2-$, C_{1-4} -alkyl- $C\equiv C-$ or $R^{22}O-C(R^{23}R^{24})-$, in which R^{22} is H or C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl, $HO-C_{1-3}$ -alkylene [sic] or phenyl,

40

45

34

phenyl which can be substituted by up to 3 identical or different radicals from the group of C₁₋₄-alkyl, CF₃, C₁₋₄-alkoxy, F or Cl,

- 5 R²⁵R²⁶CH-, in which R²⁵ is C₁₋₆-alkyl, C₅₋₈-cycloalkyl or phenyl which can be substituted by 1 to 3 F, Cl, C₁₋₃-alkyl, C₁₋₃-alkyl-O-, HO or CF₃, and R²⁶ is H or has one of the meanings stated for R²⁵,
- 10 R⁷: H, C₁₋₁₂-alkyl, C₁₋₂₀-alkyl-CO-, R¹⁹OOC-C₁₋₄-alkylene [sic], R¹⁹OOC-C₁₋₄-alkylene-CO- [sic], R²⁰R²¹N-CO-, HO₃S-C₁₋₄-alkylene-CO- [sic], or the acyl radical of a natural or unnatural bile acid,
- 15 R⁸: C₃₋₈-cycloalkyl, where the aliphatic rings can be provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups and one or more methylene group(s) can be replaced by -O-,
- 20 R²⁵R²⁶CH-, in which R²⁵ is C₁₋₆-alkyl, C₆₋₈-cycloalkyl or phenyl which means by 1 to 3 identical or different radicals from the group of 3 F, Cl, C₁₋₃-alkyl, C₁₋₃-alkyl-O-, C₁₋₆-alkyl, C₆₋₈-cycloalkyl or phenyl [sic] which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, C₁₋₃-alkyl,
- 25 C₁₋₃-alkyl-O-, HO or CF₃, or R²²O-CH₂-, in which R²² has the abovementioned meanings,
- 30 adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted on one or both aromatic rings,
- R⁹: H, C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with the formula IIc be a substituent on all ring positions apart from positions 1 and 2),

35

The structures IIa to IIc are preferably in the D configuration.

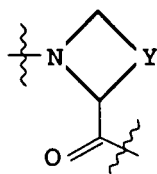
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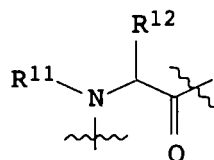
35

B:

5

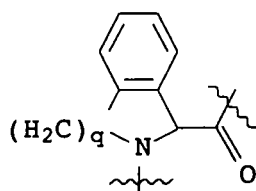


IIIa

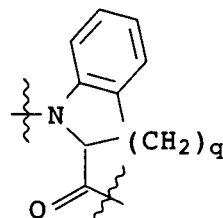


IIIb

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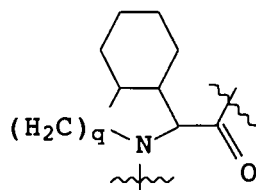


IIIc

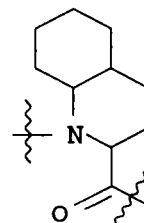


IIId

15



IIIe

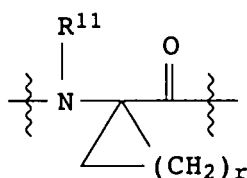


IIIf

20

or

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IIIg

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R^{11} : H or C_{3-6} -cycloalkyl

35

R^{12} : C_{1-6} -alkyl or C_{5-6} -cycloalkyl-

40

Y: $-CH=CH-$, $-CH_2-S-$, $-CH_2-O-$ or a propylene group in which the rings resulting therefrom can carry on the carbon atom in position 3 and/or 4 a C_{1-4} -alkyl group, or in which a CH_2 group can be replaced by $-O-$,

X: $=CH-$ or $=N-$.

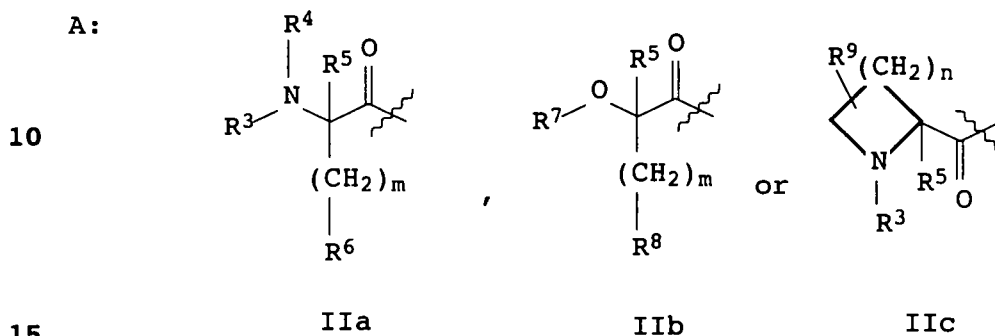
45

36

Particularly preferred compounds Ie are those detailed under b), in which the substituents R and A and B have the following meanings:

5 R^2 : H-,

A:



in which the substituents have the following meanings:

20 m: 0 or 1,

n: 2 or 3,

25 R^3 : H, C_{1-6} -alkyl, benzyl, $R^{19}OOC-C_{1-6}$ -alkylene [sic] (R^{19} is H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic], or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl or benzyl or R^{20} and R^{21} together are a $-(CH_2)_{4-5}$ - group),

30 R^4 : H,

R^5 : H or CH_3 ,

35 R^6 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups, and in which one methylene group can be replaced by $-O-$, or phenyl, which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH_3 or CH_3O , diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxyethyl, adamantyl, norbornyl [sic], 1-decalinyl, 1-tetralinyl, 40 2-tetralinyl or $(CH_3)_3Si-$,

R^7 : H, C_{1-6} -alkyl-CO- or $R^{19}OOC-C_{1-4}$ -alkylene [sic],

45 R^8 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups, and in which one methylene group can be replaced by $-O-$, or

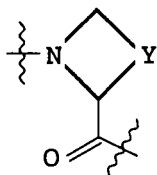
37

phenyl, which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, CH₃ or CH₃O, diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxymethyl, adamantyl, norbonyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or (CH₃)₃Si-,
 5

R⁹: H, C₁₋₄-alkyl, phenyl or C₅₋₆-cycloalkyl (R⁹ can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2).
 10

The structures IIa to IIc are preferably in the D configuration.

15 B:



20

IIIa

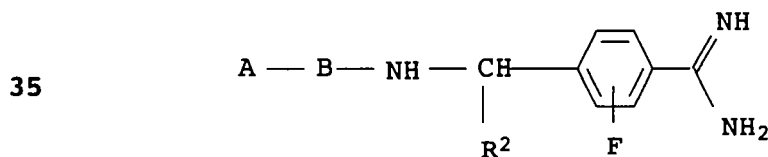
Y: -CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group,
 25

X: =CH- or =N-.

The structure IIIa is preferably in the L configuration.

30

If:



35

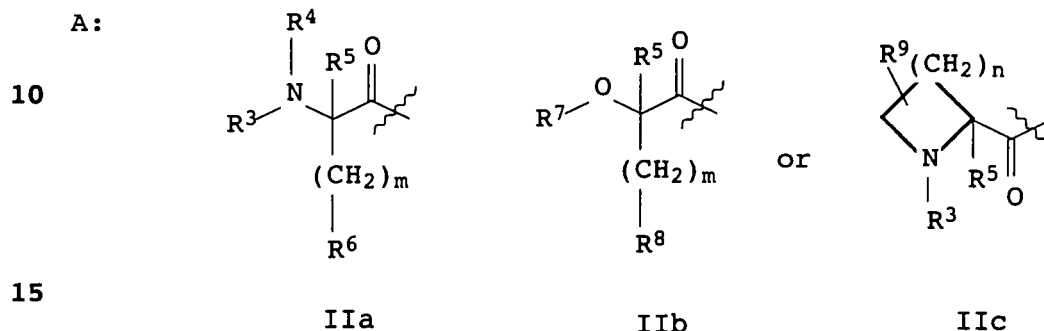
In this, the substituent R and A and B have the following
 40 meanings:

45

a)

- R²: H, C₁₋₄-alkyl, phenyl, phenyl-C₁₋₄-alkylene [sic],
 R¹⁸O-CH₂-, R¹⁸-CO-, R¹⁸-O-CO-, R¹⁸-O-CH₂-CO-, R¹⁸O-CO-CO-,
 5 R¹⁸-NH-CO-CO-, where R¹⁸ is H, C₁₋₄-alkyl, phenyl-C₁₋₄-alkylene
 [sic] or phenyl, or CF₃-CO-, C₂F₅-CO-,

A:



in which the substituents have the following meanings:

20 m: 0 or 1,

n: 2 or 3,

25 R³: H, C₁₋₁₂-alkyl, aryl-C₁₋₄-alkyl, R¹⁹OOC-C₁₋₆-alkylene [sic]
 (R¹⁹ = H, C₁₋₄-alkyl, benzyl), HO₃S-C₁₋₃-alkylene [sic],
 C₁₋₇-alkyl-OOC-, benzyl-OOC-,
 R²⁰R²¹N-CO- (R²⁰ and R²¹ are identical or different and
 are H, C₁₋₆-alkyl, aryl, aryl-C₁₋₄-alkylene [sic],
 R¹⁹OOC-C₁₋₄-alkylene [sic] or R¹⁹-NH-CO-C₁₋₄-alkylene [sic]
 or R²⁰ and R²¹ together are a -(CH₂)₄₋₅- group),

30 R⁴: H, C₁₋₁₂-alkyl or aryl-C₁₋₄-alkyl,

R⁵ H or C₁₋₄-alkyl,

35 R⁶: C₅₋₈-cycloalkyl, where the aliphatic rings are provided
 with up to 4 C₁₋₄-alkyl and/or CH₃O groups and/or one or
 more -CH₂ group(s) is(are) replaced by -O-, or
 phenyl which is substituted by 2 or 3 identical or
 40 different radicals from the group of C₁₋₄-alkyl, CF₃,
 C₁₋₄-alkoxy, F or Cl,
 adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetra-
 linyl, 1-indanyl, 2-indanyl, diphenylmethyl, dicyclo-
 hexylmethyl, dibenzosuberyl, phenyl-C(CH₃)₂-,
 C₁₋₄-alkyl-C≡C-, Me₃Si or

45

39

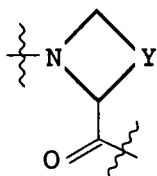
$R^{22}O-C(R^{23}R^{24})-$, in which R^{22} is H or C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl or phenyl,

- 5 R^7 : H-, C_{1-12} -alkyl, C_{1-20} -alkyl-CO-, $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene-CO- [sic], $R^{20}R^{21}N-CO-$, HO_3S-C_{1-4} -alkylene-CO- [sic], and the acyl radical of a natural or unnatural bile acid,
- 10 R^8 : C_{5-8} -cycloalkyl, where the aliphatic rings are provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups and/or one or more $-CH_2$ group(s) is(are) replaced by $-O-$, or phenyl which is substituted by 2 or 3 identical or different radicals from the group of C_{1-4} -alkyl, CF_3 , C_{1-4} -alkoxy, F or Cl,
- 15 adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, diphenylmethyl, dicyclohexylmethyl, dibenzosuberyl, phenyl- $C(CH_3)_2-$, C_{1-4} -alkyl- $C\equiv C-$, Me_3Si or
- 20 R^9 : C_{1-4} -alkyl, phenyl or C_{5-6} -cycloalkyl (R^9 can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2),

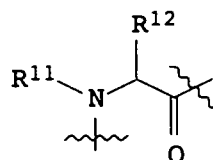
25 the structures IIa to IIc are preferably in the D configuration.

B:

30

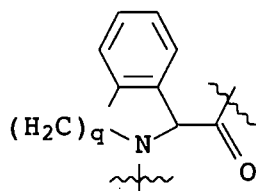


IIIa

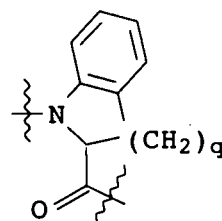


IIIb

35



IIIc



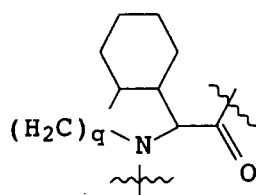
IIId

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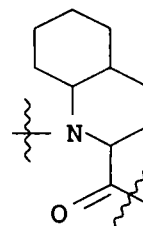
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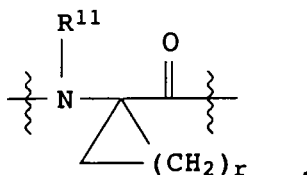
IIIe



IIIf

or

10



IIIg

15

q: 1 or 2

20

r: 3 or 4

Y a methylene group,

25

an ethylene group in which the ring resulting therefrom can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group,

30

-CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group, in which the rings resulting therefrom can carry on the carbon atom in position 3 and/or 4 a C₁₋₄-alkyl group, or in which one -CH₂- group can be replaced by -O-,

R¹¹: H or C₃₋₆-cycloalkyl,R¹²: H, C₁₋₆-alkyl or C₅₋₆-cycloalkyl.

35

The structures IIIa to IIIf are preferably in the L configuration.

Particularly preferred compounds If are those listed under a) in which the substituents R and the fragments A and B have the following meanings:

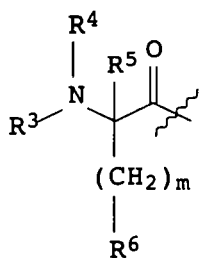
R²: H,

45

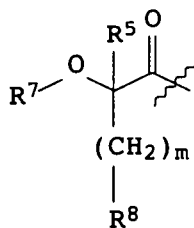
41

A:

5

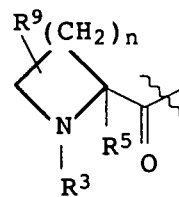


IIa



IIb

or



IIc

10 in which the substituents have the following meanings:

m: 0 or 1,

n: 2 or 3,

15

R³: H, C₁₋₆-alkyl, benzyl, R¹⁹OOC-C₁₋₆-alkylene [sic] (R¹⁹ = H, C₁₋₄-alkyl, benzyl), HO₃S-C₁₋₃-alkylene [sic], R²⁰R²¹N-CO- (R²⁰ and R²¹ are identical or different and are H, C₁₋₆-alkyl or benzyl, or R²⁰ and R²¹ together are a -(CH₂)₄₋₅- group),

20

R⁴: H,

R⁵: H or CH₃,

25

R⁶: C₅₋₈-cycloalkyl, where the aliphatic rings are provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and/or a CH₂ group is replaced by -O-, or phenyl which is substituted by 2 or 3 identical or different radicals from the group of CH₃, CF₃, CH₃O, F or Cl, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, diphenylmethyl, dicyclohexylmethyl, Me₃Si- or tert-butoxymethyl,

30

R⁷: H, C₁₋₆-alkyl-CO- or R¹⁹OOC-C₁₋₄-alkylene [sic],

35

R⁸: C₅₋₈-cycloalkyl, where the aliphatic rings are provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and/or a CH₂ group is replaced by -O-, or phenyl which is substituted by 2 or 3 identical or different radicals from the group of CH₃, CF₃, CH₃O, F or Cl, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, diphenylmethyl, dicyclohexylmethyl, Me₃Si- or tert-butoxymethyl,

40

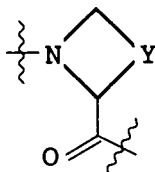
45

R^9 : C_{1-4} -alkyl, phenyl or C_{5-6} -cycloalkyl (R^9 can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2).

5 The structures IIa to IIc are preferably in the D configuration.

B:

10



IIIa

15

Y: a methylene group, an ethylene group, $-CH=CH-$, $-CH_2-S-$, $-CH_2-O-$ or a propylene group.

20 The structure IIIa is preferably in the L configuration,

or

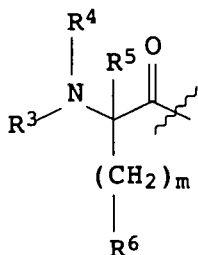
in the compound the substituents R and the fragments A and B have
25 the following meanings:

b)

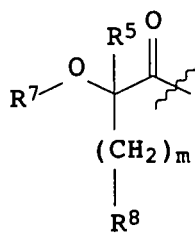
30 R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic], $R^{18}O-CH_2-$, $R^{18}-CO-$, $R^{18}-O-CH_2-CO-$, $R^{18}O-CO-CO-$, $R^{18}-NH-CO-CO-$, in which R^{18} is H and C_{1-4} -alkyl, or CF_3-CO- and C_2F_5-CO- ,

A:

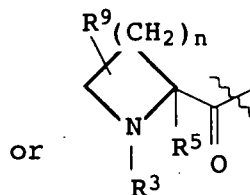
35



IIa



IIb



IIc

40

in which the substituents have the following meanings:

45

m: 0 or 1,

n: 2 or 3,

- 5 R^3 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkyl, $R^{19}OOC-C_{1-6}$ -alkylene [sic] (R^{19} is preferably H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic], C_{1-7} -alkyl- $OOC-$, benzyl- $OOC-$, or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl, aryl, aryl- C_{1-4} -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}-NH-CO-C_{1-4}$ -alkylene [sic] or R^{20} and R^{21} together are a $-(CH_2)_{4-5}-$ group),
- 10 R^4 : H, C_{1-12} -alkyl or aryl- C_{1-4} -alkylene [sic],
- R^5 : H or C_{1-4} -alkyl,
- 15 R^6 : C_{3-8} -cycloalkyl, where the aliphatic rings can be provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups and one or more methylene group(s) can be replaced by $-O-$, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetra-
- 20 linyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted on one or both aromatic rings, diphenyl-methyl which can be monosubstituted on one or both rings, dicyclohexylmethyl, phenyl- $C(CH_3)_2-$, C_{1-4} -alkyl- $C\equiv C-$, $R^{22}O-C(R^{23}R^{24})-$, in which R^{22} is H or C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl, $HO-C_{1-3}$ -alkyl or phenyl,
- 25 phenyl which can be substituted by up to 3 identical or different radicals from the group of C_{1-4} -alkyl, CF_3 , C_{1-4} -alkoxy, F or Cl,
- 30 $R^{25}R^{26}CH-$, in which R^{25} is C_{1-6} -alkyl and R^{26} is H or C_{1-6} -alkyl,
- 35 R^7 : H, C_{1-12} -alkyl, C_{1-20} -alkyl- $CO-$, $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene- $CO-$ [sic], $R^{20}R^{21}N-CO-$, HO_3S-C_{1-4} -alkylene- $CO-$ [sic], or the acyl radical of a natural or unnatural bile acid,
- 40 R^8 : C_{3-8} -cycloalkyl, where the aliphatic rings can be provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups and one or more methylene group(s) can be replaced by $-O-$, or adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetra-
- 45 linyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted on one or both aromatic rings, diphenyl-methyl which can be monosubstituted on one or both rings, dicyclohexylmethyl, phenyl- $C(CH_3)_2-$, C_{1-4} -alkyl- $C\equiv C-$,

44

$R^{22}O-C(R^{23}R^{24})-$, in which R^{22} is H or C_{1-4} -alkyl, and R^{23} and R^{24} are H, C_{1-4} -alkyl, $HO-C_{1-3}$ -alkyl or phenyl,

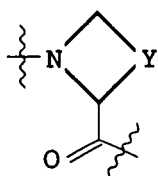
phenyl which can be substituted by up to 3 identical or different radicals from the group of C_{1-4} -alkyl, CF_3 , C_{1-4} -alkoxy, F or Cl,

$R^{25}R^{26}CH-$, in which R^{25} is C_{1-6} -alkyl and R^{26} is H or C_{1-6} -alkyl,

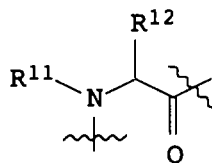
R^9 : H, C_{1-4} -alkyl, phenyl or C_{5-6} -cycloalkyl (R^9 can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2).

The structures IIa to IIc are preferably in the D configuration.

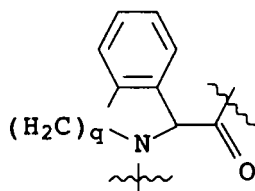
B:



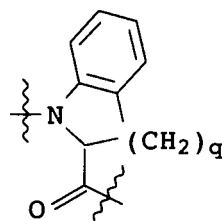
IIIa



IIIb



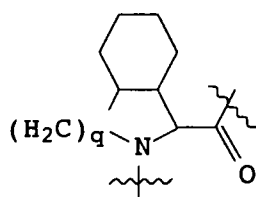
IIIc



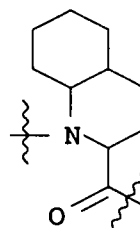
IIId

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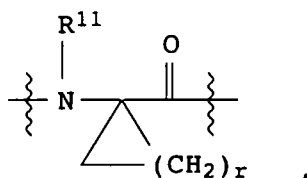
IIIIe



IIIIf

or

10



IIIIg

15

q: 1 or 2

20

r: 3 or 4

25

Y -CH=CH-, -CH₂-S-, -CH₂-O- or a propylene group, in which the rings resulting therefrom can carry on the carbon in position 3 and/or 4 a C₁₋₄-alkyl group, or in which -CH₂ group can be replaced by -O-,

R¹¹: H or C₃₋₆-cycloalkyl,R¹²: H, C₁₋₆-alkyl or C₅₋₆-cycloalkyl,

30

The structures IIIIa to IIIIf are preferably in the L configuration.

Particularly preferred compounds If listed under b) are those in which the substituents R, the fragments A and B and X have the following meanings:

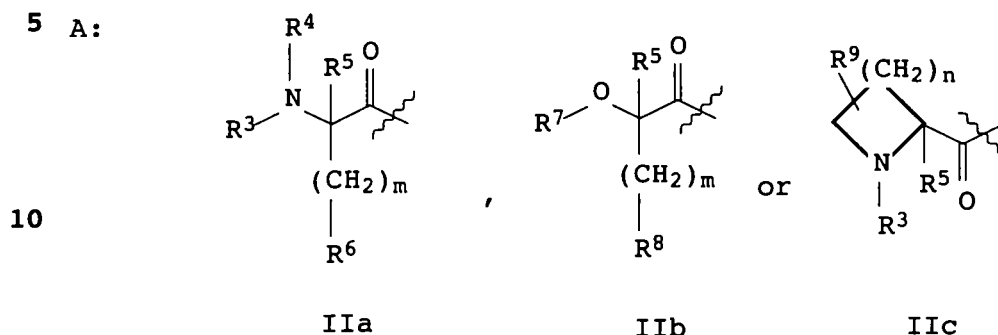
40

45

b)

 R^2 : H,

5 A:



15 in which the substituents have the following meanings:

m: 0 or 1,

n: 2 or 3,

20

R^3 : H, C_{1-6} -alkyl, benzyl, $R^{19}OOC-C_{1-6}$ -alkyl (R^{19} is H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic], or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl or benzyl or R^{20} and R^{21} together are a

25 $-(CH_2)_{4-5}$ - group),

 R^4 : H, R^5 : H or CH_3 ,

30

R^6 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups and in which one methylene group can be replaced by $-O-$, or phenyl which can be substituted by 1 to 3 identical or

35 different radicals from the group of F, Cl, CH_3 or CH_3O , diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxymethyl, adamantyl, norbornyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or $(CH_3)_3Si-$,

40

 R^7 : H, C_{1-6} -alkyl-CO- or $R^{19}OOC-C_{1-4}$ -alkylene [sic],

R^8 : C_{5-8} -cycloalkyl, where the aliphatic rings can be substituted by up to 4 C_{1-4} -alkyl and/or CH_3O groups and in which one methylene group can be replaced by $-O-$, or phenyl which can be substituted by 1 to 3 identical or

45 different radicals from the group of F, Cl, CH_3 or CH_3O ,

47

diphenylmethyl, dicyclohexylmethyl, isopropyl, tert-butyl, neopentyl, tert-butoxymethyl, phenoxyethyl, adamantyl, norbornyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl or $(\text{CH}_3)_3\text{Si}-$,

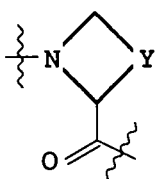
5

R^9 : H, C_{1-4} -alkyl, phenyl or C_{5-6} -cycloalkyl (R^9 can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2).

10 The structures IIa to IIc are preferably in the D configuration.

B:

15



IIIa

20

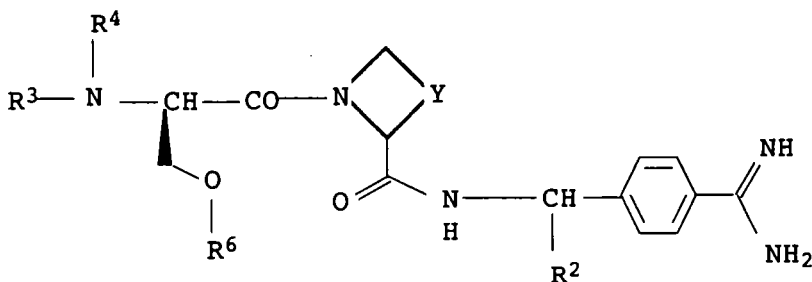
Y : $-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{S}-$, $-\text{CH}_2-\text{O}-$ or a propylene group.

The structure IIIa is preferably in the L configuration.

25

Ig:

30



35

In this, the substituents R and the function of Y have the following meanings:

40 a)

R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic], $\text{R}^{18}\text{O}-\text{CH}_2-$, $\text{R}^{18}-\text{CO}-$, $\text{R}^{18}-\text{O}-\text{CH}_2-\text{CO}-$, $\text{R}^{18}-\text{NH}-\text{CO}-\text{CO}-$, where R^{18} is H or C_{1-4} -alkyl, or $\text{CF}_3-\text{CO}-$ or $\text{C}_2\text{F}_5-\text{CO}-$,

45

48

R³: R¹⁹OOC-C₁₋₄-alkylene [sic] (R¹⁹=H-, C₁₋₄-alkyl, benzyl),
 HO₃S-C₁₋₃-alkylene [sic], or R²⁰R²¹N-CO- (R²⁰ and R²¹ are
 identical or different and are H, C₁₋₆-alkyl, aryl,
 aryl-C₁₋₂-alkylene [sic], or R²⁰ and R²¹ together are a
 5 -(CH₂)₄₋₅- group),

R⁴: H, C₁₋₁₂-alkyl or aryl-C₁₋₂-alkylene [sic],

R⁶: H, C₁₋₁₂-alkyl and
 10

Y: -CH₂-, -CH₂-CH₂- or -CH₂-CH₂-CH₂-.

The amino acid containing Y is preferably in the L configuration.

15 Particularly preferred compounds Ig listed under a) are those in
 which the substituents R and the function of Y have the following
 meanings:

a)
 20

R²: H,

R³: R¹⁹OOC-C₁₋₄-alkylene [sic] (R¹⁹=H-, C₁₋₄-alkyl, benzyl),
 HO₃S-C₁₋₃-alkylene [sic], or R²⁰R²¹N-CO- (R²⁰ and R²¹ are
 25 identical or different and are H, C₁₋₆-alkyl, or benzyl, or
 R²⁰ and R²¹ together are a -(CH₂)₄₋₅- group),

R⁴: H,

30 R⁶: H, C₁₋₄-alkyl and

Y: -CH₂-, -CH₂-CH₂- or -CH₂-CH₂-CH₂-.

The amino acid containing Y is preferably in the L configuration.
 35
 or

in the compound Ig, the substituents R and Y have the following
 meanings:

40

45

b)

5 R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic],
 $R^{18}O-CH_2-$, $R^{18}-CO-$, $R^{18}-O-CH_2-CO-$, $R^{18}-NH-CO-CO-$, where R^{18} is H
 or C_{1-4} -alkyl, or CF_3-CO- or C_2F_5-CO- ,

10 R^3 : H, C_{1-12} -alkyl, aryl- C_{1-2} -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene
 [sic] (R^{19} = H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic],
 C_{1-4} -alkyl- $OOC-$, benzyl- $OOC-$ or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are
 identical or different and are H, C_{1-6} -alkyl, aryl,
 aryl- C_{1-2} -alkyl, or R^{20} and R^{21} together are a $-(CH_2)_{4-5}-$
 group),

15 R^4 : H, C_{1-12} -alkyl or aryl- C_{1-2} -alkylene [sic],

R^6 : H, C_{1-12} -alkyl and

20 Y: an ethylene group in which the ring resulting therefrom
 carries in position 4 a hydroxyl or C_{1-4} -alkoxy group, or
 $-CH_2-S-$, $-CH_2-O-$, $-CH=CH-$ or a propylene group in which one
 CH_2 group is replaced by $-O-$ or $-S-$.

The amino acid containing Y is preferably in the L configuration.

25 Particularly preferred compounds Ig listed under b) are those in
 which the substituents R and the function of Y have the following
 meanings:

30 R^2 : H,

R^3 : H, C_{1-6} -alkyl, benzyl, $R^{19}OOC-C_{1-4}$ -alkylene [sic] (R^{19} = H,
 C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic], or $R^{20}R^{21}N-CO-$
 (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl,
 aryl or benzyl, or R^{20} and R^{21} together are a $-(CH_2)_{4-5}-$
 35 group),

R^4 : H, C_{1-12} -alkyl or aryl- C_{1-2} -alkylene [sic],

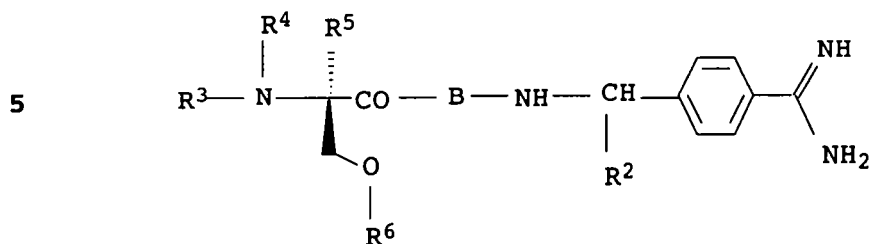
40 R^6 : H, C_{1-4} -alkyl and

Y: $-CH_2-S-$, $-CH_2-O-$ or $-CH=CH-$.

The amino acid containing Y is preferably in the L configuration.

45

Ih:



10

In this, the substituents R and B have the following meanings:

15 R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic],
 $R^{18}O-CH_2-$, $R^{18}-CO-$, $R^{18}-O-CH_2-CO-$, $R^{18}-NH-CO-CO-$, where R^{18} is H
 or C_{1-4} -alkyl, or CF_3-CO- or C_2F_5-CO- ,

20 R^3 : H, C_{1-12} -alkyl, aryl- C_{1-2} -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene
 [sic] (R^{19} = H, C_{1-4} -alkyl, benzyl), HO_3S-C_{1-3} -alkylene [sic],
 C_{1-4} -alkyl- $OOC-$, benzyl- $OOC-$ or $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are
 identical or different and are H, C_{1-6} -alkyl, aryl,
 aryl- C_{1-2} -alkylene [sic], or R^{20} and R^{21} together are a
 $-(CH_2)_{4-5}-$ group),

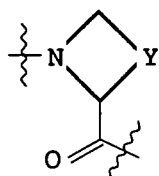
25 R^4 : H, C_{1-12} -alkyl or aryl- C_{1-2} -alkylene [sic],

R^5 : C_{1-4} -alkyl,

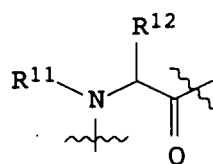
R^6 : H, C_{1-12} -alkyl.

30 B:

35

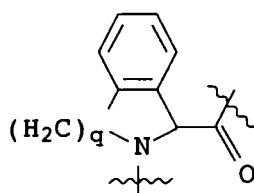


IIIa

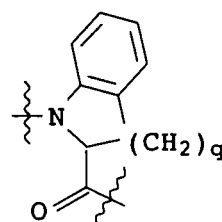


IIIb

40



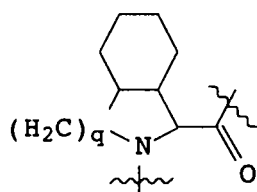
IIIc



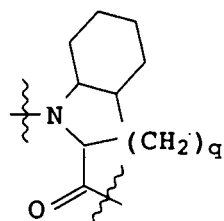
IIId

45

5



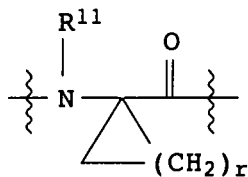
IIIIe



or

IIIIf

10



IIIIg

15

q: 1 or 2

20

r: 3 or 4

R¹¹: H or C₃₋₆-cycloalkyl,

25

R¹²: H, C₁₋₆-alkyl or C₅₋₆-cycloalkyl,

Y: a methylene group,

30

an ethylene group in which the ring resulting therefrom
can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group,

-CH₂-S-, -CH₂-O-, -CH=CH- or a propylene group in which
one -CH₂- group can be replaced by -O- or -S-.

35

The structures IIIIa to IIIIf are preferably in the L con-
figuration.

Particularly preferred compounds Ia are those in which the sub-
stituents R and B have the following meanings:

40

R²: H,R³: H, C₁₋₆-alkyl, benzyl, R¹⁹OOC-C₁₋₄-alkylene [sic] (R¹⁹=H,

45

C₁₋₄-alkyl, benzyl), HO₃S-C₁₋₃-alkylene [sic], or R²⁰R²¹N-CO-
(R²⁰ and R²¹ are identical or different and are H, C₁₋₆-alkyl
or benzyl, or R²⁰ and R²¹ together are a -(CH₂)₄₋₅- group),

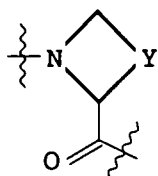
R⁴: H,

R⁵: CH₃,

5 R⁶: H, C₁₋₄-alkyl.

B:

10



IIIa

15

Y: a methylene group, an ethylene group,

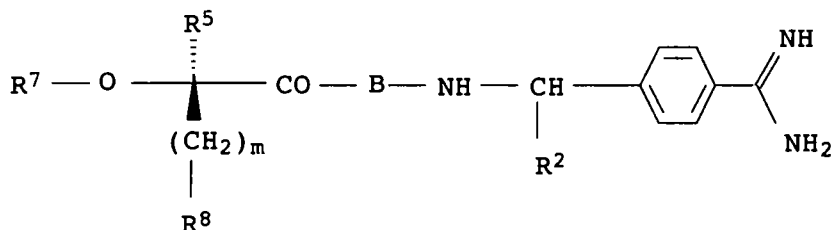
-CH₂-S-, -CH₂-O-, -CH=CH- or a propylene group.

20

The structure IIIa is preferably in the L configuration.

Ii:

25



30

In this, the substituents R, the fragment B and m have the following meanings:

m: 0, 1

35

R²: H, C₁₋₄-alkyl, phenyl, phenyl-C₁₋₄-alkylene [sic], R¹⁸O-CH₂-, R¹⁸-CO-, R¹⁸-O-CH₂-CO-, R¹⁸-NH-CO-CO-, where R¹⁸ is H or C₁₋₄-alkyl, or CF₃-CO- or C₂F₅-CO-,

40 R⁵: H or C₁₋₄-alkyl,

45

53

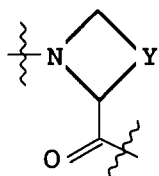
R⁷: H, C₁₋₁₂-alkyl, C₁₋₂₀-alkyl-CO-, R¹⁹OOC-C₁₋₄-alkylene [sic] (R¹⁹ = H, C₁₋₄-alkyl, benzyl), R¹⁹OOC-C₁₋₄-alkylene-CO- [sic], R²⁰R²¹N-CO-, HO₃S-C₁₋₄-alkylene [sic], and the acyl radical of a natural or unnatural bile acid (R²⁰, R²¹ are identical or different and are H, C₁₋₆-alkyl or benzyl, or R²⁰ and R²¹ together are a -(CH₂)₄₋₅- group),

R⁸: C₃₋₈-cycloalkyl, where the aliphatic rings are provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and/or one or more methylene group(s) is (are) replaced by -O-, or

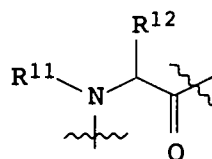
phenyl which is substituted by 2 or 3 identical or different radicals from the group of C₁₋₄-alkyl, CF₃, C₁₋₄-alkoxy, F or Cl,

adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, (CH₃)₃Si-, diphenylmethyl, dicyclohexylmethyl or dibenzosuberyl, which can be monosubstituted on one or both aromatic rings,

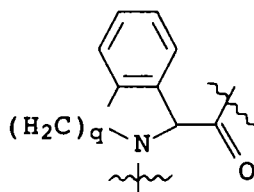
B:



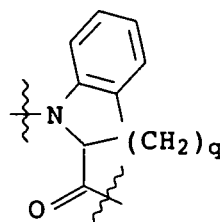
IIIa



IIIb

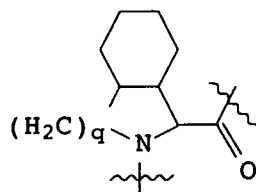


IIIc

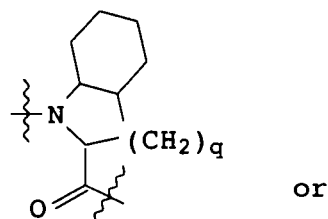


IIId

5

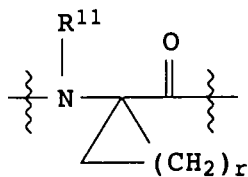


IIIe



IIIf

10



IIIg

15

q: 1 or 2

20

r: 3 or 4

Y: a methylene group,

25

an ethylene group in which the ring resulting therefrom can carry in position 4 a hydroxyl or C₁₋₄-alkoxy group,

-CH₂-S-, -CH₂-O-, -CH=CH- or a propylene group in which one -CH₂ group can be replaced by -O- or -S-.

30

R¹¹: H or C₃₋₆-cycloalkyl

R¹²: H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl.

35

The structures IIIa to IIIf are preferably in the L configuration.

Particularly preferred compounds Ii are those in which the substituents R and the fragment B have the following meanings:

40

R²: H,

R⁵: H or CH₃,

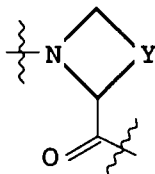
45

R⁷: H, C₁₋₆-alkyl-CO-, R¹⁹OOC-C₁₋₄-alkylene [sic], (R¹⁹ = H, C₁₋₄-alkyl, benzyl)

55

R⁸: C₅₋₈-cycloalkyl, where the aliphatic rings are substituted by up to 4 CH₃ and/or CH₃O groups, and/or one methylene group is replaced by -O-, or phenyl, which is substituted by 2 or 3 identical or different radicals from the group of CH₃, CF₃, CH₃O, F or Cl, adamantyl, norbonyl [sic], 1-decalinyl, 1-tetralinyl, 2-tetralinyl, diphenylmethyl, dicyclohexylmethyl, Me₃Si or tert-butoxymethyl,

10 B:



15 IIIa

Y: a methylene group, an ethylene group,
-CH₂-S-, -CH₂-O-, -CH=CH- or a propylene group.

The structure IIIa is preferably in the L configuration.

The terms "alkyl" and "alkylene" [sic] used above describe straight-chain and branched carbon frameworks. Aryl means carbo- and heterocyclic aromatic systems which can be mono- or bicyclic.

Preferred structures of the invention are:

- 30 (D)-(Cyclohexyl)Hyac-Pro-NH-3-(6-am)-pico
 (D)-(Cyclohexyl)Hyac-Pro-NH-4-amb
 (D)-(Cyclohexyl)Hyac-Pro-NH-(2-MeO)-4-amb
 (D)-(Cyclohexyl)Hyac-Aze-NH-4-amb
 (D)-(3-Phenyl)Hyac-Pro-NH-4-amb
- 35 (D,L)-(1-Tetralinyl)Hyac-Pro-NH-3-(6-am)-pico
 (D,L)-(1-Tetralinyl)Hyac-Pro-NH-4-amb
 O-Acetyl-(D)-(Cyclohexyl)Hyac-Pro-NH-3-(6-am)-pico
 O-Acetyl-(D)-(Cyclohexyl)Hyac-Pro-NH-4-amb
 O-Hexanoyl-(D)-(Cyclohexyl)Hyac-Pro-NH-4-amb
- 40 O-Hydroxycarbonyl-methyl-(D)-(Cyclohexyl)Hyac-Pro-NH-3-(6-am)-pico
 (D)-(β-Cyclohexyl)Hypr-Pro-NH-3-(6-am)-pico
 (D)-(β-Cyclohexyl)Hypr-Pro-NH-4-amb
 (D)-(β-Cyclohexyl)Hypr-Pro-NH-(2-MeO)-4-amb
- 45 (D,L)-(β,β-Diphenyl)Hypr-Pro-NH-3-(6-am)-pico
 (D,L)-(β,β-Diphenyl)Hypr-Pro-NH-4-amb
 (D,L)-(β,β-Dicyclohexyl)Hypr-Pro-NH-3-(6-am)-pico

- H-(D)-Chg-Aze-NH-3-(6-am)-pico
 H-(D)-Chg-Pic-NH-3-(6-am)-pico
 H-(D)-Cha-Pro-NH-3-(6-am)-pico
 H-(D)-(tert-Butyl)Ser-Pro-NH-3-(6-am)-pico
 5 H-(D)-Chg-Hyp-NH-3-(6-am)-pico
 H-(D)-Chg-1-Tic-NH-3-(6-am)-pico
 H-(D)-Chg-3-Tic-NH-3-(6-am)-pico
 H-(D)-Chg-2-Phi-NH-3-(6-am)-pico
 H-(D,L)-Chea-Pro-NH-3-(6-am)-pico
 10 H-(D)-(α-Me)Cha-Pro-NH-3-(6-am)-pico
 H-D,L-4-Tetrahydropyranyl)-Gly-Pro-NH-3-(6-am)-pico
 H-(+/-)-(threo)-(β-Hydroxy)-Phe-Pro-NH-3-(6-am)-pico
 H-(D,L)-(2-Norbornyl)Gly-Pro-NH-3-(6-am)-pico
 H-(D,L)-(1-Adamantyl)Gly-Pro-NH-3-(6-am)-pico
 15 H-(D,L)-(1-Tetralinyl)Gly-Pro-NH-3-(6-am)-pico
 H-(D,L)-(Me₃Si)Ala-Pro-NH-3-(6-am)-pico
 H-(D,L)-(3,4,5-Trimethoxy)Phe-Pro-NH-3-(6-am)-pico
 H-(D,L)-(3-Phenyl)Pro-Pro-NH-3-(6-am)-pico
 H-(D,L)-(4-Me)Pic-Pro-NH-3-(6-am)-pico
 20 H-(D)-Cha-Pyr-NH-3-(6-am)-pico
 H-(D)-Chg-(N-Cyclopropyl)Gly-NH-3-(6-am)-pico
 H-(D)-Chg-(Cyclo)Leu-NH-3-(6-am)-pico
 H-(D)-Chg-Pro-NH-5-(2-am)-pym
 H-(D)-Chg-Pro-NH-2-(5-am)-pym
 25 H-(D)-Chg-Pro-NH-(4-am)-napme
 H-(D,L)-Thpg-Pro-NH-(2-MeO)-4-amb
 H-(D,L)-Dpa-Pro-NH-(2-MeO)-4-amb
 H-(D,L)-(2-Norbornyl)Gly-Pro-NH-(2-MeO)-4-amb
 H-(D,L)-(1-Tetralinyl)Gly-Pro-NH-(2-MeO)-4-amb
 30 H-(D,L)-Cog-Pro-NH-(2-MeO)-4-amb
 H-(D)-(α-Me)Cha-Pro-NH-(2-MeO)-4-amb
 H-(D,L)-(Dibenzosuberyl)Gly-Pro-NH-(2-MeO)-4-amb
 H-(D,L)-(3,4,5-Trimethoxy)Phe-Pro-NH-(2-MeO)-4-amb
 H-(D,L)-(Me₃Si)Ala-Pro-NH-(2-MeO)-4-amb
 35 H-(+/-)-threo)-(3-Hydroxy)Phe-Pro-NH-(2-MeO)-4-amb
 H-(D)-(tert-Butyl)Ser-Pro-NH-(2-MeO)-4-amb
 H-(D,L)-(3-Phenyl)Pro-Pro-NH-(2-MeO)-4-amb
 H-(D)-Chg-Pic-NH-(2-MeO)-4-amb
 H-(D)-Chg-Pyr-NH-(2-MeO)-4-amb
 40 H-(D)-Chg-(N-cyclopropyl)Gly-NH-(2-MeO)-4-amb
 H-(D)-Chg-1-Tic-NH-(2-MeO)-4-amb
 H-(D)-Cha-Pic-NH-(2-MeO)-4-amb
 H-(D)-Chg-Pro-NH-(2-EtO)-4-amb
 H-(D)-Chg-Pro-NH-(2-I)-4-amb
 45 H-(D)-Chg-(Cyclo)Leu-NH-(2-MeO)-4-amb
 H-(D)-Chg-Pro-NH-(2-OH)-4-amb
 H-(D)-Chg-Pro-NH-(2,6-Dimethoxy)-4-amb

- H-(D)-Chg-Pro-NH-(3-MeO)-4-amb
 H-(D)-Chg-Pro-NH-(3-OH)-4-amb
 H-(D)-Chg-Pro-NH-(3-Cl)-4-amb
 H-(D)-Chg-Pro-NH-(2-COOH)-4-amb
 5 H-(D)-Chg-Pro-NH-(2-NH₂)-4-amb
 H-(D)-Chg-Pro-NH-(2-OCH₂-COOH)-4-amb
 HOOC-CH₂-(D)-Cha-Pro-NH-(2-MeO)-4-amb
 MeOOC-CH₂-(D)-Cha-Pro-NH-(2-MeO)-4-amb
 HOOC-CH₂-CH₂-(D)-Chg-Pro-NH-(2-MeO)-4-amb
 10 tBuOOC-CH₂-(D,L)-Cog-Pro-NH-(2-MeO)-4-amb
 HOOC-CH₂-(D,L)-Cog-Pro-NH-(2-MeO)-4-amb
 HOOC-CH₂-(D,L)-Dpa-Pro-NH-(2-MeO)-4-amb
 Cbz-(D)-(tert-Butyl)Ser-Pro-NH-(2-MeO)-4-amb
 HOOC-CH₂-(D)-Cha-Pic-NH-(2-MeO)-4-amb
 15 Ph-CH₂-(D)-Chg-Pro-NH-(2-MeO)-4-amb
 HOOC-CH₂-(D)-Chg-Pro-NH-(2-OH)-4-amb
 HOOC-CH₂-(D)-Cha-Pro-NH-(2-OH)-4-amb
 HOOC-CH₂-(D)-Chg-Pro-NH-(2-Cl)-4-amb
 HOOC-CH₂-(D,L)-(4-Me)Chg-Pro-NH-3-(6-am)-pico
 20 HOOC-CH₂-(D,L)-(4-iPr)Chg-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(4-tBu)Chg-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-Dch-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(3,3-Dimethyl)Chg-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-(tert-Butyl)Ser-Pro-NH-3-(6-am)-pico
 25 HOOC-CH₂-(D,L)-Cpg-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(1-Tetralinyl)Gly-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(2-norbornyl)Gly-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(Thpg)-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(Thpa)-Pro-NH-3-(6-am)-pico
 30 tBuOOC-CH₂-(D,L)-(Thpg)-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-(L)-(Thpg)-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-(Thpg)-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(Thpg)-Oxp-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(Thpa)-Oxp-NH-3-(6-am)-pico
 35 HOOC-CH₂-(D,L)-Chg-Thia-NH-3-(6-am)-pico
 tBuOOC-CH₂-(D)-Chg-Pro-NH-3-(6-ham)-pico
 BnOOC-CH₂-(D)-Chg-Pro-NH-3-(6-ham)-pico
 MeOOC-CH₂-(D)-Chg-Pro-NH-3-(6-methoxycarbonyl-am)-pico
 tBuOOC-CH₂-(D)-(tBu)Gly-Pic-NH-3-(6-am)-pico
 40 HOOC-CH₂-(D)-(tBu)Gly-Pic-NH-3-(6-am)-pico
 tBuOOC-CH₂-(D)-(neo-Pentyl)Gly-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-(neo-Pentyl)Gly-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-CH₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-(3,4,5-Trimethoxy)Phe-Pro-NH-3-(6-am)-pico
 45 HOOC-CH₂-(D)-Chg-Pro-NH-3-(6-am-2-MeO)-pico
 HOOC-CH₂-(D)-Cha-Pro-NH-3-(6-am-2-Me)-pico
 HOOC-CH₂-(D)-Chg-Pro-NH-3-(6-am-4-MeO)-pico

58

- HOOC-CH₂-(D)-Chg-Pro-NH-(6-am-4-Me)-pico
 HOOC-CH₂-(D)-Cha-Pyr-NH-(2-MeO)-4-amb
 HOOC-CH₂-(D)-Cha-Pyr-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(Thpa)-Pyr-NH-3-(6-am)-pico
 5 iPrOOC-CH₂-(D)-Chg-Pyr-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-(γ-Me)Cha-Pyr-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-Chea-Pyr-NH-3-(6-am)-pico
 tBuOOC-CH₂-(D)-Chg-Oxp-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-Chg-Oxp-NH-3-(6-am)-pico
 10 tBuOOC-CH₂-(D)-Cha-Oxp-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-Cha-Oxp-NH-3-(6-am)-pico
 tBuOOC-CH₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 MeOOC-CH₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 CyclohexyloOC-CH₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 15 (tBuOOC-CH₂)₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 (HOOC-CH₂)₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 H₂NCO-CH₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 tBuNHCO-CH₂-(D)-Chg-Pro-NH-3-(6-am)-pico
 tBuOOC-CH₂-(D)-Chg-Aze-NH-3-(6-am)-pico
 20 HOOC-CH₂-(D)-Chg-Aze-NH-3-(6-am)-pico
 tBuOOC-CH₂-(D)-Chg-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-Chg-Pic-NH-3-(6-am)-pico
 tBuOOC-CH₂-(D)-Cha-Pro-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-Cha-Pro-NH-3-(6-am)-pico
 25 tBuOOC-CH₂-(D)-Cha-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-(D)-Cha-Pic-NH-3-(6-am)-pico
 HOOC-CH₂-(D,L)-Cog-Pro-NH-5-(2-am)-pym

List of abbreviations:

- 30 AIBN: Azobisisobutyronitrile
 Ac: Acetyl
 Ala: Alanine
 am: Amidino
 35 4-amb: 4-Amidinobenzyl
 Asp: Aspartic acid
 Aze: Azetidinecarboxylic acid
 Bn: Benzyl
 Boc: tert-Butyloxycarbonyl
 40 Bu: Butyl
 Cbz: Benzyloxycarbonyl
 Cha: Cyclohexylalanine
 Chea: Cycloheptylalanine
 Chg: Cyclohexylglycine
 45 Cog: Cyclooctylglycine
 Cpa: Cyclopentylalanine
 Cpg: Cyclopentylglycine

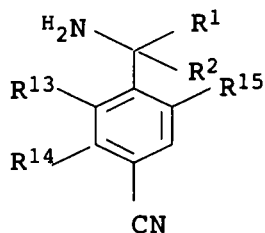
(Cyclo)Leu:	1-Aminocyclopentane-1-carboxylic acid
TLC:	Thin-layer chromatography
DCC:	Dicyclohexylcarbodiimide
Dch:	Dicyclohexylalanine
5 Dcha:	Dicyclohexylamine
DCM:	Dichloromethane
DMF:	Dimethylformamide
DIPEA:	Diisopropylethylamine
Dpa:	Diphenylalanine
10 Et:	Ethyl
Eq:	Equivalents
Gly:	Glycine
ham:	Hydroxyamidino
HOSucc:	Hydroxysuccinimide
15 HPLC:	High-performance liquid chromatography
Hyac:	Hydroxyacetyl
Hyp:	Hydroxyproline
Hypr:	2-Hydroxypropionyl
2-Ind:	2-Dihydroindolecarboxylic acid
20 iPr:	Isopropyl
Leu:	Leucine
Me:	Methyl
MPCL [sic]:	Medium through [sic] liquid chromatography
MTBE:	Methyl tert-butyl ether
25 napme:	naphthylmethyl
NBS:	N-Bromosuccinimide
Oxp:	Oxaproline (1,3-oxazolidine-4-carboxylic acid)
Ph:	Phenyl
Phe:	Phenylalanine
30 2Phi:	2-Perhydroindolecarboxylic acid
Pic:	Pipecolic acid
pico:	picolyl
pim:	piperidinylmethyl
PPA:	Propylphosphoric [sic] anhydride
35 Pro:	Proline
Py:	Pyridine
5-pym:	5-Pyrimidylmethyl
2-Pym:	2-Pyrimidylmethyl
Pyr:	3,4-Dehydroproline
40 RT:	Room temperature
t:	tertiary
tBu:	tertiary-butyl
tert:	tertiary
TBAB:	Tetrabutylammonium bromide
45 TEA:	Triethylamine [sic]
TFA:	Trifluoroacetic acid
TFFA:	Trifluoroacetic anhydride

60

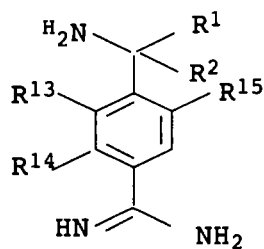
Thia:	Thiaproline (1,3-thiazolidine-4-carboxylic acid)
Thpa:	4-Tetrahydropyranylalanine
Thpg:	4-Tetrahydropyranylglycine
1Tic:	1-Tetrahydroisoquinolinecarboxylic acid
5 3Tic:	3-Tetrahydroisoquinolinecarboxylic acid
Z:	Benzyloxycarbonyl

The invention furthermore relates to the compounds of the formulae

10



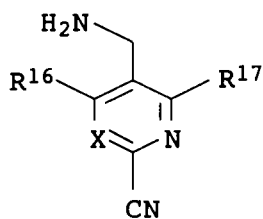
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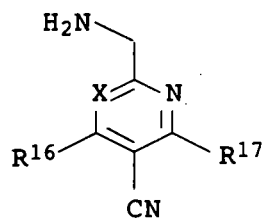
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VI

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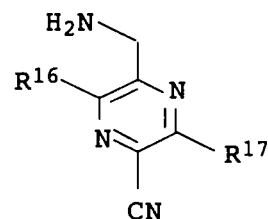


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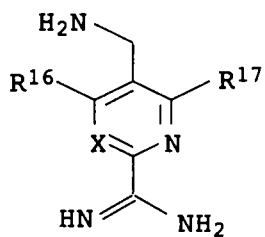
VII

VIII

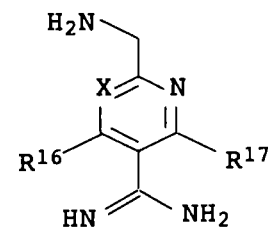


IX

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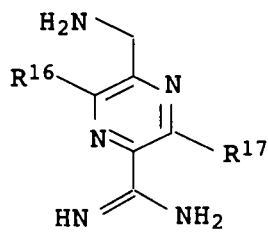


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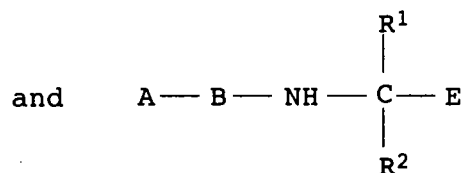
X

XI



XII

40

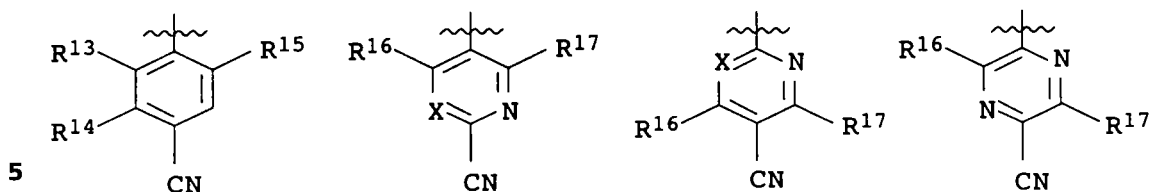


XIII,

where A, B, X, R¹, R², R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ have the stated meaning, and E is

45

61

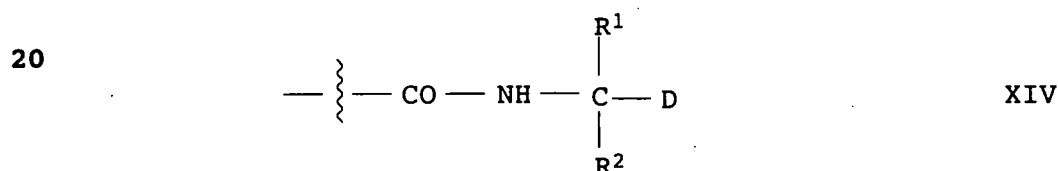


and in which the amidino functionality in formulae VI, X, XI and XII can be in mono- or diprotected form.

- 10 Particularly suitable protective groups for the protected form are the Cbz and Boc groups.

The novel intermediates are used to prepare the compounds I and are valuable building blocks for synthesizing serine protease
15 inhibitors.

The structural fragment of the formula XIV



- 25 in which D has the abovementioned meaning, is novel and is valuable as constituent of serine protease inhibitors and in particular of thrombin inhibitors.

The compounds of the formula I may exist as such or in the form
30 of their salts with physiologically tolerated acids. Examples of such acids are: hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid, fumaric acid, succinic acid, hydroxysuccinic acid, sulfuric acid, glutaric acid, aspartic
35 acid, pyruvic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

The novel compounds can be used for the therapy and prophylaxis of thrombin-dependent thromboembolic events such as deep vein
40 thromboses, pulmonary embolisms, myocardial or cerebral infarcts and unstable angina, also for the therapy of disseminated intravascular coagulation (DIC). They are furthermore suitable for combination therapy with thrombolytics such as streptokinase, urokinase, prourokinase, t-PA, APSAC and other plasminogen
45 activators for shortening the reperfusion time and prolonging the reocclusion time.

Other areas of use are the prevention of thrombin-dependent early reocclusion and late restenosis after percutaneous transluminal coronary angioplasty, the prevention of thrombin-induced proliferation of smooth muscle cells, the prevention of the
5 accumulation of active thrombin in the CNS (eg. in Alzheimer's disease), the control of tumors and the prevention of mechanisms which lead to adhesion and metastasis of tumor cells.

Their particular advantage is that they are also effective after
10 oral administration.

The compounds according to the invention can be administered in a conventional manner orally or parenterally (subcutaneously, intravenously, intramuscularly, intraperitoneally, rectally).
15 Administration can also take place with vapors or sprays through the nasopharyngeal space.

The dosage depends on the age, condition and weight of the patient and on the mode of administration. As a rule, the daily
20 dose of active ingredient per person is about 10-2000 mg on oral administration and about 1-200 mg on parenteral administration. This dose can be given in 2 to 4 single doses or once a day as depot form.

25 The novel compounds can be used in conventional solid or liquid pharmaceutical forms, eg. as uncoated or (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active ingredients can for this purpose be mixed with
30 conventional pharmaceutical auxiliaries such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag,
35 Stuttgart, 1978). The administration forms obtained in this way normally contain from 0.1 to 99 percent by weight of active ingredient.

Experimental part:

40

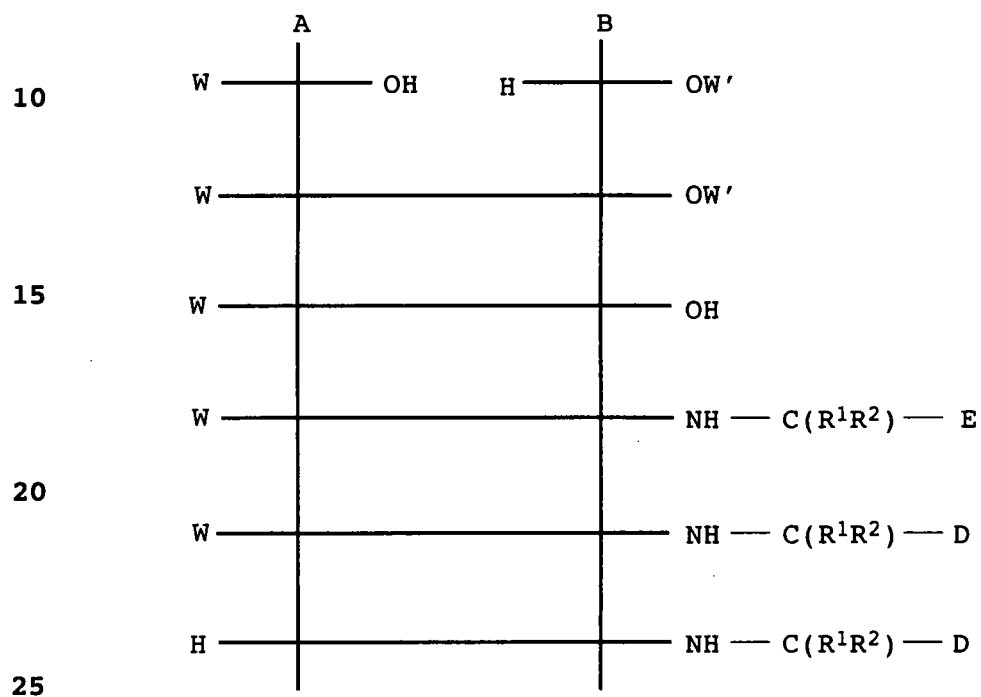
The compounds of the formula I can be prepared starting from the N-terminally protected α -amino acids or α -hydroxy carboxylic acids A-OH, the α -amino acid B-OH and the building block $H_2N-C(R^1R^2)-E$ as shown in scheme 1 and 2. Classical methods of
45 protective group and coupling chemistry are used for this purpose.

63

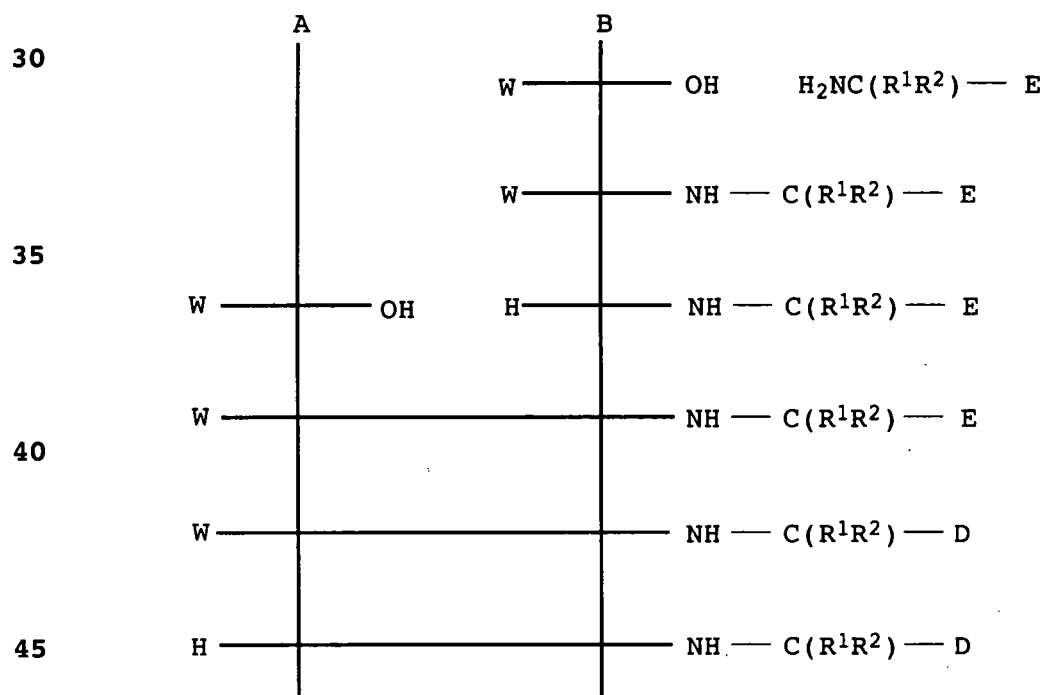
The radicals R^3 and R^4 or R^7 can alternatively be introduced after the coupling of the building blocks A-OH, B-OH and $H_2N-C(R^1R^2)-E$ to give A-B-N-C(R^1R^2)-E after cleavage of the protective group from A or are a constituent of A-OH from the outset.

5

Scheme I [sic]



Scheme II [sic]



where W is one of the conventional N-terminal protective groups (preferably Boc or Cbz) and W' is methyl, ethyl, tert-butyl or benzyl.

- 5 The required coupling reactions and the conventional reactions for introducing and eliminating protective groups are carried out under standard conditions of peptide chemistry (see M. Bodanszky, A. Bodanszky "The Practice of Peptide Synthesis", 2nd edition, Springer Verlag Heidelberg, 1994).

10

Boc protective groups are eliminated using dioxane/HCl or TFA/DCM, and Cbz protective groups are eliminated by hydrogenolysis or with HF. The hydrolysis of ester functionalities takes place with LiOH in an alcoholic solvent or

- 15 in dioxane/water. t-Butyl esters are cleaved with TFA.

N-terminal alkyl radicals (see R³ and R⁴) are introduced by reductive alkylation or direct N-alkylation.

- 20 Alkanoyl radicals (see R⁷) are introduced by standard coupling reactions or esterification reactions.

The amidino functionality can be prepared from a nitrile functionality by several methods:

25

One method is classical Pinner synthesis (R. Boder, D.G. Neilson Chem. Rev. 61 (1961) 179) or a modified Pinner synthesis which passes through imino thioester salts as intermediate (H. Vieweg et al. Pharmazie 39 (1984), 226). Catalytic hydrogenation of

- 30 N-hydroxyamidines, which are obtainable by addition of hydroxylamine onto the cyano group, with Raney nickel or Pd/C in alcoholic solvents likewise results in amidines (B.J. Broughton et al. J.Med.Chem. 18 (1975), 1117) and is particularly valuable for the synthesis of pharmaceutically active compounds.

35

The reactions were checked by TLC, normally using the following mobile phases:

- | | | |
|-------|-------------------|---------|
| A. | DCM/MeOH | 95:5 |
| 40 B. | DCM/MeOH | 9:1 |
| C. | DCM/MeOH | 8:2 |
| D. | DCM/MeOH/50% HOAc | 40:10:5 |
| E. | DCM/MeOH/50% HOAc | 35:15:5 |

45

65

Where separations by column chromatography are mentioned, these were separations on silica gel using the abovementioned mobile phases.

- 5 Reversed phase HPLC separations were carried out with acetonitrile/water and HOAc buffer.

The starting compounds can be prepared by the following methods:

- 10 A wide variety of possibilities is available in the literature for the general and specific synthesis of amino acids. A summary thereof is provided, inter alia, by Houben-Weyl, volume E16d/part 1, pages 406 et seq.
- 15 Frequently used precursors were benzophenone imine acetic acid ethyl ester, diethyl acetamidomalonate and ethyl isonitrileacetate.

- Various glycine and alanine derivatives were prepared, for example, starting from ethyl isonitrileacetate and an appropriate ketone or aldehyde (see H.-J. Prätorius, J. Flossdorf, M.-R. Kula Chem. Ber. 108 (1975) 3079).
- 20

- Boc-Cyclooctylglycine, Boc-2-norbonylglycine [sic], Boc-adamantylalanine, Boc- γ -methylcyclohexylalanine and Boc-(4-Me)cyclohexylglycine were synthesized via the corresponding ethyl 2-formylaminoacrylates (U. Schöllkopf and R. Meyer, Liebigs Ann. Chem. (1977) 1174) starting from ethyl isocyanoacetate with the respective carbonyl compounds cyclooctanone, 2-norbornanone, 1-formyladamantane, 1-formyl-1-methylcyclohexane, and 4-methylcyclohexanone by the following general methods:
- 25
- 30

35

40

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General method for synthesizing the ethyl 2-formylaminoacrylates

A solution of 100 mmol of ethyl isocyanoacetate in 50 ml of THF
5 is added dropwise to 100 mmol of potassium tert-butoxide in
150 ml of THF at 0 to -10°C . After 15 min, 100 mmol of the ap-
propriate carbonyl compound in 50 ml of THF is added at the same
temperature, the reaction mixture is slowly allowed to rise to RT
and the solvent is stripped off in a rotary evaporator. The resi-
10 due is mixed with 50 ml of water, 100 ml of acetic acid and
100 ml of DCM and the product is extracted with DCM. The DCM
phase is dried over Na_2SO_4 , and the solvent is stripped off in a
rotary evaporator. The resulting products are almost pure and
can, if required, be further purified by column chromatography on
15 silica gel (mobile phase: ethyl/petroleum ether mixtures).

General method for amino acid hydrochlorides starting from the ethyl 2-formylaminoacrylates

20 100 mmol of ethyl 2-formylaminoacrylates are hydrogenated with
Pd/C (10 %)/hydrogen in 200 ml of glacial acetic acid until con-
version is complete. The catalyst is then filtered off, the
acetic acid is stripped off as far as possible in a rotary evap-
orator, and the residue is refluxed in 200 ml of 50 % concen-
25 trated hydrochloric acid for 5 h. The hydrochloric acid is
stripped off in a rotary evaporator, and the product is dried at
 50°C under reduced pressure and washed several times with ether.
The hydrochlorides result as slightly colored crystals.

30 25.0 g of cyclooctylglycine hydrochloride were obtained starting
from 18.9 g (150 mmol) of cyclooctanone. 26.6 g of 2-norbornylgly-
cine [sic] hydrochloride were obtained starting from 16.5 g
(150 mmol) of 2-norbornanone. 26.0 g of adamantylalanine hydro-
chloride were obtained starting from 19.7 g (120 mmol) of
35 1-formyladamantane. 16.6 g of γ -methylcyclohexylalanine hydro-
chloride were obtained starting from 12.6 g (100 mmol) of
1-formyl-1-methylcyclohexane. 25.9 g of 4-methylcyclohexylglycine
hydrochloride were obtained starting from 16.8 g (150 mmol) of
4-methylcyclohexanone.

40

The amino acid hydrochlorides were converted by conventional pro-
cesses using di-tert-butyl dicarbonate in water/dioxane into the
Boc-protected form in each case and subsequently recrystallized
from ethyl acetate/hexane mixtures or purified by column chroma-
45 tography on silica gel (mobile phase: ethyl acetate/petroleum
ether mixtures).

N-tert-Butyloxycarbonyl-(D)- α -methyl-cyclohexylalanine

3.4 g (12.2 mmol) of Boc-(D)- α -methyl-Phe-OH were hydrogenated in 100 ml of MeOH at 50°C in the presence of 250 mg of 5 % Rh on Al_2O_3 under 10 bar of hydrogen for 24 h. Filtration and stripping-off of the solvent resulted in 2.8 g of Boc-(D)- α -Methyl-Cha-OH.

$^1\text{H-NMR}$ (DMSO-d_6 , δ in ppm): 12 (very broad signal, COOH); 1.7-0.8 (25 H; 1.35 (s, Boc), 1.30 (s, Me))

10

Preparation of Boc-trimethylsilylalanine

The preparation took place both in optically active form as described by B. Weidmann, *Chimica* **46** (1992) 312 and in racemic form from N-(diphenylmethylene)glycine ethyl ester and trimethylsilylmethyl iodide.

N-tert-Butyloxy-(D,L)-trimethylsilylalanine

5.67 g (21.2 mol) of N-(diphenylmethylene)glycine ethyl ester in 35 ml of THF were deprotonated with a THF solution of LDA under standard conditions. To this were added dropwise at -70°C 5.0 g (23.4 mmol) of trimethylsilyl methyl iodide in 10 ml of THF, and the reaction mixture was allowed to rise slowly to RT. Workup resulted in 7.2 g of N-(diphenylmethylene)trimethylsilylalanine ethyl ester, which was cleaved with 0.5 N HCl without further purification. The resulting hydrochloride was converted with NaHCO_3 solution into 3.4 g of trimethylsilylalanine ethyl ester and converted under conventional conditions with di-tert-butyl dicarbonate into the Boc-protected compound almost quantitatively. The ethyl ester was hydrolyzed with dilute sodium hydroxide solution in methanol, the resulting salt was protonated with dilute hydrochloric acid, and the product was extracted with ethyl acetate/ether 1:1. 4.0 g of Boc-trimethylsilylalanine were obtained.

$^1\text{H-NMR}$ (DMSO-d_6 , δ in ppm): ~12 (very broad signal, COOH); 7.00 (d, 1H, NH), 1.35 (s, 9H, 3 CH_3), 0.95 (d, 2H, CH_2).

Boc-N-Cyclopropylglycine was prepared from N-cyclopropylglycine ethyl ester, ethyl bromoacetate and cyclopropylamine (similar to J.W. Skiles et al., *J. Med. Chem.* **35** (1992) 641) and then converted under standard conditions into the Boc-protected form, then hydrolyzed with MeOH/2N NaOH and finally acidified with 1N HCl.

Boc-Suberylglycine was synthesized in a similar way to the literature method (O.P. Goel et al. *Tetrahedron Lett.* 34 (1993) 953).

- 5 Adamantylglycine can also be prepared by the method of Y.N. Belokon et al. *Zhu. Org. Khi*, 21, (1985) 1327.

Boc-(3-Ph)-Pro-OH was synthesized by a method similar to that of J.Y.L. Chung et al. (*J.Org.Chem.* 55 (1990) 270).

10

Preparation of Boc-1-tetralinylglycine

- Boc-1-Tetralinylglycine was prepared starting from 1,2-dihydronaphthalene, which was initially converted with HBr into 1-tetralyl bromide (similar to *J. Med. Chem.* 37 (1994) 1586). The bromide was then reacted with diethyl acetamidomalonate, and the α -amino acid obtained after hydrolytic cleavage was converted under standard conditions into the Boc-protected form. Another possible preparation is described by E. Reimann and D. Voss (*Arch. Pharm* 310, (1977) 102).

20

Preparation of Boc-cycloleucine

Boc-Cycloleucine was prepared by the method of E.C. Jorgensen (*J. Med. Chem.* 14 (1971) 904).

- 25 Preparation of Boc-1-(D,L)-Tic-OH

Boc-1-(D,L)-Tic-OH was prepared by a method of R. T. Shuman et al. (*J. Med. Chem.* 36 (1993) 314).

Preparation of Boc-(D,L)-Dch-OH

- 30 Boc-(D,L)-Dpa-OH (1 mmol) was hydrogenated in 12 ml of MeOH together with catalytic amounts of 5 % Rh/Al₂O₃ under 5 bar. Filtration and removal of the solvent under reduced pressure resulted in the product in quantitative yield.

- 35 Preparation of 4-isopropylcyclohexylglycine and 3,3-dimethylcyclohexylglycine

- These amino acids were prepared by reacting the ketones 4-isopropylcyclohexyl ketone [sic] and 3,3-dimethylcyclohexyl ketone [sic] with ethyl isonitrileacetate by a method of H.-J. Prätorius, J. Flossdorf and M. Kula (*Chem. Ber.* 108 (19..) 3079).

- 45 Boc-(D,L)-(3,4,5-(MeO)₃)Phe-OH was prepared by alkylation of benzophenone imine glycine ethyl ester with trimethoxybenzyl chloride, followed by introduction of the Boc protective group and ester hydrolysis.

Preparation of Boc-D,L-Chea-OH

4.0 g of cycloheptylmethyl methanesulfonate (19.39 mmol), prepared from cycloheptylmethanol and methanesulfonyl chloride, were
5 refluxed together with 4.9 g of benzophenone imine glycine ethyl ester (18.47 mmol), 8.9 g of dry, finely powdered potassium carbonate (64.65 mmol) and 1 g of tetrabutylammonium bromide (3 mmol) in 50 ml of dry acetonitrile under an inert gas atmosphere for 10 h. The potassium carbonate was then filtered off,
10 the filtrate was evaporated to dryness, and the crude product was immediately hydrolyzed with 20 ml of 2N hydrochloric acid in 40 ml of ethanol by stirring at RT for 1.5 h. The reaction solution was diluted and then benzophenone was extracted with ethyl acetate in the acid range, and subsequently H-D,L-Chea-OEt was
15 extracted with DCM in the alkaline range (pH = 9), and the solution was dried over magnesium sulfate and evaporated in a rotary evaporator. Yield: 3.7 g $\hat{=}$ 95 % of theory.

The conversion to Boc-D,L-Chea-OH took place in a conventional
20 way via Boc-D,L-Chea-OC₂H₅ and subsequent ester hydrolysis.

Preparation of (tetrahydro-4-yl) glycine [sic]

(a) 5-(4-Tetrahydropyranyl)hydantoin
25

90 g (0.774 mol) of 4-formyltetrahydropyran were added dropwise to a solution of 84.6 g (0.813 mol) of sodium bisulfite in 250 ml of water. The mixture was then diluted with 500 ml of ethanol and, at 20°C, 300 g of ammonium carbonate and
30 100 g of potassium cyanide were added. The reaction mixture was stirred at 50°C for 5 h and at RT overnight.

For workup, the ethanol was stripped off under reduced pressure. The product was deposited in the form of colorless
35 crystals after acidification of the aqueous phase with conc. hydrochloric acid. 141 g of the hydantoin were obtained.

(b) (4-Tetrahydropyranyl)glycine

40 10 g (54.3 mmol) of the hydantoin prepared above were heated with 25.7 g (81.5 mmol) of barium hydroxide in 130 ml of water under autogenous pressure in an autoclave at 165°C for 5 h. The resulting suspension was neutralized with dry ice at 50°C. After cooling to 20°C, the mixture was acidified with
45 conc. sulfuric acid, and the barium sulfate precipitate was filtered off. The aqueous solution was neutralized with ammo-

nia and left to stand for crystallization. 5.3 g of (4-tetrahydropyranyl)glycine were obtained.

(c) Boc-(4-Tetrahydropyranyl)glycine

5

3.20 g (20.1 mmol) of (4-tetrahydropyranyl)glycine were Boc-protected with 4.39 g (20.1 mmol) of di-tert-butyl dicarbonate by a conventional process. Workup resulted in 4.8 g of Boc-(4-tetrahydropyranyl)glycine.

10

¹H-NMR (DMSO-d₆, δ in ppm)
- 12.5 (broad signal, 1H, COOH), 7.05 (d, 1H, NH), 3.9-3.7 (3H, CH and 1H from each of 2CH₂), 3.3-3.1 (2H, 1H from each of 2CH₂), 1.85 (m, 1H, CH), 1.5-1.2 (13H, 2CH₂ and Boc)

15 N-tert-Butyloxycarbonyl-(D,L)-(4-tetrahydropyranyl)alanine

4-Bromomethyltetrahydropyran, which was prepared by reacting 4-hydroxymethyltetrahydropyran (see DE 92 42 33 430) with PBr₃, and diethyl acetamidomalonate, previously deprotonated with NaH
20 in DMF, were converted into diethyl acetamido(4-tetrahydropyranylmethyl)malonate, and the esters and the acetyl group were then hydrolyzed, with simultaneous decarboxylation, with 6N HCl and glacial acetic acid at 100°C to give (4-tetrahydropyranyl)alanine hydrochloride.

25

The amino group was protected with a Boc group by a process known from the literature. The crude product was taken up in ethyl acetate, extracted with 0.5N NaOH, the aqueous phase was acidified with 1N HCl, and the product was extracted with DCM. After
30 drying over Na₂SO₄, the solvent was completely stripped off. Pure N-tert-butyloxycarbonyl-(D,L)-(4-tetrahydropyranyl)alanine was obtained.

¹H-NMR (DMSO-d₆, δ in ppm): - 12.5 (broad signal, 1H, COOH), 7.10
35 (d, 1H, NH), 3.95 (m, 1H), 3.80 (m, 2H, 1H from each of 2 CH₂ groups), 3.20 (m, 2H, 1H from each of 2 CH₂ groups), 1.75 - 1.0 (16H, 3 x CH₂, CH and Boc).

Hydroxyacetic acid derivatives were prepared either by methods
40 similar to that of S. Bajusz (WO 93/18060) or starting from corresponding methyl acetate derivatives by α-hydroxylation using Davis' reagent (F.A. Davis, L.C. Vishwakarma, J.M. Billmers J.Org.Chem. 49 (1984) 3241).

45 The H₂N-C(R¹R²)-D' building blocks were prepared in the following way:

1. Preparation of 3-(6-cyano)picolylamine:

(a) 3-(6-Cyano)picolyl azide

5 14.5 g (0.07 mol) of TFAA dissolved in 20 ml of DCM were added dropwise to a solution of 8.8 g (0.07 mol) of 3-(6-cyano)picolyl alcohol and 6.9 g of TEA in 200 ml of DCM at RT and the mixture was then stirred for 2 h. The residue after removal of the DCM by distillation was dissolved in a mixture of toluene and 50 ml of DMSO, 11.2 g (0.17 mol) of NaN₃ and 0.7 g of TBAB were added, and the mixture was stirred at RT overnight.

15 The reaction mixture was poured into 300 ml of water and extracted several times with ether. After drying with Na₂SO₄ and removal of the solvent under reduced pressure, 6.8 g of yellowish crystals remained and were used without further purification in the next reaction.

20 (b) 3-(6-Cyano)picolylamine

The compound obtained in (a) was dissolved in 45 ml of THF and 1.2 ml of water and, while stirring, 11.2 g of triphenylphosphine were added in portions. The reaction mixture was left to stand at RT overnight.

After removal of the solvent by distillation, the residue was taken up in 100 ml of ether, the precipitated triphenyl [sic] oxide was filtered off with suction, and the filtrate was adjusted to pH 2 with ethereal hydrochloric acid. The precipitated hydrochloride was filtered off with suction, washed with ether and digested successively with toluene and hot isopropanol. 4.7 g of hydrochloride were isolated, melting point 253-256°C (decomposition).

35 2. Preparation of 5-aminomethyl-2-cyanopyrimidine:

(a) 2-Thiomethyl-5-hydroxycarbonylpyrimidine [sic]

40 1 Eq. of 2-methylthio-5-hydroxycarbonylpyrimidine [sic] were dissolved in dioxane and, after addition of 2 eq. of 2N LiOH, stirred overnight. The solvent was then removed under reduced pressure, and the residue was dissolved in EtOH. After addition of a stoichiometric amount of ethereal HCl, the solution was again evaporated to

45

dryness. Water which was still present was removed by azeotropic drying with toluene once.

(b) 2-Thiomethyl-5-hydroxymethylpyrimidine [sic]

5

The acid obtained in 2.(a) was reduced to the alcohol by a method of A.I. Meyers et al. (Org.Synth. Coll. Vol. VII, 530). Yield: 40%.

FAB-MS (M^+) = 156

10

(c) 2-Thiomethyl-5-aminomethylpyrimidine [sic]

The resulting alcohol was converted into the amine and isolated as hydrochloride as described above.

15

Yield: 30%. FAB-MS (M^+) = 155

(d) N-Boc-5-aminomethyl-2-thiomethylpyrimidine [sic]

20

5-Aminomethyl-2-thiomethylpyrimidine [sic] hydrochloride was protected with a Boc group under standard conditions (see M. Bodanszky, A. Bodanszky "The Practice of Peptide Synthesis", 2nd edition, Springer Verlag Heidelberg, 1994). Yield: 73%. FAB-MS (M^+) = 255

25

(e) N-Boc-5-aminomethyl-2-methylsulfonylpyrimidine

30

1 Eq. of N-Boc-5-aminomethyl-2-thiomethylpyrimidine [sic] was introduced into acetic acid at 70-80°C. Then 2.5 eq. of H_2O_2 (50% strength) were slowly added dropwise. After conversion of the precursor was complete, the reaction mixture was concentrated to one third of the volume and poured into water. The precipitated solid was filtered off and dried in a desiccator over phosphorus pentoxide. Yield: 37%. FAB-MS (M^+) = 283

35

(f) N-Boc-5-aminomethyl-2-cyanopyrimidine

40

1 Eq. of N-Boc-5-aminomethyl-2-methylsulfonylpyrimidine was dissolved in DMF and introduced into a reflux apparatus. After addition of 2 eq. of KCN and catalytic amounts of 18-crown-6, the reaction mixture was stirred at 60°C for 4 h. The suspension was then concentrated and poured into 200 ml of water. The precipitated solid was filtered off with suction and dissolved in ethyl acetate. The solution was washed with water and saturated NaCl solution, dried and evaporated in a rotary evaporator. N-Boc-5-aminomethyl-2-cyanopyrimidine was used as crude

45

product without further purification in the next reaction. Yield: 46%.

(g) 5-Aminomethyl-2-cyanopyrimidine hydrochloride

5

1 Eq. of N-Boc-5-aminomethyl-2-cyanopyrimidine was introduced into dioxane at RT and, after addition of dioxane/HCl (5M), stirred at RT for 3 h. After conversion of the precursor was complete (TLC check: mobile phase A), the reaction mixture was concentrated and poured into ether. The precipitated solid was filtered off with suction, again dissolved in MeOH and poured into ether. The product was filtered off with suction and dried under high vacuum to afford 89% of the theoretical yield of 5-aminomethyl-2-cyanopyrimidine hydrochloride. FAB-MS (M^+) = 134

3. Preparation of 4-aminomethyl-3-methoxybenzonitrile

20 (a) 3-Nitro-4-methylbenzonitrile

399 g (2.56 mol) of p-toluenitrile were added over the course of 90 minutes to 1 l of fuming nitric acid at -10°C . 1 h after the addition, the mixture was poured onto 2.5 l of ice/ H_2O , whereupon a solid precipitated and was removed on a suction filter funnel and washed to neutral pH with water. The yield of the product was 363 g (88 %). $^1\text{H-NMR}$ (CDCl_3 ; δ in ppm): 8.3 (d, 1H); 7.8 (dd, 1H); 7.5 (dd, 1H); 2.7 (s, 3H)

(b) 3-Amino-4-methylbenzonitrile:

120 g of 3-nitro-4-methylbenzonitrile were suspended in 1.2 l of EtOH and hydrogenated with 50 l of hydrogen at RT in the presence of 7 g of Pd/C (10 %). After removal of the catalyst on Celite, the solvent was stripped off to result in 95 g of pure product (97 %). $^1\text{H-NMR}$ (DMSO-d_6 ; δ in ppm): 7.1 (dd, 1H); 6.90 (d, 1H); 6.85 (dd, 1H); 5.35 (s, 2H, NH_2); 2.15 (s, 3H)

(c) 3-Hydroxy-4-methylbenzonitrile:

A solution of 49.2 g (0.72 mol) of NaNO_2 in 217 ml of water was added dropwise over the course of 30 min to 85 g (0.72 mol) of 3-amino-4-methylbenzonitrile in 1.8 l of 6N HCl at $0-5^\circ\text{C}$. The mixture was then stirred at $0-5^\circ\text{C}$ for a further 30 min and then at the boiling point for 1 h. After the solution had cooled it was possible to extract the product with ethyl acetate and, from this, the phenolate with ice-cold 5N NaOH. The aqueous phase was then acidified to pH 3 with 6N HCl and the product was extracted with ethyl acetate. 41 g (43 %) of the phenol were obtained. $^1\text{H-NMR}$ (DMSO-d_6 ; δ in

ppm): 10.3 (s, OH); 7.25 (dd, 1H); 7.15 (d, 1H); 7.1 (dd, 1H); 2.20 (s, 3H)

- (d) 3-Methoxy-4-methylbenzonitrile:
- 5 15 g (0.11 mol) of 3-hydroxy-4-methylbenzonitrile dissolved in 30 ml of DMF were added dropwise to a suspension of 0.11 mol of NaH and 30 ml of DMF, and the mixture was stirred until no further H₂ evolution was observed. Then 10.6 ml (0.17 mol) of methyl iodide were added dropwise, and the mixture was stirred at RT for 1 h. The solution was poured into ice-water, and the product was extracted with ether/ethyl acetate 7:1. After the solvent had been stripped off, the product began slowly to crystallize. 14.8 g (89 %) of the product were obtained. ¹H-NMR (CDCl₃; δ in ppm): 7.2 (m, 2H); 7.02 (s, 1H); 3.85 (s, 3H); 2.25 (s, 3H)
- (e) 4-Bromomethyl-3-methoxybenzonitrile:
- 20 14.7 g (0.1 mol) of 3-methoxy-4-methylbenzonitrile were dissolved in 210 ml of 1,2-dichloroethane, bromination was carried out at 82°C in the presence of catalytic amounts of AIBN with 19.1 g (0.11 mol) of NBS in portions over the course of 1 h and, after the addition was complete, the mixture was stirred at 82°C for a further 30 min. Addition of n-heptane was followed by removal of precipitated succinimide, and the solvent was stripped off. The product contained, besides small amounts of precursor, also traces of the corresponding benzal bromide. ¹H-NMR (DMSO-d₆; δ in ppm): 7.60 (dd, 1H); 7.50 (d, 1H); 7.40 (dd, 1H); 4.68 (s, 2H); 3.96 (s, 3H)
- 30 (f) 4-Phthalimidomethyl-3-methoxybenzonitrile:
- 24.4 g (108 mol) of 4-bromomethyl-3-methoxybenzonitrile dissolved in 125 ml of DMF and 20.0 g of potassium phthalimide were stirred at RT for 24 h and then at 50°C for 1 h. The mixture was poured into water, whereupon the product precipitated as solid. 21.5 g (68 %) of the product were obtained. ¹H-NMR (DMSO-d₆; δ in ppm): 7.9 (m, 4H); 7.5 (d, 1H); 7.35-7.25 (m, 2H); 7.78 (s, 2H); 3.92 (s, 3H)
- (g) 4-Aminomethyl-3-methoxybenzonitrile:
- 40 10.6 ml of hydrazine hydrate were added to 21.2 g (73 mmol) of 4-phthalimidomethyl-3-methoxybenzonitrile dissolved in 290 ml of THF, and the mixture was stirred at RT for 20 h. Then 180 ml of 2N HCl were added dropwise and, after 1.5 h, the solvent was completely stripped off. The residue was taken up in MTBE, extracted with 1N HCl, adjusted to pH 9-10 with 2N NaOH and extracted with DCM. 8.0 g (68 %) of the product were obtained. ¹H-NMR (DMSO-d₆; δ in ppm): 7.55 (dd,

75

1H); 7.40 (dd, 1H); 7.37 (d, 1H); 3.85 (s, 3H); 3.70 (s, 2H); 2.5-1.6 (NH₂).

4. Preparation of 4-aminomethyl-3-ethoxybenzonitrile:

5

(a) 3-Ethoxy-4-methylbenzonitrile

10 g (75 mmol) of 4-methyl-3-hydroxybenzonitrile were deprotonated with 1 eq. of NaH in 100 ml of DMF and then ethylated on the oxygen with 112 mmol of iodoethane. 8.8 g of product were obtained.

¹H-NMR (DMSO-d₆, δ in ppm): 7.4 - 7.25 (3H), 4.10 (q, 2H), 2.22 (s, 3H), 1.35 (t, 3H)

15

(b) 4-Bromomethyl-3-ethoxybenzonitrile

Preparation took place as in Example 3.(e) with NBS. ¹H-NMR (DMSO-d₆, δ in ppm): 7.59 (1H), 7.50 (1H), 7.40 (1H), 4.65 (s, 2H), 4.20 (q, 2H), 1.35 (t, 3H)

20

(c) 4-Aminomethyl-3-ethoxybenzonitrile hydrochloride

25 Synthesis took place via the stage of the corresponding phthalimide as in Example 3.(f) and to give the hydrochloride product by cleavage with hydrazine and treatment with HCl as in Example 3.(g). Starting from 10 g of precursor (a), 5.1 g of the product were obtained.

¹H-NMR (DMSO-d₆, δ in ppm): 8.5 (broad signal, NH₃⁺), 7.65 - 7.45 (3H), 4.18 (q, 2H), 4.05 (s, 2H), 1.38 (t, 3H).

30

5. Preparation of 4-aminomethyl-3-benzyloxybenzonitrile:

35

(a) 3-Benzyloxy-4-hydroxymethylbenzonitrile

33.1 g of 4-formyl-3-hydroxybenzonitrile (Liebigs Ann. Chem. (1982) 1836) were O-benzylated with 1 eq. each of benzyl bromide and K₂CO₃ and, after workup, reduced with NaBH₄ in 100 ml of MeOH/THF 2:3 at -10°C to 0°C to give the alcohol. 22.4 g were obtained. The product could be crystallized from DCM/petroleum ether.

40

¹H-NMR (CDCl₃ [sic], δ in ppm): 7.48 (1H), 7.40 - 7.3 (5H), 7.20 (1H), 7.08 (1H), 5.05 (s, 2H), 4.75 (s, 2H), 2.85 (1H, OH)

45

(b) 3-Benzyloxy-4-bromomethylbenzonitrile:

76

4.3 g (18 mmol) of the alcohol (a) underwent substitution in 40 ml of THF with 7.9 g (24 mmol) of CBr₄ and 6.3 g (24 mmol) of PPh₃, which was added in portions over the course of 30 min. The reaction mixture was stirred at RT for 20 h. The product was purified by column chromatography (mobile phase: t-butyl methyl ether/petroleum ether 2:1). 4.6 g were obtained.

¹H-NMR (DMSO-d₆, δ in ppm): 7.70 - 7.25 (8H), 5.30 (s, 2H), 4.70 (s, 2H)

10

(c) 4-Aminomethyl-3-benzyloxybenzonitrile

Synthesis took place via the stage of the corresponding phthalimide as in Example 3.(f). The hydrazine cleavage was carried out as in Example 3.(g). The free amine was generated at pH 9-10 from the initially produced hydrochloride and was extracted from the aqueous solution with ether.

¹H-NMR (DMSO-d₆, δ in ppm): 7.65 - 7.25 (8H), 5.20 (s, 2H), 3.80 (s, 2H), ca. 3.0 (broad signal, NH₂)

20

6. Preparation of 4-aminomethyl-3-iodobenzonitrile:

(a) 3-Iodo-4-methylbenzonitrile

25

25.3 g (0.15 mol) of 3-amino-4-methylbenzonitrile hydrochloride (Example 3.(b)) were converted in a Sandmeyer reaction into 22.1 g of product.

¹H-NMR (DMSO-d₆, δ in ppm): 8.30 (1H), 7.78 (1H), 7.50 (1H), 2.45 (3H)

30

(b) 4-Bromomethyl-3-iodobenzonitrile

Preparation took place as in Example 3.(e) with NBS.

¹H-NMR (DMSO-d₆, δ in ppm): 8.38 (1H), 7.89 (1H), 7.77 (1H), 4.78 (2H)

35

(c) 4-Aminomethyl-3-iodobenzonitrile hydrochloride

12.1 g (37.6 mmol) of 4-bromomethyl-3-iodobenzonitrile in 200 ml of MeOH/THF 1:1 were slowly added dropwise to 200 ml of conc. ammonia solution/MeOH (saturated with NH₃) 1:1, simultaneously passing NH₃ into the reaction mixture. The temperature was maintained at 50°C. After 4 h, the solvent was stripped off, and the product was taken up in DCM, dried and precipitated with ethereal HCl. 8.6 g of 4-aminomethyl-3-iodobenzonitrile hydro-

40

45

chloride were obtained.

$^1\text{H-NMR}$ (DMSO-d_6 , δ in ppm): 8.8 (broad signal, NH_3^+), 8.43 (1H), 7.98 (1H), 7.70 (1H), 4.13 (2H)

5 7. Preparation of 4-aminomethyl-2-methoxybenzonitrile:

(a) 2-Methoxy-4-methylbenzonitrile

10 10.7 g (78.6 mmol) of 4-methylsalicylaldehyde (J.C.S. Perkin I (1980) 1862) were methylated with 5.8 ml of MeI in the presence of 13 g of K_2CO_3 in 40 ml of DMF. The reaction mixture was poured into ice-water, and the product (11.5 g) was extracted with ether. The aldehyde was converted into the nitrile by a method similar to that in

15 Synthesis (1978) 11.

$^1\text{H-NMR}$ (DMSO-d_6 , δ in ppm): 7.60 (d, 1H), 7.05 (s, 1H), 6.90 (d, 1H), 3.90 (s, 3H), 2.40 (s, 3H)

(b) 4-Bromomethyl-2-methoxybenzonitrile

20 4.6 g (31.3 mmol) of 4-methyl-2-methoxybenzonitrile were brominated with 34.7 mmol of N-bromosuccinimide in the presence of catalytic amounts of azobisisobutyronitrile in 60 ml of 1,2-dichloroethane under reflux. 2.5 g of the

25 product were obtained.

$^1\text{H-NMR}$ (DMSO-d_6 , δ in ppm): 7.75 (d, 1H), 7.35 (s, broad, 1H), 7.15 (d, broad, 1H), 4.73 (s, 2H), 3.95 (s, 3H)

(c) 4-Aminomethyl-2-methoxybenzonitrile

30 2.5 g of the bromide (b) were introduced into 10 ml of MeOH, and NH_3 was passed in during dropwise addition of 38 ml of conc. ammonia/MeOH 1:1. After 2 h, the solvent was stripped off, the product was taken up in DCM and

35 washed with water, and the organic phase was dried over Na_2SO_4 . The product was precipitated as hydrochloride with ethereal HCl.

$^1\text{H-NMR}$ (DMSO-d_6 , δ in ppm): 8.6 (broad signal, NH_3^+), 7.79 (1H), 7.55 (1H), 7.20 (1H), 4.10 (s, 2H), 3.93 (s, 3H)

40

8. Preparation of 4-aminomethyl-2-benzyloxybenzonitrile:

(a) 2-Benzyloxy-4-hydroxymethylbenzonitrile

45 41 ml (41 mmol) of a 1 molar BBr_3 solution in DCM were added dropwise to 5.5 g (37.4 mmol) of 2-methoxy-4-methylbenzonitrile (Example 7(a)) in 100 ml

of DCM at 0°C, and the mixture was stirred at 0°C for 1 h and at RT for a further 2 days. The mixture was poured into 10 % strength ammonia solution, and the 2-hydroxy-4-methylbenzonitrile was extracted with DCM. The formyl group was generated from the methyl group by the method in Liebigs Ann. Chem. (1982) 1836, and the 4-formyl-2-hydroxybenzonitrile was converted into 2.1 g of 2-benzyloxy-4-hydroxymethylbenzonitrile as in Example 5.(a).

10 (b) 4-Aminomethyl-2-benzyloxybenzonitrile

2.1 g (8.8 mmol) of the benzyl alcohol (a) were converted as in Example 5.(b) with CBr₄ and PPh₃ into 2.2 g of 2-benzyloxy-4-bromomethylbenzonitrile. The benzylamine was synthesized as in Example 3.(f) and 3.(g) via the stage of the phthalimide to give 4-aminomethyl-2-benzyloxybenzonitrile.

9. Preparation of 4-aminomethyl-2-chlorobenzonitrile:

11.75 g (77.2 mmol) of 4-methyl-2-nitroaniline underwent a Sandmeyer reaction in a conventional process by diazotization and substitution with NaCN and CuSO₄ to give 9.6 g of crude 4-methyl-2-nitrobenzonitrile.

¹H-NMR (DMSO-d₆, δ in ppm): 8.25 (1H), 8.05 (1H), 7.80 (1H), 2.50 (3H)

The nitro group was hydrogenated as in Example 3.(b), and the resulting 2-amino-4-methylbenzonitrile was subjected to another Sandmeyer reaction to give 2-chloro-4-methylbenzonitrile. The subsequent reactions to give 4-bromomethyl-2-chlorobenzonitrile, 2-chloro-4-phthalimidomethylbenzonitrile and finally 4-aminomethyl-2-chlorobenzonitrile took place as in Examples 3.(e), 3.(f) and 3.(g).

10. Preparation of 6-carboxamido-3-picolylamine [sic] dihydrochloride:

67 g (0.46 mol) of 5-cyanopyridine-2-carboxamide (Chem. Ber. 117 (1984) 1259) were suspended in 1 l aqueous methanol (1/1) and 84.7 ml (1.9 equivs.) of conc. HCl, 21.4 g of 10 % strength Pd/C were added and hydrogenation was carried out in a shaken vessel at room temperature for 5 h (H₂ uptake: 23.2 l; theory: 22.3 l). The product dissolves [sic] during the hydrogenation (and the catalyst changed from gray to

black). TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1, NH_3 -saturated) revealed only traces of starting material.

5 The catalyst was filtered off with suction and washed with water, and the filtrate is distilled off under reduced pressure, finally with the addition of toluene and ethanol.

10 The moist residue was briefly refluxed in about 400 ml of MeOH , after cooling and stirring in an ice bath for about 30 minutes, filtered off with suction and washed with methyl t-butyl ether.

15 78 g (76.5 %) of dihydrochloride were isolated as white crystals, melting point $> 260^\circ\text{C}$.

Example 1

3-Phenyl-(D)-lactylproline (p-amidino)benzylamide acetate:

20 (a) 3-Phenyl-(D)-lactylproline p-cyanobenzylamide:

5.5 g (20.4 mmol) of O-tetrahydropyranyl-3-phenyl-(D)-lactic acid (WO 93/18060) were dissolved in 30 ml of DMF, and 5.4 g (20.4 mmol), N-(p-cyanobenzyl)prolinamide, 3.3 g (20.4 mmol) of N-hydroxybenzotriazole, 3.0 g of DIPEA and 4.33 g (20.6 mmol) of dicyclohexylcarbodiimide were successively added. The mixture was stirred at RT for 48 h. The precipitated urea was filtered off with suction and then the solvent was substantially removed under reduced pressure, 50 ml of water were added to the residue, and extraction was carried out with ethyl acetate. After washing with water and NaHCO_3 solution and drying over Na_2SO_4 , the ethyl acetate was distilled off, and the remaining oily residue was dissolved in methanol and adjusted to pH 2 with p-toluenesulfonic acid. This solution was left to stand at RT for 6 h. The methanol was then distilled off, the residue was taken up in ethyl acetate, and the solution was washed with water, 5 % strength citric acid and NaHCO_3 solution. The residue obtained after drying over Na_2SO_4 and removal of the solvent by distillation was purified by column chromatography (eluent: methylene chloride/acetone/methanol, 45/5/2). 2.5 g of white crystals were obtained, and these melted at $108\text{--}110^\circ\text{C}$ after crystallization from an ether/hexane mixture.

45 (b) 3-Phenyl-(D)-lactylproline (p-amidino)benzylamide acetate:

2.0 g of the above compound and 3 ml of triethylamine were dissolved in 30 ml of pyridine, saturated with H₂S at 0°C and left to stand at RT overnight. A TLC check (CH₂Cl₂/MeOH, 9/1) showed that conversion to the thioamide was complete. For isolation, the pyridine was substantially removed by distillation under reduced pressure, and the residue was taken up in 250 ml of ethyl acetate and washed with brine, 5 % strength citric acid and NaHCO₃ solutions. Drying and removal of the solvent by distillation resulted in 2.3 g of amorphous thioamide.

The thioamide was dissolved in 40 ml of acetone and, after addition of 4 ml of methyl iodide, left to stand at RT for 6 h. The solvent was stripped off and then the amorphous residue was stirred with dry ether and subsequently dried. The methyl S-methylthioimidate hydroiodide was dissolved in 50 ml of ethanol, 15 ml of 10 % strength ammonium acetate solution were added and the mixture was heated at 60°C for 3 h. For isolation, the solvent was stripped off, the residue was dissolved in 100 ml of CH₂Cl₂, the insoluble constituents were filtered off and then the CH₂Cl₂ was distilled off. Digestion with an ethyl acetate/diethyl ether mixture removed the impurities soluble therein. The remaining mixed iodide/acetate salt was dissolved in acetone/water (3/2) and converted into the pure acetate using IRA acetate ion exchanger and subsequently purified by column chromatography (eluent: methylene chloride/methanol/50 % strength acetic acid 40/10/1.5). The pure fractions were freeze-dried after removal of the eluent. 1.1 g of white powder remained, melting point 185 - 187°C, FAB-MS: 394 (M+).

Example 2

(D)-2-Cyclohexyl-2-hydroxyacetylproline(6-amidino)-3-picolylamide:

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(a) (D)-2-Cyclohexyl-2-hydroxyacetylproline (6-cyano)-3-picolylamide:

2.25 g of isobutyl chloroformate were added dropwise to a solution of 4.4 g (13 mmol) of O-tetrahydropyranyl-(D)-2-cyclohexyl-2-hydroxyacetylproline (WO 93/18060) and 1.6 g of N-methylmorpholine in 25 ml of DMF at -15°C. After 10 min, a solution of 2.2 g (13 mmol) of 2-cyano-5-(aminomethyl)-pyridine hydrochloride (WO 95/35309) in 20 ml of DMF and 70 ml of CH₂Cl₂ and 3.5 g of triethylamine were added

dropwise, and the reaction mixture was then stirred for 1 h, during which the temperature rose from -15°C to 0°C.

5 Addition of 150 ml of water was followed by extraction several times with ethyl acetate, and the ethyl acetate phase was washed with water, 5 % strength NaHCO₃ and 5 % strength citric acid solutions and dried over Na₂SO₄, and the ethyl acetate was distilled off. The remaining oily residue was dissolved in methanol, adjusted to pH 2 with p-toluenesulfonic acid and left to stand at RT for 6 h.

15 The residue after removal of the methanol by distillation was taken up in ethyl acetate, washed with water, 5 % strength citric acid and NaHCO₃ solution and dried over Na₂SO₄. The residue obtained after removal of the solvent by distillation was purified by column chromatography (eluent: methylene chloride/acetone/methanol 45/5/2). 3.0 g (62 % of theory) of white amorphous powder were isolated; FAB-MS (M+H⁺): 371 .

20 (b) (D)-2-Cyclohexyl-2-hydroxyacetylproline (6-amidino)-3-picolylamide acetate:

25 The compound was prepared as in Example 1 from 2.55 g of (D)-2-cyclohexyl-2-hydroxyacetylproline (6-cyano)-3-picolylamide acetate. 0.99 g of (D)-2-cyclohexyl-2-hydroxyacetate-proline [sic] (6-amidino)-3-picolylamide hydroacetate was obtained as a white amorphous powder; FAB-MS (M+H⁺): 388

Example 3

30 (D)-2-Cyclohexyl-2-hydroxyacetylproline (p-amidino)benzylamide acetate:

(a) (D)-2-Cyclohexyl-2-hydroxyacetylproline (p-cyano)benzylamide:

35 4.9 g (20.4 mmol) of (D)-2-cyclohexyl-2-tetrahydropyranyloxyacetic acid (WO 93/18060) were dissolved in 30 ml of DMF, and 5.4 g (20.4 mmol) of N-(p-cyanobenzyl)prolinamide, 3.3 g (20.4 mmol) of N-hydroxybenzotriazole, 3.0 g of DIPEA and 4.33 g (20.6 mmol) of dicyclohexylcarbodiimide were
40 successively added. The mixture was stirred at RT for 48 h. The precipitated urea was filtered off with suction and then the solvent was substantially removed under reduced pressure, 50 ml of water were added to the residue, and extraction was carried out with ethyl acetate. After washing with water and
45 NaHCO₃ solution and drying over Na₂SO₄, the ethyl acetate was distilled off, and the remaining oily residue was dissolved in methanol and adjusted to pH 2 with p-toluenesulfonic acid.

This solution was left to stand at RT for 6 h. The methanol was then distilled off, the residue was taken up in ethyl acetate, and the solution was washed with water, 5 % strength citric acid and NaHCO₃ solution. The residue obtained after drying over Na₂SO₄ and removal of the solvent by distillation was purified by column chromatography (eluent: methylene chloride/acetone/methanol, 45/5/2). 2.5 g of white amorphous powder were obtained;
FAB-MS (M+H⁺): 370.

10

(b) (D)-2-Cyclohexyl-2-hydroxyacetylproline (p-amidino)-benzylamide acetate:

Amidine formation took place as in Example 1b. Freeze-drying resulted in white crystals of the acetate. Melting point 216-218°C; FAB-MS(M+H⁺): 387.

Example 4

(D)-2-Cyclohexyl-2-hydroxyacetylproline (2-methoxy-4-amidino)-benzylamide acetate:

was obtained as in Example 3 by reacting (D)-2-cyclohexyl-2-tetrahydropyranyloxyacetic acid with N-(4-cyano-2-methoxy-benzyl)prolinamide (WO 95/35309) as white amorphous powder;
FAB-MS (M+H⁺): 417.

Example 5

(D)-2-Cyclohexyl-2-hydroxyacetylazetidine-2-carboxylic acid 4-(amidino)benzylamide:

30

(a) Methyl

(D)-2-cyclohexyl-2-tetrahydropyranyloxyacetyl-azetidine-2-carboxylate:

2.0 ml (16.2 mmol) of pivaloyl chloride were added dropwise to a solution of 3.92 g (16.2 mmol) of (D)-2-cyclohexyl-2-tetrahydropyranyloxyacetic acid and 2.26 ml (16.2 mmol) of triethylamine in 25 ml of toluene and 5 ml of DMF while cooling in ice and, after stirring for 30 min, a mixture of 2.5 g (16.2 mmol) of methyl azetidine-2-carboxylate hydrochloride and 2.26 ml (16 mmol) of triethylamine in 25 ml of DMF was added dropwise. The mixture was stirred overnight, during which the temperature rose to RT, and was diluted with water and extracted several times with toluene. After the combined toluene phases had been washed with 5 % strength KHSO₄, 10 % strength Na₂CO₃ and sodium chloride solutions, the solvent was removed by distillation and the remaining

slightly faded [sic] oil was hydrolyzed without further purification.

- 5 (b) (D)-2-Cyclohexyl-2-tetrahydropyranyloxyacetylazetidine-2-carboxylic acid:

10 The methyl ester (stage a) was dissolved in 50 ml of THF, a solution of 5 g of LiOH in 50 ml of water was added, and the mixture was stirred at RT overnight. After removal of the THF by distillation, the aqueous phase was acidified with KHSO₄ solution and extracted several times with ethyl acetate. The combined ethyl acetate phases were washed with brine, dried over Na₂SO₄ and then evaporated to dryness. 4.1 g (78 % of theory) of white crystals were isolated; FAB-MS (M+H⁺): 326.

- 15 (c) (D)-2-Cyclohexyl-2-hydroxyacetylazetidine-2-carboxylic acid (p-cyano)benzylamide:

20 8.12 g of diisopropylethylamine, and then 11 ml (15 mmol) of propanephosphonic anhydride (50 % strength solution in ethyl acetate), were added dropwise to a suspension of 2.1 g (12.5 mmol) of p-cyanobenzylamine hydrochloride and 4.1 g (12.5 mmol) of the carboxylic acid isolated in stage (b) in 70 ml of CH₂CH₂ at -5°C. The mixture was stirred for 2 h, allowing the temperature to rise to 20°C. The organic phase was washed with water, 5 % strength NaHCO₃ and 5 % strength citric acid solutions, dried over Na₂SO₄ and evaporated to dryness.

30 The remaining oily residue was dissolved in methanol, adjusted to pH 2 with p-toluenesulfonic acid and left to stand at RT for 6 h. The methanol was then distilled off, and the residue was taken up in ethyl acetate and washed with water, 5 % strength citric acid and NaHCO₃ solutions. The residue obtained after drying over Na₂SO₄ and removal of the solvent by distillation was purified by column chromatography (eluent: methylene chloride/acetone/methanol 45/5/2. 3.7 g (82 %) of white amorphous powder were isolated; FAB-MS (M+H⁺): 357.

- 40 (d) (D)-2-Cyclohexyl-2-hydroxyacetylazetidine-2-carboxylic acid (p-amidino)benzylamide acetate:

45 Amidine formation took place as in Example 1b. Freeze-drying resulted in a white amorphous powder of the acetate; FAB-MS: (M+H⁺) 374.

Example 6

(D,L)-2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-hydroxyacetyl-proline
(6-amidino)-3-picolylamide:

5 (a) Methyl (1,2,3,4-tetrahydro-1-naphthyl)glycolate:

4.12 g (20 mmol) of 1,2,3,4-tetrahydro-1-naphthylglycolic
acid (Chem. Ber. 117 (1984) 332-325) were dissolved in 30 ml
of dry methanol, 4 drops of conc. H_2SO_4 were added and the
mixture was refluxed for 3 h. The methanol was distilled out
under reduced pressure at RT, and the residue was taken up in
 CH_2Cl_2 and washed with $NaHCO_3$ solution and water until
neutral. After drying over Na_2SO_2 [sic] and removal of the
solvent by distillation, the methyl ester was obtained as a
colorless oil in quantitative yield.

(b) O-Tetrahydropyranyl-(1,2,3,4-tetrahydro-1-naphthyl)glycolic
acid:

The above methyl ester was dissolved in 20 ml of CH_2Cl_2 and,
while stirring, 2 ml (22 mmol) of dihydropyran and 0.3 ml of
10 % strength hydrochloric acid solution in ethyl acetate
were added dropwise. After standing overnight, the mixture
was diluted with methylene chloride and washed with $NaHCO_3$
solution and water until neutral, and the solvent was removed
by distillation at RT.

The residue was dissolved in 40 ml of methanol, 20 ml of 1N
 $LiOH$ solution were added, the mixture was left to stand at RT
overnight and then the methanol was substantially removed by
distillation at RT. The slightly cloudy solution was ex-
tracted with CH_2Cl_2 , adjusted to pH 3 with 1M $KHSO_4$ solution
while cooling, and extracted several times with CH_2Cl_2 . The
combined CH_2Cl_2 extracts were washed with water, dried over
 Na_2SO_4 and distilled at RT. The oily residue was reacted im-
mediately in the next stage.

(c) N-(6-Cyano-3-picolyl)prolinamide:

25.3 g (0.15 mmol) of 2-cyano-5-(aminomethyl)pyridine hy-
drochloride ((WO 95/35309) were added to a solution of 32.5 g
(0.15 mol) of Boc-Pro-OH in 500 ml of CH_2Cl_2 . A clear solution
was obtained by adding 97 g (0.75 mol) of diisopropylethyl-
amine at $-5^\circ C$, and then 150 ml of a 50 % strength solution of
propanephosphonic anhydride in ethyl acetate were added drop-
wise. The mixture was stirred for 2 h, during which the tem-
perature rose to $20^\circ C$. The organic phase was washed with

water, 5 % strength NaHCO_3 and 5 % strength citric acid solutions, dried over Na_2SO_4 and evaporated to dryness. 40 g (81 %) of colorless oil remained.

5 36 g (0.11 mol) were dissolved in 400 ml of isopropanol and, at RT, a solution of 20 g of HCl in 150 ml of isopropanol was added. The solution was heated at 50°C for 5 h, during which a white precipitate separated out and this, after cooling, was filtered off with suction and washed until free of acid
10 with cold isopropanol and finally with diisopropyl ether. 19.8 g of hydrochloride were isolated, melting point $226-228^\circ\text{C}$ (decomposition); TLC: $\text{CH}_2\text{Cl}_2/\text{MeOH}/50$ % strength acetic acid, 85/15/2.

15 (d) The compounds of stages b and c were coupled as in Example 3a and converted into the amidine by method 1b. The acetate was obtained as a white amorphous powder; FAB-MS ($\text{M}+\text{H}^+$): 436.

20 Example 7

(D,L)-2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-hydroxyacetyl-proline (4-amidino)benzylamide:

The compound was prepared as in Example 6 by coupling O-tetrahy-
25 dropyranyl-(1,2,3,4-tetrahydro-1-naphthyl)prolinamide hydrochloride (WO 95/35309), subsequent elimination of protective groups and conversion to the amidine. The acetate was in the form of a white amorphous powder after freeze-drying; FAB-MS ($\text{M}+\text{H}^+$): 435.

30 Example 8

(D)-2-Cyclohexyl-2-acetoxyacetylproline (6-amidino)-3-picolylamide:

(a) (D)-2-Cyclohexyl-2-acetoxyacetylproline (6-cyano)-3-picolyl-
35 amide:

3.7 g (10 mmol) of (D)-2-cyclohexyl-2-hydroxycetylproline (6-cyano)-3-picolylamide (see Example 1a for preparation), 1.5 g (15 mmol) of triethylamine and 30 mg of DMAP were
40 dissolved in 30 ml of CH_2Cl_2 and, while cooling, 1.1 g (11 mmol) of acetic anhydride were added. The reaction mixture was left to stand at RT overnight and then washed with water, 5 % strength citric acid and 5 % strength NaHCO_3 solutions, dried over Na_2SO_4 and evaporated to dryness. The
45 remaining residue was used without further purification for

the next reaction;
FAB-MS ($M+H^+$): 413.

(b) Amidine formation

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Amidine formation took place as in Example 1b. The acetate was isolated after freeze-drying in the form of a white amorphous powder; FAB-MS ($M+H^+$): 430.

10 Example 9

(D)-2-Cyclohexyl-2-acetoxyacetylproline (4-amidino)benzylamide:

The compound was isolated as in Example 8 by reacting (D)-2-cyclohexyl-2-acetoxyacetylproline (6-cyano)-3-picolylamide
15 (stage 8a) with N-(4-cyanobenzyl)prolinamide hydrochloride (WO 95/35309) and subsequent amidation as a white amorphous acetate; FAB-MS ($M+H^+$): 429.

Example 10

20 (D)-2-Cyclohexyl-2-hexanoyloxyacetylproline (4-amidino)-benzylamide:

The compound was obtained as in Example 8 by reacting (D)-2-cyclohexyl-2-hydroxyacetylproline (p-cyano)benzylamide with
25 hexanoyl chloride followed by amidation. Acetate: white amorphous powder; FAB-MS ($M+H^+$): 468.

Example 11

O-Hydroxycarbonylmethyl-(D)-2-cyclohexyl-2-hydroxyacetylproline
30 (6-amidino)-3-picolylamide:

(a) Methyl O-t-butoxycarbonylmethyl-(D)-2-cyclohexyl-2-hydroxyacetate:

35 1.7 g of methyl (D)-2-cyclohexyl-2-hydroxyacetate (WO 93/18060) were added to a stirred suspension, free of mineral oil, of 480 mg of NaH (55 % dispersion in mineral oil, 10 mmol) in 20 ml of DMF. After evolution of gas had
40 ceased, a solution of 1.95 g (10 mmol) of t-butyl bromoacetate in 2 ml of DMF was added dropwise, and the mixture was stirred overnight.

The reaction product was poured into water and extracted several times with ether, the combined ether extracts were
45 washed with water and dried over Na_2SO_4 , and the ether was

distilled off. The remaining oily residue was purified by column chromatography (ether/n-hexane 1/1) yield: 80%.

- 5 (b) O-t-Butoxycarbonylmethyl-(D)-2-cyclohexyl-2-hydroxyacetic acid:

The ester was hydrolyzed with 1 N LiOH as in Example 6b. The crude acid was used immediately in the subsequent coupling.

- 10 (c) O-t-Butoxycarbonylmethyl-(D)-2-cyclohexyl-2-hydroxyacetyl-proline (6-cyano)-3-picolylamide:

The above acid was coupled as in Example 2a with
N-(6-cyano-3-picolyl)prolinamide hydrochloride (stage 6c).
15 White amorphous powder; FAB-MS ($M+H^+$): 485.

- (d) O-t-Butoxycarbonylmethyl-(D)-2-cyclohexyl-2-hydroxyacetyl-proline (6-amidino)-3-picolylamide acetate:

20 Conversion into the amidine took place as in 1b. White amorphous powder; FAB-MS ($M+H^+$): 502.

- (e) O-Hydroxycarbonylmethyl-(D)-2-cyclohexyl-2-hydroxyacetyl-proline (6-amidino)-3-picolylamide:

25 The above t-butyl ester was dissolved in trifluoroacetic acid and left to stand at RT overnight. The trifluoroacetic acid was removed by distillation under reduced pressure at 20°C, finally with addition of toluene, and the residue was treated
30 with ether, resulting in a white crystalline powder. This was converted by chromatography on silica gel with a methanol/conc. NH_3 eluent (50/2) to the free betaine which, after the eluent had been stripped off, was freeze-dried. White amorphous powder; FAB-MS ($M+H^+$): 446.

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Example 12

3-Cyclohexyl-(D)-lactylproline (6-amidino)-3-picolylamide:

The compound was obtained by reacting O-tetrahydro-
40 pyran-3-yl-3-cyclohexyl-(D)-lactic acid (WO 93/18060) with N-(6-cyano-3-picolyl)prolinamide (Example 6c) as in Example 3a, followed by amidine formation as in 1b. White amorphous powder; FAB-MS ($M+H^+$): 402.

45 Example 13

3-Cyclohexyl-(D)-lactylproline (4-amidino)benzylamide acetate:

(a) 3-Cyclohexyl-(D)-lactylproline (4-cyano)benzylamide:

2.25 g of isobutyl chloroformate were added dropwise to a solution of 3.3 g (13 mmol) of O-tetrahydropyranyl-3-cyclohexyl-(D)-lactic acid (WO 93/18060) and 1.6 g of N-methylmorpholine in 25 ml of DMF at -15°C . After 10 min, a solution of 3.5 g (13 mmol) of N-(4-cyanobenzyl)prolinamide hydrochloride in 20 ml of DMF and 70 ml of CH_2Cl_2 and 3.5 g of triethylamine were added dropwise. The reaction mixture was then stirred for 1 h, during which the temperature rose from -20°C to 0°C , and subsequently poured into 100 ml of water. Further workup took place as in 1a. Purification by column chromatography resulted in isolation of 2.7 g of white powder which melted at 122°C after crystallization from an ether/hexane mixture.

(b) Conversion into the amidine took place as in 1b. The acetate melted at $136-140^{\circ}\text{C}$; (FAB-MS ($\text{M}+\text{H}^+$)): 401.

20 Example 14

3-Cyclohexyl-(D)-lactylproline (2-methoxy-4-amidino)benzylamide:

As in Example 1, O-tetrahydropyranyl-3-cyclohexyl-(D)-lactylproline was reacted with 4-aminomethyl-3-methoxybenzonitrile (WO 95/35309) and subsequently converted into the amidine. The acetate was isolated as a white amorphous powder after freeze-drying; FAB-MS ($\text{M}+\text{H}^+$): 431.

Example 15

30 3,3-Diphenyl-(D,L)-lactylproline (6-amidino)-3-picolylamide:

As in Example 1, O-tetrahydropyranyl-3,3-diphenyl-(D,L)-lactylproline was reacted with (2-cyano-5-aminomethyl)pyridine hydrochloride (WO 95/35309) and subsequently converted into the amidine. Acetate: white amorphous powder, FAB-MS ($\text{M}+\text{H}^+$): 472.

Example 16

3,3-Diphenyl-(D,L)-lactylproline (4-amidino)benzylamide acetate:

40 As in Example 1, O-tetrahydropyranyl-3,3-diphenyl-(D,L)-lactylproline was reacted with p-cyanobenzylamine and subsequently converted into the amidine. The mixture of diastereomeric acetates melted at $99-106^{\circ}\text{C}$; FAB-MS ($\text{M}+\text{H}^+$): 471.

45 Example 17

(D)-Cyclohexylalanylproline (6-amidino)-3-picolylamide:

(a) Boc-(D)-Cha-Pro-OH

30.7 g (0.113 mol) of Boc-(D)-Cha-OH and 18.7 g (0.113 mol) of H-Pro-OCH₃ HCl were suspended in 300 ml of CH₂Cl₂ and dissolved by dropwise addition of 58.3 g (0.45 mol) of diisopropylethylamine. After cooling to -15°C, 113 ml (0.147 mol) of propanephosphonic anhydride (50% strength solution in ethyl acetate) were added dropwise, and the mixture was stirred at RT for 1 hour.

10

After addition of 200 ml of water, the organic phase was separated off and washed with aqueous K₂CO₃ solution, 0.5 N hydrochloric acid and 5% strength NaHCO₃ solution. After drying with Na₂SO₄, the solvent was distilled off, and the oily residue (42 g) was dissolved in 400 ml of ethanol, mixed with 120 ml of 1 N NaOH and stirred at RT for 2 h.

15

The alcohol was distilled off and then the aqueous phase was diluted with water and extracted several times with methyl tert-butyl ether. The aqueous phase was acidified with KHSO₄ solution and extracted 3x with CH₂Cl₂. After drying and removal of the methylene chloride by distillation, the oily residue was crystallized from diisopropyl ether/n-hexane (1/3). 29 g of white crystals were isolated.

25

(b) Boc-(D)-Cha-Pro-NH-3-(6-CN)-pico:

27.6 g (0.075 mol) of Boc-(D)-Cha-Pro-OH and 12.7 g (0.075 mol) of 6-cyano-3-picolyamine hydrochloride were suspended in 300 ml of CH₂Cl₂, and 47 g (0.364 mol) of diisopropylethylamine were added. Then, at -10°C, 66 ml of propanephosphonic anhydride (50% strength solution in ethyl acetate) were added dropwise, the mixture was stirred at RT for 1 hour, 200 ml of water were added, and the CH₂Cl₂ phase was separated off. The organic phase was washed with 0.1 N sodium hydroxide solution and water and then dried, and the solvent was distilled off. The residue was taken up in 100 ml of ethyl acetate, whereupon crystallization rapidly started and was completed by adding 150 ml of n-hexane. Filtration with suction and drying resulted in 32.4 g (89% of theory) of white crystals being isolated.

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(c) Boc-(D)-Cha-Pro-NH-3-(6-am)-pico:

1.15 g (16.5 mmol) of hydroxylamine hydrochloride were suspended in 5 ml of ethanol, 1.2 g of 25% strength ammonia solution were added and the mixture was stirred for 10 min. The

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salt which precipitated after addition of 45 ml of ethanol was filtered off with suction, and 3.18 g (6.6 mmol) of the above compound (stage c) were added to the solution. The hydroxyamidine compound separated out after a short time and, after stirring for 30 min, was filtered off with suction and washed with a little cold water and ethanol. The residue moist with ethanol was dissolved in 40 ml of ethanol and 8 ml of glacial acetic acid, 250 mg of 10% Pd/C were added and hydrogenation was carried out at about 50°C. After 5 h, TLC (CH₂Cl₂/MeOH/50% strength acetic acid, 20/5/1) showed no detectable starting material.

The catalyst was removed by filtration with suction through a Cellite [sic] layer and then the solvent was removed by distillation, adding toluene towards the end. Addition of 50 ml of acetone was followed by crystallization of the amidine acetate, and it was filtered off. White crystals, FAB-MS (M+H⁺): 501.

20 d) H-(D)-Cha-Pro-NH-3-(6-am)-pico:

The Boc group was eliminated from compound c) under standard conditions. Dihydrochloride: white crystals, FAB-MS (M+H⁺): 401.

25

Example 18

(D)-Cyclohexylglycylazetidine-2-carboxylic acid (6-amidino)-3-picolylamide:

30 By a method similar to that described above, Boc-(D)-cyclohexylglycine was coupled to methyl azetidine-2-carboxylate hydrochloride, hydrolyzed with LiOH to the free dipeptide acid and again coupled with 6-cyano-3-picolylamine hydrochloride. Addition of hydroxylamine onto the cyano group, catalytic hydrogenation of the N-hydroxyamidine with Raney nickel or Pd/C in dioxane (HCl [sic] or CF₃COOH/CH₂Cl₂ led to the title compound. The di-hydrochloride was obtained as white powder; FAB-MS (M+H⁺): 373.

40 Example 19

(D)-Cyclohexylglycylpiperidine-2-carboxylic acid (6-amidino)-3-picolylamide:

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The required product was obtained by the above procedure starting from Boc-(D)-cyclohexylglycine and methyl (L)-piperidine-2-carboxylate hydrochloride. Acetate: white amorphous powder; FAB-MS (M+H)⁺: 401.

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Example 20

H-(D)-(O-tert-butyl)serylproline (6-amidino)-3-picolylamide:

As in Example 17, Z-Ser(tBu)-OH was coupled with H-Pro-OCH₃·HCl to
10 give the dipeptide Z-Ser(tBu)-Pro-OCH₃, the ester was hydrolyzed, coupling was carried out with 6-cyano-3-picolylamine dihydrochloride to give Z-Ser(tBu)-Pro-NH-3-(6-CN)-pico, and the cyano group was converted via the hydroxyamidine stage into the ami-
15 tive group.

H-(D)-Ser(tBu)-Pro-NH-3-(6-am)-pico dihydrochloride was obtained as white amorphous powder. FAB-MS (M+H)⁺: 391.

20 Example 21

(D)-Cyclohexylglycylhydroxyproline (6-amidino)-3-picolylamide:

(a) 2.5 g of Fmoc-Hyp(tBu)-OH, 0.9 g of 3-aminomethyl-6-cyano-
25 pyridine dihydrochloride and 4.7 ml of DIPEA were introduced into 20 ml of DCM at 0°C. Then 5 ml of PPA (50% strength in ethyl acetate) were added and the reaction mixture was stirred at 0°C for 1 h. Then the temperature was allowed to rise to RT over the course of 18 h. For workup, the reaction mixture was diluted with 100 ml of ethyl acetate, and the
30 organic phase was extracted 5x with aqueous NaHSO₄ solution (20% strength), 5x with saturated NaHCO₃ solution and 1x with NaCl solution. The organic phase was dried and concentrated under reduced pressure. 2.2 g of the crude product remained and were used without further purification in the next reac-
35 tion.

(b) 2.2 g of Fmoc-Hyp(tBu)-NH-3-(6-CN)-pico were dissolved in 38.8 ml of DMF and 4.2 ml of diethylamine and left to stand at RT for 2 h. The solution was then concentrated under
40 reduced pressure. The crude product H-Hyp(tBu)-NH-3-(6-CN)-pico (1.3 g) was used without further workup in the next reaction.

(c) 1.3 g of H-Hyp(tBu)-NH-3-(6-CN)-pico were introduced together
45 with 3.9 ml of DIPEA and 1 g of Boc-(D)-Chg-OH into 20 ml of methylene chloride at 0°C. Then 4 ml of PPA (50% strength in ethyl acetate) were added and the reaction mixture was

- stirred at 0°C for 1 h. Then the temperature was allowed to rise to RT over the course of 18 h. For workup, the reaction mixture was diluted with 100 ml of ethyl acetate, and the organic phase was extracted 5x with aqueous NaHSO₄ solution (20% strength), 5x with saturated NaHCO₃ solution and 1x with NaCl solution. The organic phase was dried and concentrated under reduced pressure. 2.4 g of the crude product Boc-(D)-Chg-Hyp(tBu)-NH-3-(6-CN)-pico remained and were used without further purification in the next reaction.
- (d) 2.4 g of the crude product were dissolved in 14 ml of pyridine and dissolved [sic] 6.4 ml of triethylamine. Then H₂S was passed into the solution for 30 min. The solution was left to stand at RT for 18 h. The reaction mixture was then added to 1 l of 5% strength citric acid, and the precipitated product was filtered off. The aqueous phase was then extracted 2x with methylene chloride. The filtered product was dissolved in methylene chloride and combined with the organic extraction phases. The combined product phases were then extracted 1x with 20% strength aqueous NaHSO₄ solution and 1x with 1 N HCl and dried. The organic phase was concentrated under reduced pressure. The residue of crude thioamide was dissolved in 14 ml of acetone and, after addition of 2.4 ml of iodomethane, stirred at RT for 18 h. The reaction mixture was then concentrated in a rotary evaporator. The residue was dissolved in 5.5 ml of anhydrous MeOH and, after addition of 5.5 ml of a methanolic NH₄OAc solution, stirred at RT for 18 h. For work-up, the reaction mixture was concentrated under reduced pressure and taken up in methylene chloride, and the organic phase was washed with water. The organic phase was dried with magnesium sulfate and then the solvent was removed under reduced pressure. The residue was dissolved in a little MeOH and then precipitated in diisopropyl ether. The precipitated product was filtered off.
- (e) To remove the protective groups, the product was stirred in dioxane/HCl at RT for 18 h, the reaction mixture was concentrated under reduced pressure, and the remaining product was taken up in water and lyophilized. 63 mg remained.
- FAB-MS (M⁺): 460.

Example 22

H-(D,L)-Cycloheptylalanylproline (6-amidino)-3-picolylamide:

- As in Example 17, Boc-(D,L)-Chea-OH (see above for preparation) was coupled with H-Pro-OCH₃·HCl to give the dipeptide Boc-(D,L)-Chea-Pro-OCH₃, the ester was hydrolyzed, coupling was

carried out with 6-cyano-3-picolylamine dihydrochloride to give Boc-(D,L)-Chea-Pro-NH-3-(6-CN)-pico, and the cyano group was converted via the hydroxyamidine stage into the amidine. The Boc protective group was eliminated with HCl.

5

H-(D,L)-Chea-Pro-NH-3-(6-am)-pico dihydrochloride was obtained as white powder. FAB-MS (M+H)⁺: 415

Example 23

10 (D)-(α-Methyl)cyclohexylalanylproline (6-amidino)-3-picolylamide:

(a) H-Pro (6-carboxymido)-3-picolylamide [sic]:

15 100 ml of diisopropylethylamine and 30 g (133.8 mmol) of 6-carboxamido-3-picolylamine [sic] dihydrochloride (see the preparation of the precursors in Example 10) were added to 28.8 g (133.8 mmol) of Boc-Pro-OH in 300 ml of DCM at -5°C. Then 100 ml of PPA (50% strength ethyl acetate solution) in 100 ml of DCM were added dropwise at -5°C over the course of 20 1 h, and the mixture was stirred at 0°C for a further 2 h. The mixture was washed with 0.5 N sodium hydroxide solution, with KHSO₄ solution and then with water, and the organic phase was dried over Na₂SO₄. The solvent was stripped off to result in 44.4 g of Boc-Pro (6-carboxamido)-3-picolylamide 25 [sic].

30 30 g of the Boc-protected compound (86 mmol) were dissolved in 370 ml of isopropanol, and the protective group was cleaved by adding 430 mmol of HCl (isopropanolic HCl) at 50°C. 28 g of H-Pro (6-carboxamido)-3-picolylamide [sic] hydrochloride were obtained.

35 ¹H-NMR (DMSO-d₆, δ in ppm): 10.35 (m, 1H); 9.65 (t, 1H); 8.70-8.55 (2H); 8.38 (1H); 8.20 (1H); 8.10 (1H); 7.88 (1H); 4.50 (d, 2H); 4.30 (m, 1H); 3.30-3.10 (2H); 2.37 (m, 1H); 2.00-1.80 (3H).

(b) (D)-(α-Methyl)cyclohexylalanylproline (6-amidino)-3-picolylamide:

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5.00 g of diisopropylethylamine and then 6.7 ml (9.2 mmol) of PPA (50% strength solution in ethyl acetate) were added dropwise to a solution of 2.20 g (7.7 mmol) of Boc-(D)-(α-methyl)-Cha-OH and 2.19 g (7.7 mmol) of H-Pro 45 (6-carboxamido)-3-picolylamide [sic] hydrochloride in 60 ml of DCM at -5°C. The mixture was stirred for 2 h, during which the temperature rose from -5°C to 20°C. The organic phase was

washed with 5% strength NaHCO_3 , 50% strength citric acid solution and water, dried over Na_2SO_4 and evaporated to dryness. 2.98 g of Boc-(D)-(α -methyl)-Cha-Pro (6-carboxamido)-3-picolylamide [sic] were obtained.

- 5 2.9 g (5.6 mmol) of carboxamido [sic] derivative were reacted in 50 ml of DCM and 2.4 ml of diisopropylethylamine at 0°C with 0.9 ml of trifluoroacetic anhydride to give the
- 10 corresponding nitrile. After 2 h, the solvent was stripped off, leaving 2.7 g of solid. This was stirred in 50 ml of DCM/MeOH 1:1 at RT [sic] with 375 mg (5.4 mmol) of hydroxylamine hydrochloride and 3.7 ml of diisopropylethylamine at 40°C for 5 h. The solvent was
- 15 stripped off, the resulting hydroxyamidine derivative was taken up in DCM, and the organic phase was washed with 10% strength sodium bicarbonate solution and water and dried over Na_2SO_4 . The solvent was stripped off to result in 2.61 g of solid, which was hydrogenated in 50 ml of MeOH and one mole
- 20 equivalent of acetic acid with 200 mg of Raney nickel until the theoretically required amount of hydrogen had been taken up. The temperature was generally kept at from 20°C to 40°C during this. The catalyst was then filtered off, and the solvent was removed in a rotary evaporator.
- 25 The product was purified by column chromatography on silica gel (mobile phase: DCM/20% MeOH/3.5% HOAc (50% strength)) to result in 1.53 g of Boc-(D)-(α -methyl)-Cha-Pro (6-amidino)-3-picolylamide hydroacetate (HPCL [sic] purity: 96.8%); FAB-MS ($\text{M}+\text{H}^+$): 515.
- 30 The Boc protective group was eliminated in isopropanolic HCl (5 equivalents of HCl) at 50°C . 1.41 mg of H-(D)-(α -methyl)-Cha-Pro (6-amidino)-3-picolylamide dihydrochloride were obtained; FAB-MS ($\text{M}+\text{H}^+$): 415.

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Example 24

(D,L)-(4-Tetrahydropyranyl)glycylproline (6-amidino)-3-picolylamide:

- 40 As in Example 23, 2.70 g (10.4 mmol) of H-(D,L)-Thpg-OH and 2.96 g (10.4 mmol) of H-Pro (6-carboxamido)-3-picolylamide [sic] hydrochloride resulted in 1.60 g of Boc-(D,L)-Thpg-Pro (6-amidino)-3-picolylamide hydroacetate (HPLC purity: 95%); FAB-MS ($\text{M}+\text{H}^+$): 489. Cleavage of the Boc protective group resulted in 1.33 g of
- 45 H-(D,L)-Thpg-Pro (6-amidino)-3-picolylamide dihydrochloride; FAB-MS ($\text{M}+\text{H}^+$): 389.

Example 25

(D,L)-2-Norbornylglycylproline (6-amidino)-3-picolylamide:

As in Example 17, Boc-(D,L)-(2-norbornyl)Gly-OH (see above for
5 preparation) was coupled with H-Pro-OCH₃·HCl to give the dipeptide
Boc-(D,L)-(2-norbornyl)Gly-Pro-OCH₃, the ester was hydrolyzed,
coupling was carried out with 6-cyano-3-picolylamine dihydro-
chloride to give Boc-(D,L)-(2-norbornyl)Gly-Pro-NH-3-(6-CN)-pico,
and the cyano group was converted via the hydroxyamidine stage
10 into the amidine. Elimination of the Boc protective group with
HCl resulted in H-(D,L)-(2-norbornyl)Gly-Pro-NH-3-(6-am)-pico
dihydrochloride as white amorphous powder. FAB-MS (M+H⁺): 399.

Example 26

15 (D,L)-1-Adamantylglycylproline (6-amidino)-3-picolylamide:

As in Example 17, Boc-(D,L)-(1-adamantyl)Gly-OH (see above for
preparation) was coupled with H-Pro-OCH₃·HCl to give the dipeptide
Boc-(D,L)-(1-adamantyl)Gly-Pro-OCH₃, the ester was hydrolyzed,
20 coupling was carried out with 6-cyano-3-picolylamine dihydro-
chloride to give Boc-(D,L)-(1-adamantyl)Gly-Pro-NH-3-(6-CN)-pico,
and the cyano group was converted via the hydroxyamidine stage
into the amidine. Elimination of the Boc protective group with
HCl resulted in H-(D,L)-(1-adamantyl)Gly-Pro-NH-3-(6-am)-pico
25 dihydrochloride as white amorphous powder. FAB-MS (M+H⁺): 439.

Example 27

H-(D,L)-1-Tetralinylglycylproline (6-amidino)-3-picolylamide:

30 As in Example 17, Boc-(D,L)-(1-tetralinyl)Gly-OH (see above for
preparation) was coupled with H-Pro-OCH₃·HCl to give the dipeptide
Boc-(D,L)-(1-tetralinyl)Gly-Pro-OCH₃, the ester was hydrolyzed,
coupling was carried out with 6-cyano-3-picolylamine dihydro-
chloride to give Boc-(D,L)-(1-tetralinyl)Gly-Pro-
35 NH-3-(6-CN)-pico, and the cyano group was converted via the
hydroxyamidine stage into the amidine. Elimination of the Boc
protective group with HCl resulted in H-(D,L)-(1-tetralinyl)Gly-
Pro-NH-3-(6-am)-pico dihydrochloride as white solid substance.
FAB-MS (M+H⁺): 435.

40

Example 28

(D,L)-(Trimethylsilyl)alanylproline (6-amidino)-3-picolylamide:

As in Example 23, 1.88 g (7.2 mmol) of Boc-(D,L)-triethyl-
45 silyl)Ala-OH and 2.05 g (7.2 mmol) of H-Pro (6-carboxa-
mido)-3-picolylamide [sic] hydrochloride resulted in 1.45 g of
Boc-(D,L)-(trimethyl-silyl)Ala-Pro (6-amidino)-3-picolylamide hy-

droacetate as 1:1 mixture of diastereomers with a purity of 96% (HPLC); FAB-MS ($M+H^+$): 491.

Cleavage of the Boc protective group resulted in 1.22 g of
 5 H-(D,L)-(trimethylsilyl)Ala-Pro (6-amidino)-3-picolylamide dihydrochloride; FAB-MS ($M+H^+$): 391.

Example 29

(D,L)-(3,4,5-Trimethoxy)phenylalanylproline [sic] (6-amidi-
 10 no)-3-picolyl-amide:

As in Example 17, Boc-(D,L)-(3,4,5-trimethoxy)Phe-OH (see above for preparation) and H-Pro-Me.HCl were used to prepare the dipeptide Boc-(D,L)-(3,4,5-trimethoxy)Phe-Pro-oCH₃, the ester was hydrolyzed, coupling was carried out with 6-cyano-3-picolylamine dihydrochloride to give Boc-(D,L)-(3,4,5-(OCH₃)₃)Phe-Pro-NH-3-(6-CN)-pico, and the cyano group was converted via the hydroxyamidine stage into the amidine. The Boc protective group was eliminated with HCl.

20

H-(D,L)-(3,4,5-trimethoxy)Phe-Pro-NH-3-(6-am)-pico dihydrochloride was obtained as white amorphous powder. FAB-MS ($M+H^+$): 485

Example 30

25 (D,L)-(3-Phenyl)prolylproline (6-amidino)-3-picolylamide:

As in Example 23, 1.50 g (5.1 mmol) of Boc-(D,L)-(3-phenyl)Pro-OH (the transamino acid described in J. Org. Chem. 55 (1990) 270 was used) and 1.45 g (5.1 mmol) of H-Pro (6-carboxamido)-3-picolylamide [sic] hydrochloride resulted in 1.01 g of Boc-(D,L)-(3-phenyl)Pro-Pro (6-amidino)-3-picolylamide hydroacetate with a purity of 98% (HPLC); FAB-MS ($M+H^+$): 521.

Cleavage of the Boc protective group resulted in 0.92 g of
 35 H-(D,L)-(3-phenyl)Pro-Pro (6-amidino)-3-picolylamide dihydrochloride; FAB-MS ($M+H^+$): 421.

Example 31

(D,L)-(4-Methyl)pipecolylproline (6-amidino)-3-picolylamide:
 40

As in Example 23, 1.50 g (6.2 mmol) of trans-(D,L)-(4-methyl)-Pic-OH (literature: Biochem. Biophys. Res. Commun. (1981) 440) and 1.76 g (6.2 mmol) of H-Pro (6-carboxamido)-3-picolylamide [sic] hydrochloride resulted in 1.08 g of
 45 Boc-(D,L)-(4-methyl)Pic-Pro (6-amidino)-3-picolylamide hydroacetate in a purity of 95% (HPLC); FAB-MS ($M+H^+$): 473.

Cleavage of the Boc protective group resulted in 0.90 g of H-(D,L)-(4-methyl)Pic-Pro (6-amidino)-3-picolylamide dihydrochloride; FAB-MS ($M+H^+$): 373.

5 Example 32

(D)-Cyclohexylalanyl-3,4-dehydroproline (6-amidino)-3-picolylamide:

a) Boc-Pyr-NH-3-(6-CONH₂)-pico:

10

5.0 g of Boc-Pyr-OH (23.4 mmol) were suspended together with 5.25 g of 6-carboxyamido-3-picolylamine [sic] dihydrochloride and 32.1 ml of diisopropylethylamine (187 mmol) in 50 ml of CH₂Cl₃ and, while stirring at 0-5°C, 23.5 ml of propanephosphonic anhydride (50% strength solution in ethyl acetate) were added dropwise. The mixture was then stirred at RT overnight. The solution was diluted to 150 ml with CH₂Cl₂, extracted successively with 20% strength sodium bisulfate solution and 5% strength citric acid solution until no diisopropylethylamine was detectable by TLC, dried over sodium sulfate and concentrated in a rotary evaporator. The aqueous phases were then back-extracted three times with CH₂Cl₂, and the organic phase was dried, concentrated in a rotary evaporator and used together with the above product but without further purification in the next reaction. Propanephosphonic acid was also present as subsidiary component.

15

20

25

b) H-Pyr-NH-3-(6-CONH₂)-pico hydrochloride:

30

35

The crude product from above was dissolved in 100 ml of CH₂Cl₂ and after addition of 10 ml of 5 M hydrochloride in ether, stirred at RT for 2 h (TLC check). The crude product after complete concentration and codistillation with toluene under reduced pressure was recrystallized from 200 ml of ethanol. This resulted in 5.03 g and, after concentration of the mother liquor, a further 0.3 g of product (80.4% of theory). Elemental analysis showed that the product was in the form of the monohydrochloride.

40

c) Boc-(D)-Cha-Pyr-NH-3-(6-CONH₂)-pico:

45

5.06 g of Boc-(D)-Cha-OH (18.66 mmol) were stirred together with 5.28 g of H-Pyr-NH-3-(6-CONH₂)-pico hydrochloride (18.66 mmol) and 9.55 ml of diisopropylethylamine (56 mmol) in 75 ml of CH₂Cl₂ and, at 0-5°C, 18.6 ml of propanephosphonic anhydride (50% strength solution in ethyl acetate) were added dropwise. The mixture was then stirred at RT overnight, dur-

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ing which a precipitate separated out. The precipitate was filtered off with suction and the solution was extracted five times with 25 ml of 5% strength citric acid each time (TLC showed no diisopropylethylamine left in the organic phase) and then washed several times with saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under reduced pressure. To minimize the propanephosphonic acid byproduct, the residue was taken up in ethyl acetate, extracted several times with saturated NaHCO_3 solution and then dried over sodium sulfate and concentrated in a rotary evaporator. Yield 7.0 g of product as solid foam (75% of theory).

d) Boc-(D)-Cha-Pyr-NH-3-(6-CN)-pico:

7.0 g of Boc-(D)-Cha-Pyr-NH-3-(6- CONH_2)-pico (14 mmol) were dissolved together with 9.5 ml of diisopropylethylamine (56 mmol) in 100 ml of CH_2Cl_2 and cooled to 0-5°C, and 3.5 ml of trifluoroacetic anhydride (25.2 mmol) were added dropwise. After stirring at RT for 2 h, the precursor was completely converted. The solution was then extracted three times with 20% strength sodium sulfate, three times with saturated sodium bicarbonate and once with saturated sodium chloride solution, dried over sodium sulfate and concentrated in a rotary evaporator. Yield: 6.6 g (98% of theory).

e) H-(D)-Cha-Pyr-NH-3-(6-am)-pico:

The nitrile functionality in Boc-(D)-Cha-Pyr-NH-3-(6-CN)-pico was converted as in Example 93 (c-e) into the thioamide with H_2S , into the imino thiomethyl ester with methyl iodide and subsequently into the amidine with ammonium acetate. The Boc protective group was eliminated with ethereal hydrochloric acid in methylene chloride. FAB-MS ($\text{M}+\text{H}^+$): 398.

35

Example 33

(D)-Cyclohexylglycol-(N-cyclopropyl)glycine (6-amidino)-3-picolyl-amide:

40 (a) H-(N-Cyclopropyl)Gly (6-carboxamido)-3-picolylamide [sic]:

As in Example 23(a), 12.5 g of Boc-(N-cyclopropyl)Gly-OH (58 mmol) were reacted with 13.0 g (58 mmol) of (6-carboxamido)-3-picolylamine [sic] dihydrochloride to give 11.3 g of H-(N-cyclopropyl)Gly (6-carboxamido)-3-picolylamide hydrochloride; (FAB-MS) ($\text{M}+\text{H}^+$): 249.

(b) H-(D)-Chg-(N-Cyclopropyl)Gly (6-amidino)-3-picolylamide:

As in Example 23(b), 2.5 g (8.8 mmol) of H-(N-cyclopropyl)Gly (6-carboxamido)-3-picolylamide [sic] hydrochloride and 2.3 g
5 (8.8 mmol) of Boc-(D)-Chg-OH resulted in 1.88 g of Boc-(D)-Chg-(N-cyclopropyl)Gly (6-amidino)-3-picolylamide hydroacetate; FAB-MS ($M+H^+$): 487.

Elimination of the Boc protective group resulted in 1.73 g of
10 H-(D)-Chg-(N-cyclopropyl)Gly (6-amidino)-3-picolylamide dihydrochloride; FAB-MS ($M+H^+$): 387.

Example 34

(D)-Cyclohexylglycylproline (4-amidino)-1-naphthylmethanamide di-
15 hydrochloride:

1-Azidomethyl-4-cyanonaphthalene:

24.6 g (0.1 mol) of 1-bromomethyl-4-cyanonaphthalene
20 (M.J.S. Dewar, P.J. Grisdale, J. Amer. Chem. Soc. 84 (1996 [sic]) 3541) were dissolved in 100 ml of dimethylformamide, 98 g (0.15 mol) of sodium azide were added and the mixture was stirred at RT overnight.

25 After addition of 100 ml of water and 100 ml of an ethyl acetate/methyl t-butyl ether mixture (1/1), the organic phase was separated off, washed twice with water and dried over $MgSO_4$, and the solvent was distilled off under reduced pressure. The resulting pale yellowish crude product was used without further purification
30 in the next reaction.

1-Aminomethyl-4-cyanonaphthalene hydrochloride:

The azide dissolved in 30 ml of THF was slowly added dropwise to
35 a solution of 26.2 g (1 mol) of triphenylphosphine in 70 ml of THF at 10°C (evolution of nitrogen). After the addition was complete, 2.75 ml (0.15 mol) of water were added dropwise and the reaction mixture was stirred at RT overnight. The residue after stripping off the solvent was taken up in dilute hydrochloric
40 acid, the insoluble constituents were filtered off with suction, and the filtrate was washed several times with toluene to remove the triphenylphosphine oxide completely. The acid phase was adjusted to pH 9 with 1 N NaOH and then extracted with ethyl acetate several times, the combined ethyl acetate phases were dried
45 with $MgSO_4$ and, after reduction to about one half of the initial volume, acidified with ethereal hydrochloric acid solution. Filtration with suction and drying resulted in 19.5 g (87% of

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theory) of hydrochloride being isolated. White crystals, m.p. > 240°C.

Boc-(D)-Cyclohexylglycylproline (4-amidino)-1-naphthylmethanamide
5 acetate:

Boc-(D)-Cyclohexylglycylproline, prepared by reacting
Boc-(D)-cyclohexylglycine with proline methyl ester and subse-
quent hydrolysis, was coupled by general method 2 with 1-amino-
10 methyl-4-cyanonaphthalene hydrochloride and then the cyano group
was converted into the amidine functionality by general method 1.
The acetate was isolated in the form of white crystals. m.p.
144-147°C; FAB-MS (M+H⁺): 526.

15 (D)-Cyclohexylglycylproline (4-amidino)-1-naphthylmethanamide di-
hydrochloride:

The Boc group was eliminated from the above compound using iso-
propanolic hydrochloric acid to afford the dihydrochloride in the
20 form of white crystals. m.p. 228-232°C; FAB-MS (M+H⁺): 436.

Example 35

(D,L)-(4-Tetrahydropyranyl)glycylproline (2-methoxy-4-amidino)-
benzylamide:

25

(a) Boc-(D,L)-Thpg-Pro (2-MeO-4-CN)benzylamide:

2.9 g (11.2 mmol) of Boc-(D,L)-Thpg-OH were reacted as in
Example 26(b) with 3.3 g (11.2 mmol) of H-Pro 2-MeO-4-CN-
30 benzylamide hydrochloride. 4.8 g of product were obtained.

¹H-NMR (DMSO-D₆; δ in ppm): 8.40 and 7.95 (1H, NH (2
diastereomers or 2 rotamers)), 7.5-6.9 (m, 4H), 4.45-3.95
(m, 3H), 3.90-3.70 (m, 6H), 3.65-3.05 (m, 4H), 2.2-1.1 (m, 18H)

35

(b) (D,L)-(4-Tetrahydropyranyl)glycylproline (2-methoxy-4-amidi-
no)benzylamide:

2.0 g (4.0 mmol) of the nitrile were reacted as in Example
40 26(b) with hydroxylamine hydrochloride (10 mmol) and DIPEA
(24 mmol) to give 2.0 g of the corresponding hydroxyamidine.
Hydrogenation of the hydroxyamidine with Raney nickel/H₂ in
MeOH and one equivalent of acetic acid and subsequent puri-
fication by column chromatography on silica gel (mobile
45 phase: DCM/15% MeOH/5% HOAc (50% strength)) resulted in 1.3 g

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(60%) of the Boc-protected product in the form of 2 diastereomers (in the ratio 1:1) and of an HPLC purity of 99%.

5 The Boc protective group was eliminated in DCM/hydrogen chloride. 1.1 g of the product were obtained with an HPLC purity of 99%; FAB-MS ($M+H^+$): 418.

Example 36

10 (D,L)- β,β -Diphenylalanylproline (2-methoxy-4-amidino)benzylamide:

(a) Boc-(D,L)-Dpa-Pro (2-MeO-4-CN)-benzylamide:

15 6.0 g (17.6 mmol) of Boc-(D,L)-Dpa-OH and 5.2 g (17.6 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were converted as in Example 23 (b) with subsequent purification by column chromatography on silica gel (mobile phase: DCM/4.5% MeOH) into 5.6 g of product.

20 1H -NMR (DMSO- d_6 ; δ in ppm): 8.45 and 7.95 (1H, NH (2 diastereomers or rotamers)), 7.5-6.9 (m, 14H), 5.35-4.95 (m, 1H), 4.5-4.1 (m, 3H), 4.0-3.0 (m, 3H), 3.90 and 3.85 (s, 3H (2 diastereomers)), 2.1-1.1 (m, 13H).

25 (b) Boc-(D,L)-Dpa-Pro-NH-(2-MeO)-4-amb:

The hydroxyamidine was obtained by reacting the nitrile with hydroxylamine hydrochloride as in Example 26(b).

30 1H -NMR (DMSO- d_6): 5.90-5.78 ppm (2s, 1H, OH (2 diastereomers)).

(c) H-(D,L)-Dpa-Pro-NH-(2-MeO)-4-amb:

35 Cleavage of the OH group by hydrogenolysis as in Example 26(b) and subsequent purification by column chromatography on silica gel (mobile phase: DCM/10 % - 20 % MeOH/3 % HOAc (50 % strength)) resulted in Boc-(D,L)-Dpa-Pro-NH-2-MeO-4-amb dihydroacetate as 1:1 mixture of diastereomers in a purity of almost 100 % (HPLC). The Boc protective group was eliminated in DCM with hydrochloride gas, and the product was obtained
40 as dihydrochloride with the same purity and same diastereomer ratio as the previous stage.

45 1H -NMR (DMSO- d_6 ; δ in ppm): 9.70-9.25 (4H, amidine), 8.9-8.4 (4H, NH and NH_3^+), 7.7-7.0 (13H), 5.2-4.9 (m, 1H), 4.5-3.7 (8H), 3.25 (m, 1H), 2.95 (m, 1H), 2.2-1.2 (4H).

Example 37

(D,L)-(2-Norbornyl)glycylproline (2-methoxy-4-amidino)benzylamide:

- 5 3.0 g (11.1 mmol) of Boc-(D,L)-(2-norbornyl)Gly-OH and 3.3 g (11.1 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed as in Example 23(b) to give 5.0 g of Boc-(D,L)-(2-norbornyl)Gly-Pro (2-MeO-4-CN)-benzylamide and further converted via the hydroxyamidine stage with subsequent hydrogenation
10 into 3.1 g of Boc-(D,L)-(2-norbornyl)Gly-Pro (2-MeO-4-am)-benzylamide. The Boc protective group was eliminated in DCM/hydrochloride gas, and the corresponding amidine dihydrochloride resulted after the solvent was stripped off; FAB-MS (M+H⁺): 428.

15 Example 38

(D,L)-(1-Tetralinyl)glycylproline (2-methoxy-4-amidino)benzylamide:

- 3.0 g (9.8 mmol) of Boc-(D,L)-(1-tetralinyl)Gly-OH and 2.9 g
20 (9.8 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed as in Example 23(b) to give 4.2 g of Boc-(D,L)-(1-tetralinyl)Gly-Pro (2-MeO-4-CN)-benzylamide and further converted via the hydroxyamidine stage with subsequent hydrogenation into 2.6 g of the corresponding amidine hydroacetate.

25

The amidine dihydrochloride was obtained after cleavage of the Boc protective group in DCM with gaseous hydrogen chloride; FAB/MS (M+H⁺): 464.

30 Example 39

(D,L)-Cyclooctylglycylproline (2-methoxy-4-amidino)benzylamide:

- (a) 4.8 g (16 mmol) of Boc-(D,L)-Cog-OH and 5.0 g (16.9 mmol) of
H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed
35 as in Example 23(b) to give 4.7 g of Boc-(D,L)-Cog-Pro (2-MeO-4-CN)-benzylamide.

- ¹H-NMR (DMSO-d₆, δ in ppm): 8.35 and 7.95 (t, 1H, NH
(2 diastereomers)), 7.50-7.25 (3H), 7.10 and 6.85 (d, 1H, NH
40 (2 diastereomers)), 4.45-3.95 (4H), 3.85 (s, 3H, OMe),
3.90-3.50 (4H), 2.20-1.15 (28H).

- (b) 2.0 g of the nitrile were further converted as in Example
23(b) via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 1.7 g of
45 H-(D,L)-Cog-Pro (2-Me-4-am)-benzylamide dihydrochloride.

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¹H-NMR (DMSO-d⁶, δ in ppm): 9.60 and 9.30 (4H, amidine (2 diastereomers)), 8.80 (NH), 8.60 and 8.30 (NH₃⁺ (2 diastereomers)), 7.60-7.25 (3H), 4.50-4.10 (4H), 4.00-3.40 (4H), 3.90 (s, 3H), 2.20-1.20 (19H).

5

Example 40

(D)-(α-Methyl)cyclohexylalanylproline (2-methoxy-4-amidino)benzyl-amide:

- 10 2.7 g (9.5 mmol) of Boc-(D)-(α-methyl)-Cha-OH and 2.8 g (9.5 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed as in Example 23(b) to give 2.5 g of Boc-(D)-(α-methyl)-Cha-Pro (2-MeO-4-CN)-benzylamide. 1.0 g of this were further converted via the hydroxyamidine stage with subsequent
15 hydrogenation and cleavage of the Boc protective group into 0.6 g of H-(D)-(α-methyl)-Cha-Pro (2-MeO-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 444.

Example 41

- 20 (D,L)-Dibenzosuberylglycylproline (2-methoxy-4-amidino)benzylamide:

- 4.4 g (12.0 mmol) of Boc-(D,L)-(dibenzosuberyl)-Gly-OH and 3.5 g (12.0 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were
25 condensed as in Example 23(b) to give 6.4 g of Boc-(D,L)-(dibenzosuberyl)-Gly-Pro (2-MeO-4-CN)-benzylamide. 2.0 g of this were further converted via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 0.9 g of H-(D,L)-(dibenzosuberyl)-Gly-Pro (2-MeO-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 526.
30

Example 42

(D,L)-(3,4,5-Trimethoxy)phenylalanylproline (2-methoxy-4)-amidino)benzylamide:

35

- 2.10 g (5.9 mmol) of Boc-(3,4,5-trimethoxy)-Phe-OH and 1.75 g (5.9 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed as in Example 23(b) to give 3.0 g of Boc-(D,L)-(3,4,5-trimethoxy)-Phe-Pro (2-MeO-4-CN)-benzylamide. 1.2 g of
40 this were further converted via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 0.4 g of H-(D,L)-(3,4,5-trimethoxy)-Phe-Pro (2-Me-4-am)-benzylamide [sic] dihydrochloride; FAB-MS (M+H⁺): 485.

45

Example 43

(D,L)-(Trimethylsilyl)alanylproline (2-methoxy-4-amidino)benzylamide:

- 5 2.00 g (7.65 mmol) of Boc-(trimethylsilyl)-Ala-OH and 2.26 g (7.65 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed as in Example 23(b) to give 3.22 g of Boc-(D,L)-(trimethylsilyl)-Ala-Pro (2-MeO-4-CN)-benzylamide.
- 10 1.60 g of this were further converted via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 0.65 g of H-(D)-(trimethylsilyl)-Ala-Pro (2-MeO-4-am)-benzylamide dihydrochloride; FAB-MS ($M+H^+$): 420.
- 15 Example 44
- (D)-(tert-Butyl)-serylproline (2-methoxy-4-amidino)benzylamide:
- 5.0 g (16.9 mmol) of Z-(D)-(tBu)-Ser-OH and 5.0 g (16.9 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed as in
- 20 Example 23(b) to give 8.8 g of Z-(D)-(tBu)-Ser-Pro (2-MeO-4-CN)-benzylamide. 4.1 g of this were further converted via the hydroxyamidine stage with subsequent hydrogenation into 3.0 g of Z-(D)-(tBu)-Ser-Pro (2-MeO-4-am)-benzylamide hydroacetate. Cleavage of the Z protective group by hydrogenolysis was carried out
- 25 in 80 ml of methanol and one equivalent of acetic acid in the presence of 185 mg of Pd/C (10 %) at RT. 2.3 g of impure product were obtained as dihydroacetate, which was purified by MPLC; FAB-MS ($M+H^+$): 419.
- 30 1H -NMR (DMSO- d_6 , δ in ppm): 9.3-8.7 (7H, amidine and NH_3^+), 8.1 (1H, NH), 7.5-7.3 (3H), 4.1-4.0 (dd, 1H), 3.95 (s, 3H), 3.9-3.2 (7H), 2.2-1.5 (4H), 1.05 (s, 9H).

Example 45

- 35 (D,L)-(3-Phenyl)prolylproline (2-methoxy-4-amidino)benzylamide:

- 1.3 g (4.5 mmol) of Boc-(D,L)-(3-phenyl)-Pro-OH (see also Example 30) and 1.3 g (4.5 mmol) of H-Pro (2-MeO-4-CN)-benzylamide hydrochloride were condensed as in Example 23 (b) to give
- 40 1.7 g of Boc-(D,L)-(3-phenyl)-Pro-Pro (2-MeO-4-CN)-benzylamide and further converted via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 0.7 g of H-(D,L)-(3-phenyl)-Pro-Pro (2-MeO-4-am)-benzylamide dihydrochloride; FAB-MS ($M+H^+$): 450.

Example 46

(D)-Cyclohexylglycylpiperidine-2-carboxylic acid (2-methoxy-4-amidino)benzylamide:

- 5 The compound was prepared as in Example 48 or 23 (b). To do this, 1.5 g (4.1 mmol) of Boc-(D)-Chg-Pic-OH, which have been prepared by condensation of Boc-(D)-Chg-OH with H-Pic-OMe hydrochloride and subsequent alkaline hydrolysis of the ester, were condensed with 0.8 g (4.1 mmol) of (2-MeO-4-CN)-benzylamine hydrochloride
10 to give 1.9 g of Boc-(D)-Chg-Pic (2-MeO-4-CN)-benzylamide. This substance was further converted via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 1.0 g of H-(D)-Chg-Pic (2-MeO-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 430.

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Example 47

(D)-Cyclohexylglycyl(N-cyclopropyl)glycine (2-methoxy-4-amidino)-benzylamide:

- 20 Example 47 was prepared as in Examples 48 and 23 (b). To do this, 1.5 g (4.2 mmol) of Boc-(D)-Chg-(N-cyclopropyl)-Gly-OH, which had been prepared by condensation of Boc-(D)-Chg-OH with H-(N-cyclopropyl)-Gly-OMe hydrochloride and subsequent alkaline hydrolysis of the ester, were condensed with 0.83 g (4.2 mmol) of
25 (2-MeO-4-CN)-benzylamino [sic] hydrochloride to give 1.5 g of Boc-(D)-Chg-(N-cyclopropyl)-Gly (2-MeO-4-CN)-benzylamide. This substance was further converted via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 0.85 g of H-(D)-Chg-(N-cyclopropyl)-Gly (2-MeO-4-am)-benzy-
30 lamide dihydrochloride; FAB-MS (M+H⁺): 416.

Example 48

(D)-Cyclohexylalanyl piperidine-2-carboxylic acid (2-methoxy-4-amidino)benzylamide:

35

a) Boc-(D)-Cha-Pic-OH:

- 7.55 g (27.8 mmol) of Boc-(D)-Cha-OH, 5.0 g (27.8 mmol) of H-Pic-OMe hydrochloride and 20.5 ml of DIPEA were mixed at
40 -5°C. A solution of 23 ml (31 mmol) of PPA (50 % strength solution in ethyl acetate) and 23 ml of DCM was added dropwise to this at -5°C over the course of 30 min. The mixture was stirred at 0°C for a further 2 h and then washed with
45 0.5 N sodium hydroxide solution, then with 1 N hydrochloric acid and finally with saturated brine, and the organic phase was dried over Na₂SO₄ and the solvent was stripped off. 9.7 g of Boc-(D)-Cha-Pic-OMe were obtained and were hydrolyzed in

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50 ml of methanol with 21 ml of 3 N sodium hydroxide solution at RT for 2 h. The solvent was stripped off, DCM was added, dilute hydrochloride was added to acidify, and the DCM phase was dried over Na₂SO₄. The solvent was stripped off to result in 8.5 g of Boc-(D)-Cha-Pic-OH.

b) Boc-(D)-Cha-Pic (2-MeO-4-CN)-benzylamide:

8.5 g (22.2 mmol) of Boc-(D)-Cha-Pic-OH were stirred in 50 ml of THF with 2.56 g of HOSucc and 4.58 g of DCC at 0°C for 30 min. Then, at 5°C, 4.4 g (22.2 mmol) of (2-MeO-4-CN)-benzylamine hydrochloride, 25 ml of THF and finally 3.1 ml of TEA were added, and the mixture was stirred at 0°C for 1 h and allowed to warm to RT overnight. The solid was filtered off, the solvent was stripped off from the filtrate, and the product was taken up in ethyl acetate and washed successively with 0.5 N sodium hydroxide solution, 0.5 N hydrochloric acid and saturated brine. After drying over Na₂SO₄, the solvent was completely stripped off. 11.5 g of Boc-(D)-Cha-Pic (2-Me-4-CN)-benzylamide [sic] were obtained.

¹H-NMR (DMSO-d₆, δ in ppm): 8.50 and 7.95 (together 1H, NH, 2 rotamers), 7.5-7.0 (4H), 4.55-4.20 (3H), 3.85 (s, 3H), ca. 3.8 (1H), ca. 3.4-3.1 (2H), 2.3-0.8 (28H).

c) H-(D)-Cha-Pic (2-MeO-4-amidino)benzylamide:

3.0 g (5.7 mmol) of the nitrile from Example 46 (b) were converted as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 1.9 g of H-(D)-Cha-Pic (2-MeO-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 444.

Example 49

(D)-Cyclohexylglycylproline (2-ethoxy-4-amidino)benzylamide:

Preparation took place as in Examples 23 (b) and 48. 4.1 g (11.5 mmol) of Boc-(D)-Chg-Pro-OH were condensed as in 48 (b) with 2.4 g (11.5 mmol) of (2-EtO-4-CN)-benzylamine hydrochloride to give 4.7 g of Boc-(D)-Chg-Pro (2-EtO-4-CN)-benzylamide hydrochloride. This substance was further converted via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 3.7 g of H-(D)-Chg-Pro (2-EtO-4-am)-benzylamide dihydrochloride.

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¹H-NMR (DMSO-d₆, δ in ppm): 9.48 and 9.25 (4H, amidine), 8.83 (t, 1H, NH), 8.60 (3H, NH₃⁺), 7.45-7.30 (3H), 4.40-4.15 (6H, 2xCH₂, 2xCH), 3.98-3.82 (2H, CH₂), 2.20-1.00 (18H, CH₃, 7xCH₂, CH).

5 Example 50

(D)-Cyclohexylglycylproline (2-iodo-4-amidino)benzylamide:

Preparation took place as in Examples 23 (b) and 48. 10.4 g (29.2 mmol) of Boc-(D)-Chg-Pro-OH were condensed as in 48 (b) with 8.6 g (29.2 mmol) of (2-I-4-CN)-benzylamine hydrochloride to give 14.2 g of Boc-(D)-Chg-Pro (2-I-4-CN)-benzylamide. 3.0 g of this compound were further converted via the hydroxyamidine stage with subsequent hydrogenation into 0.9 g of Boc-(D)-Chg-Pro (2-I-4-am)-benzylamide hydroacetate. Elimination of the Boc protective group resulted in 0.3 g of H-(D)-Chg-Pro (2-I-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 512.

Example 51

20 (D)-Cyclohexylglycylproline (2-hydroxy-4-amidino)benzylamide:

1.94 g (5.46 mmol) of Boc-(D)-Chg-Pro-OH were condensed with 1.50 g (5.46 mmol) of (2-BnO-4-CN)-benzylamide hydrochloride as in Example 48 (b) to give Boc-(D)-Chg-Pro (2-BnO-4-CN)-benzylamide almost quantitatively. 1.30 g of this compound were hydrogenated, as in Example 23 (b), via the hydroxyamidine stage with Raney nickel/hydrogen to give a mixture of Boc-(D)-Chg-Pro (2-BnO-4-am)-benzylamide hydroacetate and Boc-(D)-Chg-Pro (2-OH-4-am)-benzylamide hydroacetate. To complete the benzyl cleavage, the hydrogenation was repeated as in Example 44 with Pd/C/hydrogen. Cleavage of the Boc protective group resulted in 0.61 g of H-(D)-Chg-Pro (2-OH-4-am)-benzylamide dihydrochloride (HPLC purity 98.2 %), FAB-MS (M+H⁺): 402.

35 Example 52

(D)-Cyclohexylglycylproline (3-methoxy-4-amidino)benzylamide:

a) Boc-(D)-Chg-Pro (3-MeO-4-CN)-benzylamide:

40 From 2.7 g (7.6 mmol) of Boc-(D)-Chg-Pro-OH and 1.5 g (7.6 mmol) of (3-MeO-4-CN)-benzylamine hydrochloride as in Example 48 (b), 3.0 g of the product (a) were obtained.

45 ¹H-NMR (DMSO-d₆, δ in ppm): 8.05 (1H, NH), 7.60 (d, 1H), 7.10 (1H), 7.05 (1H, NH), 6.95 (1H), 4.50-4.20 (3H), 3.95 (s, 3H), ca. 3.9-ca. 3.3 (3H), 2.1-1.0 (24H).

b) H-(D)-Chg-Pro (3-MeO-4-am)-benzylamide:

3.0 g of the nitrite [sic] (a) were [lacuna] as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 1.3 g of H-(D)-Chg-Pro (3-MeO-4-am)-benzylamide dihydrochloride (HPLC purity > 99%); FAB-MS (M+H⁺): 416.

Example 53

10 (D)-Cyclohexylglycylproline (3-hydroxy-4-amidino)benzylamide:

1.94 g (5.46 mmol) of Boc-(D)-Chg-Pro-OH were condensed with 1.50 g (5.46 mmol) of (3-BnO-4-CN)-benzylamine hydrochloride as in Example 48 (b) to give 2.12 g of Boc-(D)-Chg-Pro (3-BnO-4-CN)-benzylamide. 1.0 g of this compound were hydrogenated as in Example 23 (b) via the hydroxyamidine stage, in contrast to Example 51, immediately with Pd/C/hydrogen. Cleavage of Boc protective group resulted in 0.42 g of H-(D)-Chg-Pro (2-OH-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 402.

20

Example 54

(D)-Cyclohexylglycylproline (3-chloro-4-amidino)benzylamide:

2.38 g (9.33 mmol) of Boc-(D)-Chg-Pro-OH were condensed with 2.80 g (9.33 mmol) of (3-Cl-4-CN)-benzylamine hydrochloride as in Example 23 (b) to give 4.35 g of Boc-(D)-Chg-Pro (3-Cl-4-CN)-benzylamide. 1.60 g of this compound were further converted as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the Boc protective group into 0.91 g of H-(D)-Chg-Pro (3-Cl-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 420.

Example 55

(D)-Cyclohexylglycylproline (2-hydroxycarbonylmethyleneoxy-4-amidino)benzylamide [sic]:

2.00 g (3.48 mmol) of Boc-(D)-Chg-Pro (2-BnO-4-CN)-benzylamide (see Example 51) were hydrogenated as in Example 44 with Pd/C/hydrogen. 1.35 g of Boc-(D)-Chg-Pro (2-OH-4-CN)-benzylamide were obtained and were stirred with an equimolar amount of K₂CO₃ in 30 ml of DMF and 0.41 ml (2.80 mmol) of tert-butyl bromoacetate at RT for 3 d. The product was extracted into the organic phase by adding 100 ml of water and 100 ml of ethyl acetate/ether 1:1 and, after drying over Na₂SO₄, the solvent was stripped off. The crude product obtained in this way was converted as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation and simultaneous cleavage of the Boc protective group and of the

tert-butyl ester in dioxane/hydrochloride, after MPLC, into 280 mg of H-(D)-Chg-Pro (2-(HOOC-CH₂O)-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 460.

5 Example 56

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanylproline [sic] (2-methoxy-4-amidino)benzylamide:

3.2 g (7.8 mmol) of H-(D)-Cha-Pro (2-MeO-4-CN)-benzylamide which
10 had been obtained from the condensation of Boc-(D)-Cha-OH with H-Pro (2-MeO-4-CN)-benzylamide hydrochloride to give Boc-(D)-Cha-Pro (2-MeO-4-CN)-benzylamide and subsequent cleavage of the Boc protective group in DCM/MeOH 20:1 by passing in hydrochloride gas at 0°C was reacted in 100 ml of DCM and 4.7 ml of DIPEA at RT with
15 1.5 g of tert-butyl bromoacetate in 3 d to give 3.2 g of tBuOOC-CH₂-(D)-Cha-Pro (2-MeO-4-CN)-benzylamide hydrochloride, after washing the DCM phase with 0.5 N hydrochloric acid. This compound was converted as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation into crude tBuOOC-CH₂-(D)-Cha-Pro
20 (2-MeO-4-am)-benzylamide dihydroacetate. Purification by column chromatography on silica gel (mobile phase: DCM/10-20% MeOH/3.5% HOAc (50% strength)) resulted in 1.2 g with a purity > 99% (HPLC). Cleavage of the tert-butyl ester in DCM with hydro chloride gas [sic] at 0-5°C resulted in 1.1 g of HOOC-CH₂-(D)-Cha-Pro
25 (2-MeO-4-am)-benzylamide dihydrochloride being isolated; FAB-MS (M+H⁺): 488.

Example 57

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydropro-
30 line [sic] (2-methoxy-6-amidino)benzylamide:

As in Example 26 (a), Boc-Pyr-OH was condensed with (2-MeO-4-CN)-benzylamide hydrochloride to give Boc-Pyr (2-MeO-4-CN)-benzylamide and the Boc protective group was then eliminated. The subse-
35 quent coupling with Boc-(D)-Cha-OH took place as in Example 26 (b). Elimination of the Boc protective group and reaction with tert-butyl bromoacetate as in Example 80 (b) resulted in tBuOOC-CH₂-(D)-Cha-Pyr (2-MeO-4-CN)-benzylamide.

40 The cyano group was converted via the thioamide stage into the corresponding amidine hydroiodide as in Example 108. The hydroiodide was converted into the hydroacetate on an ion exchanger, and the tert-butyl ester was then converted with hydrochloride gas in DCM at 0°C into HOOC-CH₂-(D)-Cha-Pyr (2-MeO-4-am)-benzylamide
45 dihydrochloride; FAB-MS: (M+H⁺): 486.

Example 58

N-(Hydroxycarbonylethylene)-(D)-cyclohexylglycylproline [sic]
(2-methoxy-4-amidino)benzylamide):

- 5 3.0 g (7.5 mmol) of H-(D)-Chg-Pro (2-MeO-4-CN)-benzylamide (see Example 56) were stirred in 70 ml of ethanol with 1.2 g (7.5 mmol) of benzyl acrylate at 60°C for 6 h and at RT for a further 2 d. The solvent was stripped off and the resulting product BnOOC-CH₂-CH₂-(D)-Chg-Pro (2-MeO-4-CN)-benzylamide was purified on a silica gel column (mobile phase: DCM/5% MeOH), isolating 2.3 g. This substance was converted as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation (Raney nickel/hydrogen) into 610 mg of BnOOC-CH₂-CH₂-(D)-Chg-Pro (2-MeO-4-am)-benzylamide dihydroacetate. A further hydrogenation step (Pd-C/hydrogen) as in Example 44 yielded 580 mg of HOOC-CH₂-CH₂-(D)-Chg-Pro (2-MeO-4-am)-benzylamide hydroacetate (HPLC purity: 95.9%); FAB-MS (M+H⁺): 488.

Example 59

- 20 N-(tert-Butoxycarbonylmethylene)-(D,L)-cyclooctylglycylproline [sic] (2-methoxy-4-amidino)benzylamide:

- 2.6 g (4.9 mmol) of Boc-(D,L)-Cog-Pro (2-MeO-4-CN)-benzylamide (see Example 39) were, after elimination of the Boc protective group, reacted as in Example 56 with tert-butyl bromoacetate to give 1.4 g of tBuOOC-CH₂-(D,L)-Cog-Pro (2-MeO-4-CN)-benzylamide. This substance was converted as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation into 1.0 g of tBuOOC-CH₂-(D,L)-Cog-Pro (2-MeO-4-am)-benzylamide hydroacetate; FAB-MS (M+H⁺): 558.

Example 60

N-(Hydroxycarbonylmethylene)-(D,L)-cyclooctylglycylproline [sic]
(2-methoxy-4-amidino)benzylamide:

- 35 700 mg (1.13 mmol) of the compound from Example 59 were converted by cleavage of the tert-butyl ester with hydrochloride gas [sic] at 0°C in DCM over the course of 2 h into 600mg of HOOC-CH₂-(D,L)-Cog-Pro (2-MeO-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 502.

Example 61

N-(Hydroxycarbonylmethylene)-(D,L)-diphenylalanylproline [sic]
(2-methoxy-4-amidino)benzylamide:

45

111

1.6 g (3.1 mmol) of H-(D,L)-Dpa-Pro (2-MeO-4-CN)-benzylamide hydrochloride which was obtained by protective group cleavage from the corresponding Boc-protected compound (Example 36) was reacted with 3.1 mmol of tert-butyl bromoacetate as in Example 56 to give 0.6 g of tBuOOC-CH₂-(D,L)-Dpa-Pro (2-MeO-4-CN)-benzylamide hydrochloride; FAB-MS (M+H⁺): 597.

This 0.6 g of the nitrile was converted by a known method first with H₂S into the thioamide and then with methyl iodide and subsequently ammonium acetate into the amidine hydroiodide. The product was purified by column chromatography on silica gel (mobile phase: DCM/20% MeOH/5% HOAc (50% strength)) and the iodide was replaced by acetate using an ion exchanger (IRA 420); FAB-MS (M+H⁺): 614.

The tert-butyl ester was cleaved as in Example 56 to give 0.25 g of HOOC-CH₂-(D,L)-Dpa-Pro (2-MeO-4-am)-benzylamide dihydrochloride (HPLC purity: 91%), FAB-MS (M+H⁺): 558; byproducts FAB-MS (M+H⁺): 572 and 600.

20

Example 62

Benzylloxycarbonyl-(D)-(tert-butyl)serylproline (2-methoxy-4-amidino)benzylamide:

25 The preparation is described in Example 44.

¹H-NMR (DMSO-d₆, δ in ppm): 8.60 and 8.05 (m, 1H, NH (2 rotamers)), 7.65 and 7.50 (d, 1H, NH (2 rotamers)), 7.40-7.15 (8H), 4.95-4.70 (2d, 2H), 4.45-4.10 (4H), 3.90 (s, 3H), 3.75-3.65 (2H), 3.55-3.35 (4H), 1.10 (s, 9H).

30

Example 63

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanylproline-2-carboxylic [sic] acid (2-methoxy-4-amidino)benzylamide:

35

4.0 g (7.6 mmol) of Boc-(D)-Cha-Pic (2-MeO-4-CN)-benzylamide (Example 48) were, after elimination of the Boc protective group, reacted as in Example 56 with tert-butyl bromoacetate to give 4.0 g of crude tBuOOC-CH₂-(D)-Cha-Pic [sic] (2-MeO-4-CN)-benzylamide hydrochloride. The substance was converted further as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation and cleavage of the tert-butyl ester into 1.8 g of crude HOOC-CH₂-(D)-Cha-Pic (2-MeO-4-am)-benzylamide dihydrochloride. A portion of the substance was purified by MPLC; FAB-MS (M+H⁺): 502.

45

Example 64

N-Benzyl-(D)-cyclohexylglycylproline
(2-methoxy-4-amidino)benzylamide:

- 5 2.7 g (6.8 mmol) of H-(D)-Chg-Pro (2-MeO-4-CN)-benzylamide were reacted with 6.8 mmol of benzyl bromide at 60°C in 40 ml of ethanol for 4 h and subsequently purified to give 0.6 g of Ph-CH₂-(D)-Chg-Pro (2-MeO-4-CN)-benzylamide hydrobromide. The substance was further converted as in Example 23 (b) via the
- 10 hydroxyamidine stage with subsequent hydrogenation into 0.20 g of Ph-CH₂-(D)-Chg-Pro (2-MeO-4-am)-benzylamide hydroacetate (HPLC purity: 95.6%); FAB-MS(M+H⁺): 506.

Example 65

- 15 N-(Hydroxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic]
(2-hydroxy-4-amidino)benzylamide:

- 1.8 g (3.1 mmol) of Boc-(D)-Chg-Pro (2-BnO-4-CN)-benzylamide were stirred in 35 ml of DCM and 35 ml of trifluoroacetic acid at RT
- 20 for 2 h. The solvent was stripped off, and the product was again taken up in DCM and made weakly alkaline with NaHCO₃ solution. The DCM phase was dried and then the solvent was stripped off. H-(D)-Chg-Pro (2-BnO-4-CN)-benzylamide was obtained in quantitative yield. This substance was reacted as in Example 56
- 25 with 3.1 mmol of tert-butyl bromoacetate and subsequently purified by column chromatography on silica gel (mobile phase: DCM/5% MeOH). 1.35 g of t-BuOOC-CH₂-(D)-Chg-Pro (2-BnO-4-CN)-benzylamide were isolated. The subsequent reactions with hydroxylamine and Raney nickel/H₂ as in Example 23 (b)
- 30 yielded, after purification by column chromatography on silica gel (mobile phase: DCM/15% MeOH/3.5% HOAc (50% strength)), 0.9 g of t-BuOOC-CH₂-(D)-Chg-Pro (2-BnO-4-amidino)benzylamide dihydroacetate. The O-benzyl group was eliminated by hydrogenolysis in MeOH with Pd/10% C/H₂ at RT, and then the
- 35 tert-butyl ester was converted into the carboxylic acid as in Example 56. Purification by column chromatography on silica gel (mobile phase: DCM/20% MeOH/5% HOAc) resulted in 0.24 g of HOOC-CH₂-(D)-Chg-Pro (2-OH-4-amidino)benzylamide dihydrochloride with a purity of 94% (HPLC); FAB-MS (M+H⁺): 460.

40

Example 66

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanylproline [sic]
(2-hydroxy-4-amidino)benzylamide:

- 45 2.4 g (4.1 mmol) of Boc-(D)-Cha-Pro (2-BnO-4-CN)-benzylamide, which had been obtained by condensing Boc-(D)-Cha-OH and H-Pro (2-BnO-4-CN)-benzylamide hydrochloride as in Example 23 (b), was

converted by the process described in Example 65 in several stages into 0.6 g of HOOC-CH₂-(D)-Cha-Pro (2-OH-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 474.

5 Example 67

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (2-chloro-4-amidino)benzylamide:

3.3 g (7.51 mmol) of H-(D)-Chg-Pro (2-Cl-4-CN)-benzylamide
 10 hydrochloride, which had been obtained by condensing Boc-(D)-Chg-Pro-OH with (2-Cl-4-CN)-benzylamine hydrochloride and subsequent cleavage of the Boc protective group, were reacted as in Example 56 with tert-butyl bromoacetate to give 2.1 g of tBuOOC-CH₂-(D)-Chg-Pro (2-Cl-4-CN)-benzylamide hydrochloride;
 15 FAB-MS (M+H⁺): 517.

These 2.1 g were further converted as in Example 23 (b) via the hydroxyamidine stage with subsequent hydrogenation into 1.0 g of the corresponding amidine hydroacetate (HPLC purity: 99%) and,
 20 after cleavage of the tert-butyl ester, into 0.6 g of HOOC-CH₂-(D)-Chg-Pro (2-Cl-4-am)-benzylamide dihydrochloride; FAB-MS (M+H⁺): 478.

Example 68

25 N-(hydroxycarbonylmethylene)-(D,L)-(4-tetrahydropyranyl)alanyl-proline [sic] (6-amidino)-3-picolylamide:

(a) Boc-(D,L)-Thpa-Pro (6-CN)-3-picolylamide:

30 4.70 g (17.2 mmol) of Boc-(D,L)-Thpa-OH were stirred in 60 ml of DCM and 11.8 ml of DIPEA at -5°C with 4.90 g (17.2 mmol) of H-Pro (6-carboxamido)-3-picolylamide and 14 ml of PPA (50% strength solution in ethyl acetate) for 5 min and at 0°C for a further 2 h. The DCM phase was washed with NaHSO₄ solution
 35 and then with K₂CO₃ solution and saturated NaCl solution and dried over Na₂SO₄. The solvent was completely stripped off to result in 6.33 g of Boc-(D,L)-Thpa-Pro (6-carboxamido)-3-picolylamide, which was then reacted in 50 ml of DCM and 5.4 ml of DIPEA at 0°C with 2.0 ml of TEAA over the course of
 40 2 h to give 5.5 g of required product.

¹H-NMR (DMSO-d₆, δ in ppm): 8.65 (1H, aromatic H), 8.50 and 8.20 (1H, NH, 2 diastereomers), 8.05-7.80 (2H, aromatic H), 7.12 and 7.02 (1H, NH, 2 diastereomers), 4.5-4.2 (4H, CH₂ and
 45 2 CH), 3.9-3.1 (6H, 3 CH₂), 2.2-1.0 (20H, 5 CH₂, CH and Boc)

(b) $\text{tBuOOC-CH}_2\text{-(D,L)-Thpa-Pro (6-CN)-3-picolylamide}$:

5.5 g (11.3 mmol) of the above compound (a) were converted quantitatively in 60 ml of isopropanol which contained
5 57 mmol of HCl at 50°C over the course of 1.5 h into
H-(D,L)-Thpa-Pro (6-CN)-3-picolylamide hydrochloride. The hydrochloride was taken up in 80 ml of DCM, 8.6 ml of DIPEA were added and, after addition of 1.63 ml (11.3 mmol) of
10 tert-butyl bromoacetate, the reaction mixture was stirred at RT for 3 days. The solution was then washed successively on [sic] 5% strength citric acid, NaHCO_3 solution and saturated NaHCO_3 [sic] solution and dried over Na_2SO_4 . The solvent was stripped off to result in 4.2 g of $\text{tBuOOC-CH}_2\text{-(D,L)-Thpa-Pro (6-CN)-3-picolylamide}$.

15

(c) $\text{HOOC-CH}_2\text{-(D,L)-Thpa-Pro (6-am)-3-picolylamide}$:

4.2 g (8.4 mmol) of the above compound (b) were stirred in 75 ml of DCM/MeOH 1:1 with 584 mg (8.4 mmol) of hydroxylamine
20 hydrochloride and 8.6 ml of DIPEA at 40°C for 5 h and at RT for a further 12 h. Dilute acetic acid was added until the pH reached 5-6, and the product was extracted with DCM. Drying and stripping off the solvent resulted in 4.1 g of the corresponding hydroxyamidine. This was hydrogenated in 100 ml of
25 methanol and one equivalent of acetic acid in the presence of 250 mg of Pd/C (10%) at RT until the required amount of hydrogen had been taken up. The catalyst was filtered off, and the solvent was stripped off to result in 4.2 g of crude
30 $\text{tBuOOC-CH}_2\text{-(D,L)-Thpa-Pro (6-am)-3-picolylamide}$ hydroacetate, which was purified by column chromatography on silica gel (mobile phase: DCM/20% MeOH/3.5% HOAc (50% strength)). Cleavage of the tert-butyl ester on 1.6 g of the purified material with gaseous HCl at 0°C in DCM resulted in 1.4 g of $\text{HOOC-CH}_2\text{-(D,L)-Thpa-Pro (6-am)-3-picolylamide}$ dihydrochloride with
35 a purity > 99% (HPLC); FAB-MS ($\text{M}+\text{H}^+$): 461.

Example 69

N-(Hydroxycarbonylmethylene)-(D,L)-(4-tetrahydropyranyl)glycyl-proline [sic] (6-amidino)-3-picolylamide:

40

8.2 g (17.4 mmol) of Boc-(D,L)-Thpg-Pro (6-CN)-3-picolylamide, which had been prepared as in Example 68 from Boc-(D,L)-Thpg-OH and H-Pro (6-carboxamido)-3-picolylamide, were converted by the process described in Example 68 into 0.4 g of $\text{HOOC-CH}_2\text{-(D,L)-Thpg-Pro (6-am)-3-picolylamide}$ dihydrochloride with a purity of 93%
45 (HPLC); FAB-MS ($\text{M}+\text{H}^+$): 447.

Example 70

N-(Hydroxycarbonylmethylene)-(D,L)-(4-methylcyclohexyl)glycylproline [sic] (6-amido)-3-picolylamide [sic] dihydrochloride:

- 5 As in Example 68, Boc-(D,L)-(4-Me)Chg-OH (see precursor syntheses for preparation) was first coupled with H-Pro-NH-3-(6-CONH₂)-pico to give Boc-(D,L)-(4-Me)Chg-Pro-NH-3-(6-CONH₂)-pico, the primary amide was dehydrated to the nitrile, subsequently the Boc protective group was eliminated and the free amino group was alkylated
10 with tertiary-butyl bromoacetate. The nitrile functionality in tBuOOC-CH₂-(D,L)-(4-Me)Chg-Pro-NH-3-(6-CN)-pico was converted via the hydroxyamidine to the amidine, and subsequently the t-butyl ester was cleaved with HCl. The final product was obtained after purification as crystalline white powder.
15 FAB-MS (M+H⁺): 459.

Example 71

N-(Hydroxycarbonylmethylene)-(D,L)-4-isopropylcyclohexylglycylproline [sic] (6-amidino)-3-picolylamide dihydrochloride:

- 20 As in Example 68, Boc-(D,L)-(4-iPr)Chg-OH (see precursor syntheses for preparation) was first coupled with H-Pro-NH-3-(6-CONH₂)-pico to give Boc-(D,L)-(4-iPr)Chg-Pro-NH-3-(6-CONH₂)-pico, the primary amide was dehydrated to the nitrile,
25 subsequently the Boc protective group was eliminated and the free amino group was alkylated with tertiary-butyl bromoacetate. The nitrile functionality in tBuOOC-CH₂-(D,L)-(4-iPr)Chg-Pro-NH-3-(6-CN)-pico was converted via the hydroxyamidine into the amidine and subsequently the t-butyl ester was
30 cleaved with HCl. The final product was obtained after purification as crystalline white powder.
FAB-MS (M+H⁺): 487.

Example 72

- 35 N-(Hydroxycarbonylmethylene)-(D,L)-(4-tert-butylcyclohexyl)glycylproline [sic] (6-amido)-3-picolylamide [sic] dihydrochloride:

- As in Example 68, Boc-(D,L)-(4-tBu)Chg-OH (see precursor syntheses for preparation) was first coupled with H-Pro-NH-3-
40 (6-CONH₂)-pico to give Boc-(D,L)-(4-tBu)Chg-Pro-NH-3-(6-CONH₂)-pico, the primary amide was dehydrated to the nitrile, subsequently the Boc protective group was eliminated and the free amino group was alkylated with tertiary-butyl bromoacetate. The nitrile functionality in tBuOOC-CH₂-(D,L)-(4-tBu)Chg-Pro-NH-3-
45 (6-CN)-pico was converted via the hydroxyamidine to the amidine, and subsequently the t-butyl ester was cleaved with HCl. The final product was obtained after purification as crystalline

white powder.

FAB-MS ($M+H^+$): 501.

5 Example 73

N-(Hydroxycarbonylmethylene)-(D,L)-(3,3-dimethylcyclohexyl)glycylproline [sic] (6-amido)-3-picolylamide [sic] dihydrochloride:

As in Example 68, Boc-(D,L)-(3,3-Me₂)Chg-OH (see precursor syntheses for preparation) was first coupled with H-Pro-NH-3-(6-CONH₂)-pico to give Boc-(D,L)-(3,3-Me₂)Chg-Pro-NH-3-(6-CONH₂)-pico, the primary amide was dehydrated to the nitrile, subsequently the Boc protective group was eliminated and the free amino group was alkylated with tertiary-butyl bromoacetate. The nitrile functionality in tBuOOC-CH₂-(D,L)-(3,3-Me₂)Chg-Pro-NH-3-(6-CN)-pico as converted via the hydroxyamidine to the amidine, and subsequently the t-butyl ester was cleaved with HCl. The final product was obtained after purification as crystalline white powder.

FAB-MS ($M+H^+$): 473.

Example 74

N-(Hydroxycarbonylmethylene)-(D)-(tert-butyl)serylproline [sic] (6-amido)-3-picolylamide [sic] acetate:

As in Example 68, Z-(D)-Ser(tBu)-OH was first coupled with H-Pro-NH-3-(6-CONH₂)-pico to give Z-(D)-Ser(tBu)-Pro-NH-3-(6-CONH₂)-pico, the Z protective group was eliminated by hydrolysis, the free amino group was initially alkylated with benzyl bromoacetate and subsequently reacted with Z-Cl to give BuOOC-CH₂-(Z)-(D)-Ser(tBu)-Pro-NH-3-(6-CONH₂)-pico. After dehydration of the amide to the nitrile functionality the latter was converted via the hydroxyamidine by hydrogenolysis into the amidine, with simultaneous elimination of the benzyl and Z groups. The final product was obtained after purification as white amorphous powder; FAB-MS ($M+H^+$): 449.

Example 75

N-(Hydroxycarbonylmethylene)-(D,L)-cyclopentylglycylproline (6-amidino)-3-picolylamide dihydrochloride:

As in Example 68, Boc-(D,L)-Cpg-OH (see precursor syntheses for preparation) was first coupled with H-Pro-NH-3-(6-CONH₂)-pico to give Boc-(D,L)-Cpg-Pro-NH-3-(6-CONH₂)-pico, the primary amide was dehydrated to the nitrile, subsequently the Boc protective group was eliminated and the free amino group was alkylated with tertiary-butyl bromoacetate. The nitrile functionality in tBuOOC-

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CH₂-(D,L)-Cpg-Pro-NH-3-(6-CN)-pico was converted via the hydroxyamidine to the amidine, and subsequently the t-butyl ester was cleaved with HCl. The final product was obtained after purification as crystalline white powder.

5 FAB-MS (M+H⁺): 431.

Example 76

N-(Hydroxycarbonylmethylene)-(D,L)-(1-tetralinyl)glycylproline

10 [sic] (6-amidino)-3-picolylamide dihydrochloride:

As in Example 68, Boc-(D,L)-(1-tetralinyl)Gly-OH (see precursor syntheses for preparation) was first coupled with H-Pro-NH-3-(6-CONH₂)-pico to give Boc-(D,L)-(1-tetralinyl)Gly-Pro-NH-3-(6-CONH₂)-pico, the primary amide was dehydrated to the nitrile, subsequently the Boc protective group was eliminated and the free amino group was alkylated with tertiary-butyl bromoacetate. The nitrile functionality in tBuOOC-CH₂-(D,L)-(1-tetralinyl)Gly-Pro-NH-3-(6-CN)-pico was converted via the hydroxyamidine to the amidine, and subsequently the t-butyl ester was cleaved with HCl. The final product was obtained after purification as crystalline white powder.
FAB-MS (M+H⁺): 493.

25 Example 77

N-(Hydroxycarbonylmethylene)-(D,L)-(2-norbornyl)glycylproline

[sic] (6-amidino)-3-picolylamide dihydrochloride:

As in Example 68, Boc-(D,L)-(2-norbornyl)Gly-OH (see precursor syntheses for preparation) was first coupled with H-Pro-NH-3-(6-CONH₂)-pico to give Boc-(D,L)-(2-norbornyl)Gly-Pro-NH-3-(6-CONH₂)-pico, the primary amide was dehydrated to the nitrile, subsequently the Boc protective group was eliminated and the free amino group was alkylated with tertiary-butyl bromoacetate. The nitrile functionality in tBuOOC-CH₂-(D,L)-(2-norbornyl)Gly-Pro-NH-3-(6-CN)-pico was converted via the hydroxyamidine to the amidine, and subsequently the t-butyl ester was cleaved with HCl. The final product was obtained after purification as crystalline white powder.

40 FAB-MS (M+H⁺): 457.

Example 78

N-(t-Butoxycarbonylmethyl)-(D) or (L)-(4-tetrahydropyranyl)-glycylpipercolic acid (6-amidino)-3-picolylamide:

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- (a) Coupling of Boc-(D,L)-Thpg-OH with methyl (L)-pipecolate hydrochloride
- (b) Hydrolysis with 1 N lithium hydroxide
- 5 (c) Coupling of the dipeptide acid with 6-carboxyamido-3-picolyl-amine [sic] dihydrochloride
- (d) Dehydration of the carboxyamido [sic] group with trifluoroacetic anhydride to give the nitrile
- 10 (e) Elimination of the Boc protective group with isopropanolic hydrochloric acid
- 15 (f) Alkylation of the Thpg nitrogen with t-butyl bromoacetate
- (g) Addition of hydroxylamine onto the cyano group
- (h) Catalytic hydrogenation of the N-hydroxyamidine with Pd/C in
- 20 methanol
- (i) Separation of the diastereomers by preparative thick-layer chromatography, mobile phase: CH₂Cl₂/MeOH/50% strength acetic acid (24/6/1.5).
- 25 Acetate of isomer I:
white crystals, melting point 168-170°C (decomposition),
Rf 0.21; FAB-MS (M+H⁺): 517
Acetate of isomer II:
white crystals, melting point 97-98°C (decomposition),
- 30 Rf 0.16; FAB-MS (M+H⁺): 517.

Examples 79 and 80

N-(Hydroxycarbonylmethylene)-(D)- [sic] or (L)-(4-tetrahydropyran-yl)-glycylpipecolic acid (6-amidino)-3-picolylamide:

- 35 The separated diastereomers from Example 78, stage (i) were hydrolyzed with trifluoroacetic acid to give the trifluoroacetates of the carboxylic acids and converted by chromatography on silica gel (eluent: methanol/25% strength aqueous NH₃, 25/1)
- 40 into the free betaines.

- Isomer I: Melting point 157-160°C (decomposition, Rf 0.28 (mobile phase: MeOH/25% strength aqueous NH₃, 50 (2.5); FAB-MS (M+H⁺): 461.
- 45 Isomer II: Melting point 132-135°C (decomposition, Rf 0.24; FAB-MS (M+H⁺): 461.

Example 81

N-(Hydroxycarbonylmethylene)-(D,L)-(4-tetrahydropyranyl)-glycyl-1,3-oxazolidine-4-carboxylic [sic] acid (6-amidino)-3-picolyl-amide:

5

6.1 g (12.9 mmol) of Boc-(D,L)-Thpg-Oxp (6-CN)-3-picolylamide, which had been prepared as in Example 68 from Boc-(D,L)-Thpg-OH and H-Oxp (6-carboxamido)-3-picolylamide [sic] (see also Example 98)) were converted by the process described in Example 68 into 0.2 g of HOOC-CH₂-(D,L)-Thpg-Oxp (6-CN)-3-picolylamide dihydrochloride with a purity of 95.6%;
FAB-MS (M+H⁺): 449.

Example 82

15 N-(Hydroxycarbonylmethylene)-(D)-cyclohexylglycyl-1,3-thiazolidine-4-carboxylic [sic] acid (6-amidino)-3-picolylamide:

- (a) 10.0 g of Boc-Thia-OH and 10.6 g of 3-aminomethyl-6-amidopyridine [sic] x 2 HCl were reacted as in Example 23 and [sic]
20 12.9 g of Boc-Thia-NH-3-(6-amido)-pico [sic]. FAB-MS (M⁺): 366
- (b) 12.5 g of Boc-Thia-NH-3-(6-amido)-pico [sic] were deprotected with TFA/DCM. After workup, 14.9 g of H-Thia-NH-3-(6-amido)-pico [sic] x 2 TFA remained. FAB-MS (M+H⁺):
25 267
- (c) 6.9 g of Boc-(D)-Chg and 14.5 g of H-Thia-NH-3-(6-amido)-pico [sic] x 2 TFA were reacted as in Example 23 with PPA to give
30 11.7 g of Boc-(D)-Chg-Thia-NH-3-(6-amido)-pico [sic]. FAB-MS (M⁺): 505
- (d) 11.5 g of Boc-D-Chg-Thia-NH-3-(6-amido)-pico [sic] were converted as in Example 23 with TFAA to 8.6 g of the nitrile
35 Boc-(D)-Chg-Thia-NH-3-(6-CN)-pico. FAB-MS (M⁺): 487
- (e) 8.5 g of Boc-(D)-Chg-Thia-NH-3-(6-CN)-pico were reacted with TFA/DCM to give 9.9 g of H-(D)-Chg-Thia-NH-3-(6-CN)-pico x 2 TFA. FAB-MS (M+H⁺): 388
40
- (f) 9.5 g of Boc-(D)-Chg-Thia-NH-3-(6-CN)-pico x 2 TFA were reacted with 3.6 g of t-butyl bromoacetate as in Example 68 to give 5.6 g of t-BuOOCCH₂-(D)-Chg-Thia-NH-3-(6-CN)-pico. FAB-MS (M⁺): 501
45

120

(g) 5.4 g of t-BuOOC-CH₂-(D)-Chg-Thia-NH-3-(6-CN)-pico were converted with (Boc)₂O into 5.1 g of the corresponding Boc-protected derivative t-BuOOCCH₂-D-(Boc)Chg-Thia-NH-3-(6-CN)-pico. FAB-MS (M⁺): 602

5

(h) 5.0 g of t-BuOOC-CH₂-(D)-(Boc)Chg-Thia-NH-3-(6-CN)-pico were converted as in Example 1b into the amidine. After workup, 3.5 g of t-BuOOCCH₂-D-(Boc)Chg-Thia-NH-3-(6-am)-pico were isolated. FAB-MS (M+H⁺): 680

10

(i) 3.3 g of t-BuOOC-CH₂-(D)-(Boc)Chg-Thia-NH-3-(6-CN)-pico were deprotected as in Example 68 to give the free compound HOOC-CH₂-(D)-Chg-Thia-NH-3-(6-am)-pico. Yield: 1.6 g; FAB-MS (M⁺): 462

15

Example 83

N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-hydroxyamidino)-3-picolylamide:

20 (a) Boc-(D)-Cyclohexylglycylproline (6-carboxyamido)-3-picolylamide [sic]:

89 g (0.251 mol) of Boc-(D)-Chg-Pro-OH and 56.2 g (0.251 mol) of 6-carboxyamido)-3-picolylamine [sic] were dissolved or
 25 suspended in 500 ml of CH₂Cl₂. Addition of 162.3 g (1.25 mol) of diisopropylethylamine at RT resulted in them substantially dissolving. After cooling to -15°C, 251 ml (0.326 mol) of propanephosphanic [sic] anhydride solution (50% strength in ethyl acetate) were added dropwise, during which the temperature rose to about -5°C. The mixture was left to stir at -5°C
 30 for 2 h. The methylene chloride phase was washed with water, 5% strength NaHCO₃ and 0.5 N KHSO₄ solution, dried over Na₂SO₄ and evaporated to dryness. 106.5 g (87%) of white crystals were isolated, melting point 133-135°C.

35

(b) Boc-(D)-Cyclohexylglycylproline (6-cyano)-3-picolylamide:

31.5 g (0.15 mol) of trifluoroacetic anhydride were added dropwise to a solution of 48.8 g (0.1 mol) of the above compound and 36.3 g (0.36 mol) of triethylamine in 350 ml of
 40 CH₂Cl₂ at -5°C, and the mixture was stirred for 15 min. The solution was washed with water, 5% strength NaHCO₃ and 10% strength KHSO₃ [sic] solution, dried over Na₂SO₄ and distilled to remove methylene chloride. 38.5 g (82%) of pale yellowish
 45 crystals were isolated. A sample recrystallized from ethyl acetate/n-hexane melted at 150-151°C.

(c) (D)-Cyclohexylproline (6-cyano)-3-picolylamide:

Elimination of the Boc protective group took place with isopropanolic hydrochloric acid.

5

(d) N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-cyano)-3-picolylamide:

75 g (0.185 mol) of the isopropanol-containing hydrochloride obtained from the above Boc cleavage were suspended in 350 ml of acetonitrile and, while stirring at RT, 90.8 g (0.73 mol) of diisopropylethylamine were added, resulting in a clear solution. Subsequently, at 20-25°C, 36 g (0.184 mol) of t-butyl bromoacetate were added dropwise over the course of 30 min, and the mixture was left to stir at RT for 2 days. After this, the TLC revealed only small amounts of remaining starting compound and traces of the dialkylation product (TLC: CH₂Cl₂/acetone/MeOH, 45/5/2).

For isolation, the acetonitrile and excess DIPEA were substantially removed by distillation under reduced pressure at 40°C, the residue was taken up in 280 ml of MTB and 30 ml of CH₂Cl₂, and the solution was extracted with 100 ml of water and then washed 2x with 50 ml of water each time.

25

To remove residues of initial base, the organic phase was extracted with a solution of 0.9 g of sulfamic acid ($\cong$ 0.05 equivalent of initial base) in 10 ml of water. Two washes with 30 ml of water and 5% strength NaHCO₃ solution were followed by drying over Na₂SO₄ and then removal of the solvent by distillation at 40°C.

30

The viscous oily residue was dissolved in a mixture of 100 ml of MTB and 200 ml of (i-Pr)₂O, 2 ml of water were added and the mixture was stirred while heating gently until a clear solution was obtained. A dense mass of crystals separated out from the solution over the course of 1 h, and was filtered off with suction and washed with a little cold MTB/(i-Pr)₂O mixture.

35

40

70.9 g (79.3% of theory) of white crystals were isolated, melting point 89-91°C
TLC: CH₂Cl₂/acetone/MeOH, 45/5/2 or MTB/EtOH, 45/5

45 (e) N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-hydroxyamidino)-3-picolylamide:

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50 g (0.72 mol) of hydroxylamine hydrochloride were suspended in 800 ml of CH_2Cl_2 and, while stirring, 92.8 g (0.85 mol) of diisopropylethylamine were added, and the mixture was stirred at RT for 30 min. 180 g (0.37 mol) of nitrile compound were added to this, and the mixture was stirred overnight. The reaction solution was washed 3x with 150 ml of water, dried over Na_2SO_4 and distilled to remove methylene chloride.

The viscous oily residue was mixed with 600 ml of ethyl acetate and heated, whereupon the hydroxyamidine rapidly separated out as a mass of white crystals. After 30 min, they were filtered off with suction and washed with cold ethyl acetate and finally with n-hexane. 175 g (91% of theory) of white crystals were obtained, melting point 154-156°C.

10 g of amorphous yellowish residue remained in the mother liquor and substantially consisting [sic] of hydroxyamidine.

Example 84

20 N-(Benzyloxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-hydroxyamidino)-3-picolylamide:

The compound was obtained as in Example 83, using benzyl bromoacetate for alkylation in stage (d). White crystals, melting point 124-125°C; FAB-MS ($\text{M}+\text{H}^+$): 551.

Example 85

N-(Methoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-methoxycarbonylamidino)-3-picolylamide:

30 (a) Boc-(D)-Cyclohexylglycylproline (6-methoxycarbonylamidino)-3-picolylamide:

A solution of 0.5 g (12.5 mmol) of NaOH in 4 ml of water was added to a suspension of 5.47 g (10 mmol) of Boc-(D)-cyclohexylglycylproline (6-amidino)-3-picolylamide acetate in 40 ml of CH_2Cl_2 at 0°C while stirring vigorously. After stirring for 5 min, a clear interphase system had formed, into which solutions of 0.9 g (9.5 mmol) of methyl chloroformate in 5 ml of CH_2Cl_2 and of 0.6 g of NaOH in 7 ml of water were simultaneously added dropwise.

After 10 min, the mixture was washed with water, 5% strength citric acid and 7% strength NaHCO_3 solution, dried over Na_2SO_4 and evaporated to dryness. 4.8 g of a foam-like residue which

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was pure by TLC (CH_2Cl_2 /acetone/methanol, 45/5/3) were isolated.

- 5 (b) (D)-Cyclohexylglycylproline (6-methoxycarbonylamidino)-3-picolylamide:

10 The above compound (8.8 mmol) was dissolved in 35 ml of trifluoroacetic acid and, after 5 min, concentrated under reduced pressure. The residue was treated with ether, whereupon a white powder formed, and this was dissolved in 100 ml of CH_2CH_2 [sic] and shaken with 30 ml of 1 N NaOH. The organic phase was separated off, dried over Na_2SO_4 and concentrated. Renewed treatment of the residue with ether gave 3.5 g of white crystalline powder (TLC: CH_2Cl_2 /MeOH/50% strength acetic acid, 40/10/2.5).

- (d) N-(Methoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-methoxycarbonylamidino)-3-picolylamide

20 The above compound (7.4 mmol) was dissolved in 15 ml of CH_2Cl_2 , and 2.9 g (22.2 mmol) of diisopropylethylamine and 1.2 g (7.4 mmol) of methyl bromoacetate were added. After standing overnight, the solution was concentrated, the residue was taken up in 90 ml of ethyl acetate, and the solution was washed with water, 5% strength citric acid and 5% strength NaHCO_3 solution, dried and distilled.

30 The residue was mixed with 50 ml of ether, adding a little ethyl acetate and 0.1 ml of water to produce a solution, which was left to stand overnight. The crystals which had separated out were filtered off with suction and recrystallized from ethyl acetate. 22.4 g (63%) of white crystals were isolated, melting point 95-97°C; FAB-MS ($\text{M}+\text{H}^+$): 517.

35

Example 86

N-(t-Butoxycarbonylmethylene)-(D)-(t-butyl)glycylpipecolic [sic] acid (6-amidino)-3-picolylamide:

40 The title compound was obtained as in Example 78 starting from Boc-t-butylglycine and methyl pipecolate hydrochloride. Acetate: white crystals, melting point 170-171°C (decomposition); FAB-MS ($\text{M}+\text{H}^+$): 489.

45

Example 87

N-(Hydroxycarbonylmethylene)-(D)-(t-butyl)glycylpipecolic [sic] acid (6-amidino)-3-picolylamide:

- 5 The above t-butyl ester was cleaved with trifluoroacetic acid and converted into the betaine by chromatography on silica gel (eluent: methanol/conc. NH_3 , 25/1). White crystals, melting point 145-147°C (decomposition); FAB-MS ($\text{M}+\text{H}^+$): 433.

10 Example 88

N-(t-Butoxycarbonylmethylene)-(D)-(neopentyl)glycylpipecolic [sic] acid (6-amidino)-3-picolylamide:

- The title compound was obtained as in Example 78 starting from
15 Boc-neopentylglycine and methyl pipecolate hydrochloride.
Acetate: white crystals, melting point 154-155°C; FAB-MS ($\text{M}+\text{H}^+$): 503.

Example 89

- 20 N-(Hydroxycarbonylmethylene)-(D)-(neopentyl)glycylpipecolic [sic] acid (6-amidino)-3-picolylamide:

- The compound was obtained as in Example 87 from the above t-butyl ester, white crystals, melting point 176-177°C (decomposition);
25 FAB-MS ($\text{M}+\text{H}^+$): 477.

Example 90

N-(Hydroxycarbonylethylene)-(D)-cyclohexylglycylproline [sic] (6-amidino)-3-picolylamide:

- 30 2.6 g (20 mmol) of t-butyl acrylate were added to a solution of 7.38 g (20 mmol) of D-cyclohexylglycylproline (6-cyano)-3-picolyl-amide (Example 83, stage c) in 45 ml of ethanol, and the mixture was heated at 45-60°C for 40 h. The solvent was then removed
35 by distillation, and the residue was purified by column chromatography (eluent: CH_2Cl_2 /acetone/ CH_2Cl_2 , 45/5/3). 7.5 g (75%) of a pale yellowish foam were isolated; FAB-MS ($\text{M}+\text{H}^+$): 498.

- This was converted into the amidine as in Examples 83 and 102,
40 and subsequently the tert-butyl group was eliminated with trifluoroacetic acid, and the betaine was liberated with ammonia. Amorphous powder; FAB-MS ($\text{M}+\text{H}^+$): 459.

Example 91

- 45 N-(Hydroxycarbonylmethylene)-(D,L)-(3,4,5-trimethoxy)phenylalanylproline [sic] (6-amidino)-3-picolylamide acetate:

125

As in Example 68, starting from Boc-(D,L)-(3,4,5-trimethoxy)Phe-Pro-NH-3-(6-CN)-pico (Example 29), first the Boc protective group was eliminated, the free amine was alkylated with tert-butyl bromoacetate, the cyano group was converted via the hydroxyamidine into the amidine, the tert-butyl ester was cleaved and the crude product was purified by MPLC on an RP column, and the solutions were lyophilized. HOOC-CH₂-(D,L)-(3,4,5-trimethoxy)Phe-Pro-NH-3-(6-am)-pico acetate was obtained as an amorphous powder.

FAB-MS (M+H⁺): 543

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Example 92

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanylproline [sic]
(6-amidino-2-methyl)picolylamide:

15 a) Preparation of Boc-(D)-Cha-Pro-NH-3-(2-Me)-pico:

6.6 g of Boc-(D)-Chg-Pro-OH (18.05 mmol) were introduced together with 4.0 g of 2-methyl-3-picolyamine (20.5 mmol, for preparation, see Arch. Pharm. 308 (1975) 969-76 and 14 ml of DIPEA (81.8 mmol) into 200 ml of DCM and, after cooling to 5°C, 18.8 ml of 50% strength propanephosphonic anhydride solution in ethyl acetate (23.92 mmol) were added dropwise. Reaction was allowed to continue for 1 h after warming to room temperature, and the mixture was then concentrated under reduced pressure. The residue was taken up in ethyl acetate, and the ethyl acetate phase was extracted about 10 times with water, dried over magnesium sulfate and concentrated in a rotary evaporator. The residue was stirred with diisopropyl ether to result in 7.4 g (87%) of Boc-(D)-Chg-Pro-NH-3-(2-Me)-pico as white solid.

(b) Preparation of H-(D)-Cha-Pro-NH-3-(2-Me)pico:

8.0 g of Boc-(D)-Cha-Pro-NH-3-(2-Me)-pico (17.0 mmol) were stirred in 35 ml of DCM and 35 ml of ethereal hydrochloric acid (> 3 M) at room temperature for 2 h, concentrated under reduced pressure and codistilled several times with methanol/DCM, and the residue was extracted by stirring with ether. 7.5 g (100%) of H-(D)-Cha-Pro-NH-3-(2-Me)-pico x 2 HCl were obtained as a white solid.

c) Preparation of tBuOOC-CH₂-(D)-Cha-Pro-NH-3-(2-Me)-pico:

9.7 g of H-(D)-Chg-Pro-NH-3-(2-Me)-pico x 2 HCl (21.79 mmol) were stirred together with 11.26 g (14.9 ml) of DIPEA (81.16 mmol) and 4.89 g (3.69 ml) of tert-butyl bromoacetate (25.0 mmol) in 150 ml of DCM (dried over molecular sieves) at

room temperature for 16 h. Since TLC showed that precursor was still present, a further 0.4 ml of tert-butyl bromoacetate and 1.5 ml of DIPEA were added, and the mixture was stirred at RT for a further 3 h. The reaction mixture was then concentrated first under a water pump vacuum and then under 1 mbar at max. 40°C. The residue was extracted by stirring with ether, filtered off and washed with ether. The crystals were taken up in water and, at pH 7.5, extracted several times with ethyl acetate, and these ethyl acetate extracts were combined with the above ether filtrate, dried and concentrated under reduced pressure. The residue was taken up in ether and then ethereal hydrochloric acid was added to pH 3, the precipitate was filtered off with suction, thoroughly washed with ether and then extracted by stirring twice with ether. 9.3 g (82%) of tBuOOC-CH₂-(D)-Cha-Pro-NH-3-(2-Me)-pico x HCl were obtained as a white solid.

d) Preparation of t-BuOOC-CH₂-(Boc)(D)-Cha-Pro-NH-3-(2-Me)-pico:

9.8 g of tBuOOC-CH₂-(D)-Cha-Pro-NH-3-(2-Me)-pico x HCl (18.66 mmol) were introduced together with 18.66 g of (Boc)₂O (18.66 mmol) into 160 ml of DCM and, over the course of 5 min, 5.3 g (7.03 ml) of DIPEA (41.05 mmol) were added, and the mixture was then stirred at RT overnight. After further addition of DCM, washing was carried out with 0.5 M HCl solution until DIPEA was no longer present in the DCM (TLC check), and the solution was dried over magnesium sulfate and concentrated under reduced pressure.

Column chromatography on silica gel with DCM and 0-5% methanol resulted in 5.9 g (54%) of tBuOOC-CH₂-(Boc)(D)-Cha-Pro-NH-3-(2-Me)-pico as white solid.

e) Preparation of tBuOOC-CH₂-(Boc)(D)-Cha-Pro-NH-3-(2-Me-1-Oxo)-pico:

5.9 g of tBuOOC-CH₂-(Boc)-(D)-Cha-Pro-NH-3-(2-Me)-pico (10.12 mmol) were stirred together with 9.99 g of 70% pure m-chloroperbenzoic acid (40.5 mmol) in 200 ml of DCM at RT for 2 h. Gaseous ammonia was then passed in to saturation, the mixture was stirred at room temperature for 1 h, the precipitate was filtered off with suction and washed with DCM, and the filtrate was again saturated with ammonia. The DCM phase was then washed 3 times with water, dried over magnesium sulfate and concentrated under reduced pressure. 6.1 g (100%) were obtained.

- f) Preparation of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-1-MeO)-pico}^{\oplus}\text{-CH}_3\text{OSO}_3^{\ominus}$:

5 6.1 g of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-1-Oxo)-pico}$ (10.12 mmol) were dissolved in 25 ml of DCM, and 28 ml of a 5% strength dimethyl sulfate solution in DCM were added. The mixture was stirred at 40°C for 5 h and left to stand at RT overnight and then diluted to 100 ml with DCM, rapidly washed 3 times with water, dried over magnesium sulfate and concentrated under reduced pressure. The resulting $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-1-MeO)-pico}^{\oplus}\text{-CH}_3\text{OSO}_3^{\ominus}$ was used as crude product in the next reaction.

- g) Preparation of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-CN)-pico}$:

20 The crude $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-1-MeO)-pico}^{\oplus}\text{CH}_3\text{OSO}_3^{\ominus}$ obtained from the above reaction was added dropwise over the course of 20 min to a solution of 1.1 g of sodium cyanide (21.3 mmol) in 50 ml of DMF, keeping the temperature at $23\text{--}25^{\circ}\text{C}$ by cooling. After a further 20 min, DMF was removed by distillation under reduced pressure (1 mbar), the residue was taken up in ether, and the ether phase was washed successively with water, KHSO_4 solution (pH 2), water and saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography on silica gel (eluent: DCM with 0-2% MeOH) resulted in 4.1 g of solid which was extracted by stirring with ether.

30 Yield: 4.1 g (66%) of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-CN)-pico}$

- h) Preparation of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-ham)-pico}$:

35 4.0 g of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-CN)-pico}$ (6.6 mmol) were refluxed together with 1.15 g of hydroxylamine hydrochloride (16.52 mmol) and 5.12 g (6.78 ml) of DIPEA (39.6 mmol) in 75 ml of DCM (dried over molecular sieves) for 2 h and then stirred at RT overnight. After addition of further DCM, the mixture was washed with dilute hydrochloric acid (pH 4), and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The resulting 4.3 g of crude $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-ham)-pico}$ were used as crude product in the next reaction.

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- i) Preparation of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-am)-pico}$:

4.3 g of crude $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-am)-pico}$ were hydrogenated in a mixture of 15 ml of acetic acid and 80 ml of ethanol over Pd/C (10%) with hydrogen at 50°C for 5 h. The catalyst was then filtered off and washed with ethanol, the filtrate was concentrated under reduced pressure (1 mbar), and the residue was codistilled several times with toluene/DCM, taken up in 100 ml of ether and washed 3 times with 4 ml of water each time. The combined aqueous phases were concentrated under reduced pressure (1 mbar) at 35-40°C, and the residue was codistilled with ethanol. 4.3 g of almost pure $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Chg-Pro-NH-3-(2-Me-6-am)-pico} \times \text{CH}_3\text{COOH}$ were obtained (94% over two stages) as white solid.

- j) Preparation of $\text{HOOC-CH}_2\text{-(D)-Cha-Pro-NH-3-(2-Me-6-am)-pico}$:

2.24 g of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pro-NH-3-(2-Me-6-am)-pico} \times \text{CH}_3\text{COOH}$ (3.25 mmol) were stirred in 30 ml of DCM together with 15 ml of ethereal hydrochloric acid at room temperature for several hours, during which a solid slowly precipitated. The solid was filtered off with suction, extracted by stirring with hot DCM several times and subsequently chromatographed on silica gel (mobile phase methanol/25% aqueous ammonia solution in the ratio 95/5). 1.35 g (94%) of $\text{HOOC-CH}_2\text{-(D)-Cha-Pro-NH-3-(2-Me-6-am)-pico}$ were obtained as a white solid. FAB-MS ($\text{M}+\text{H}^+$): 473

Example 93

- (a) $\text{tBuOOC-CH}_2\text{-(D)-Cha-Pyr-NH-3-(6-CN)-pico}$:

4.3 g of $\text{H-(D)-Cha-Pyr-NH-3-(6-CN)-pico}$ (11.27 mmol) (see Example 32) and 5.3 ml of diisopropylethylamine (33.81 mmol) were introduced into 50 ml of methylene chloride and, while stirring at RT, 2.16 g of tertiary-butyl bromoacetate (11.04 mmol) were added dropwise and the mixture was stirred at RT overnight. The solution was diluted with methylene chloride, extracted twice with 5% strength citric acid and twice with saturated NaHCO_3 solution, dried over magnesium sulfate and concentrated under reduced pressure. The crude product was taken up in ether, cooled to 0°C and adjusted to pH 1 with ethereal hydrochloric acid, and the precipitated product was rapidly filtered off with suction, washed several

times with ether and dried. 5.85 g of almost pure crystalline product were obtained ($\cong$ 97% of theory).

(b) $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-CN)-pico}$:

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5.8 g of $\text{tBuOOC-CH}_2\text{-CH}_2\text{-(D)-Cha-Pyr-NH-3-(6-CN)-pico-HCl}$ (11 mmol) were stirred together with 2.4 g of $(\text{Boc})_2\text{O}$ (11 mmol) and 4.7 ml of diisopropylethylamine in 60 ml of methylene chloride at room temperature overnight and then diluted with about 100 ml of methylene chloride, extracted three times with 5% strength citric acid solution, dried with sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: methylene chloride with 0 to 5% methanol). The yield of pure product was 4.1 g ($\cong$ 63% of theory).

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(c) $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-CSNH}_2\text{)-pico}$:

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4.1 g $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-CN)-pico}$ (6.88 mmol) were dissolved in 25 ml of pyridine and 12 ml of triethylamine and saturated with gaseous hydrogen sulfide and stirred overnight at RT. Nitrogen was blown through the solution which was then substantially concentrated, and the residue was dissolved in 75 ml of ethyl acetate, washed successively with 5% strength citric acid, 20% strength NaHSO_4 and twice with saturated NaHCO_3 solution, dried over magnesium sulfate and concentrated, resulting in 4.25 g of pure product as a yellow powder. This was dried under high vacuum overnight. Yield: 98% of theory.

(d) $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-C(NH)SCH}_3\text{)-pico} \times \text{HI}$:

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4.25 g of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-CSNH}_2\text{)-pico}$ (6.75 mmol) were dissolved in 75 ml of acetone, 4.65 ml of methyl iodide were added, and the mixture was stirred in a closed flask at RT overnight. The reaction solution was completely concentrated, dissolved in the minimum amount of ethyl acetate and added dropwise to 200 ml of n-hexane while stirring, and the solid was filtered off with suction and dried. 5.2 g of yellow powder were obtained. Yield: about 100% of theory.

(e) $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-am)-pico} \times \text{CH}_3\text{COOH}$:

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5.2 g of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-C(NH)SCH}_3\text{)-pico} \times \text{HI}$ (6.74 mmol) were dissolved in 11 ml of methanol, 10.3 ml of 10% strength ammonium acetate solution in methanol

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were added, and the mixture was stirred at RT overnight. The reaction solution was concentrated, the residue was taken up in ethyl acetate, the mixture was filtered with suction to remove solid, and the solution was substantially concentrated and added dropwise to diisopropyl ether. The precipitated solid was filtered off with suction and dried. The almost pure crude product was completely purified by MPLC on an RP column. 2.58 g of the required compound were obtained as a pale yellow solid. Yield: 57% of theory.

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(f) $\text{HOOC-CH}_2\text{-(D)-Cha-Pyr-NH-3-(6-am)-pico} \times \text{HCl}$:

2.43 g of $\text{tBuOOC-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-3-(6-am)-pico} \times \text{CH}_3\text{COOH}$ (3.61 mmol) were added to 15 ml of ethereal hydrochloric acid and stirred at RT for 5 h. The almost pure crude product after concentration under reduced pressure was purified by MPLC on an RP column. 1.77 g of final product were obtained as a white lyophilisate. Yield: 95% of theory, FAB-MS ($\text{M}+\text{H}^+$): 457.

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Example 94

N-(Hydroxycarbonylmethylene)-(D,L)-4-tetrahydropyranylalanyl-3,4-dehydroproline [sic] (6-amidino)-3-picolylamide acetate:

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Boc-(D,L)-Thpa-Pyr-NH-3-(6- CONH_2)-pico was prepared as in Example 68 c-k starting from Boc-(D,L)-Thpa-OH (see above for preparation) and H-Pyr-NH-3-(6- CONH_2)-pico HCl (see Example 68), the primary amide functionality was dehydrated to the nitrile, the terminal Boc protective group was eliminated, the free amine was alkylated with tert-butyl bromoacetate, the secondary amine was Boc-protected, the nitrile functionality was converted into the thioamide, and the latter was methylated to give the imino thiomethyl ester, and the latter was reacted with ammonium acetate to give the amidine. After elimination of the protective groups using ethereal hydrochloric acid in methylene chloride and purification of the crude product by MPLC on an RP column, the mixture of diastereomers of $\text{HOOC-CH}_2\text{-(D,L)-Thpa-Pyr-NH-3-(6-am)-pico}$ was obtained as acetate.

40 FAB-MS ($\text{M}+\text{H}^+$): 459

Example 95

N-(Isopropoxycarbonylmethylene)-(D)-cyclohexylglycyl-3,4-dehydroproline [sic] (6-amidino)-3-picolylamide acetate:

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131

As in Example 93 a-j, Boc-Pyr-OH was coupled with H₂N-3-(6-CONH₂)-pico HCl (see above for preparation) to give Boc-Pyr-NH-3-(6-CONH₂)-pico, the Boc protective group was eliminated, the free amino group was coupled with Boc-(D)-Chg-OH to give Boc-(D)-Chg-Pyr-NH-3-(6-CONH₂)-pico, the primary amide functionality was dehydrated to the nitrile, the terminal Boc protective group was eliminated, the free amine was alkylated with tert-butyl bromoacetate, the secondary amine was Boc-protected, the nitrile functionality was converted into the thioamide, and the latter was methylated to give the imino thiomethyl ester and converted with ammonium acetate into the amidine tBuOOC-CH₂-(D)(Boc)Chg-Pyr-NH-3-(6-am)-pico HI. Elimination of the protective groups with isopropanolic hydrochloric acid resulted in two products which were separated by MPLC on an RP column. These were HOOC-CH₂-(D)-Chg-Pyr-NH-3-(6-am)-pico-CH₃COOH
 FAB-MS (M+H⁺): 443
 and by esterification iPrOOC-CH₂-(D)-Chg-Pyr-NH-3-(6-am)-pico-CH₃COOH
 FAB-MS (M+H⁺): 485

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Example 96

N-(Hydroxycarbonylmethylene)-(D,L)-γ-methylcyclohexylalanyl-3,4-dehydroproline [sic] 6-amidino-picolylamide [sic] acetate:

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Preparation took place as in Example 93. The diastereomeric mixture HOOC-CH₂-(D,L)-(γ-Me)Cha-Pyr-NH-3-(6-am)-pico could be separated into the two diastereomers by MPLC on an RP column. FAB-MS (M+H⁺): 471

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Example 97

N-(Hydroxycarbonylmethylene)-(D,L)-cycloheptylalanyl-3,4-dehydroproline [sic] 6-amidino-picolylamide [sic] acetate:

35 Preparation took place as in Example 108. The diastereomeric mixture HOOC-CH₂-(D,L)-Chea-Pyr-NH-3-(6-am)-pico could be separated into the two diastereomers by MPLC on an RP column.
 FAB-MS (M+H⁺): 471.

40 Example 98

N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycyl-(L)-1,3-oxazolidine-4-carboxylic [sic] acid (6-amidino)-3-picolylamide:

Starting from Boc-(D)-cyclohexylglycine, Boc-(L)-1,3-oxazolidine-4-carboxylic acid (Tetrahedron 50 (1994) 13943) and 6-carboxyamido-3-picolylamine [sic] dihydrochloride, the title com-

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pound was obtained as in Example 78. Acetate: white crystals, melting point 187-190°C, FAB-MS (M+H⁺): 503.

Example 99

- 5 N-(Hydroxycarbonylmethylene)-(D)-cyclohexylglycyl-(L)-1,3-oxazolidine-4-carboxylic [sic] acid (6-amidino)-3-picolylamide:

The t-butyl ester (Example 98) was cleaved with trifluoroacetic acid and converted into the betaine with ammonia.

- 10 White crystals, melting point 210-213°C (decomposition); FAB-MS (M+H⁺): 446.

Example 100

- N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylalanyl-(L)-1,3-oxazolidine-4-carboxylic [sic] acid (6-amidino)-3-picolylamide:
 15 Acetate: white crystals, melting point 161-163°C (decomposition); FAB-MS (M+H⁺): 517.

Example 101

- 20 N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanyl-(L)-1,3-oxazolidine-4-carboxylic [sic] acid (6-amidino)-3-picolylamide:
 White crystals, melting point 172-174°C; FAB-MS (M+H⁺): 461.

Example 102

- 25 N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-amidino)-3-picolylamide:

- 110 g (0.212 mol) of N-(t-butoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-hydroxyamidino)-3-picolylamide
 30 (Example 83) were dissolved in 1.5 l of ethanol and 300 ml of glacial acetic acid, 1.5 g of 10% Pd/carbon were added, and hydrogenation was carried out at about 50°C (waterbath) for 6 h. The catalyst was filtered off with suction and then the filtrate was concentrated under reduced pressure at a maximum waterbath temperature of 40°C, and the residue was distilled 4x after addition
 35 of 200 ml of toluene each time. The remaining brown oil was dissolved in 400 ml of acetone and, after seeding, a thick mass of crystals of the amidine acetate rapidly separated out and were filtered off with suction after 1 h and washed with acetone and
 40 finally with ether.

93 g (78% of theory) of acetate were isolated as white crystals, melting point 191-194°C (decomposition); FAB-MS (M+H⁺): 501.

Example 103

N-(Methoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic]
(6-amidino)-3-picolylamide:

- 5 N-(Hydroxycarbonylmethylene)-(D)-cyclohexylproline [sic]
(6-amidino)-3-picolylamide (WO 95/35309) was refluxed in methanolic hydrochloric acid for 12 h. The solvent was stripped off and then the residue was dissolved in water and converted into the acetate using an IRA acetate ion exchanger and subsequently
10 freeze-dried. White powder, melting point 75-76°C; FAB-MS (M+H⁺): 459.

Example 104

- N-(Cyclohexyloxycarbonylmethylene)-(D)-cyclohexylglycylproline
15 [sic] (6-amidino)-3-picolylamide:

The compound was obtained as in Example 83, using cyclohexyl bromoacetate for alkylation in stage (d). White amorphous powder; FAB-MS (M+H⁺): 528.

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Example 105

N,N-bis(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycylproline
[sic] (6-amidino)-3-picolylamide:

- 25 A solution of N-(t-butoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-cyano)-3-picolylamide (compound 83, stage d), 1.2 equivalents of t-butyl bromoacetate and diisopropylethylamine was heated at 60-70°C for 5 h. Workup and subsequent conversion into the amidine took place as for compound 83.
30 Acetate: white crystals, melting point 208-211°C (decomposition); FAB-M (M+H⁺): 615.

Example 106

- N,N-bis(Hydroxycarbonylmethylene)-(D)-cyclohexylglycylproline
35 [sic] (6-amidino)-3-picolylamide:

Obtained from Example 105 by elimination of the t-butyl group. White crystals, melting point 211-215°C (decomposition); FAB-MS (M+H⁺): 503.

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Example 107

N-(Carboxyamidomethylene)-(D)-cyclohexylglycylproline [sic]
(6-amidino)-3-picolylamide:

- 45 N-(Methoxycarbonylmethylene)-(D)-cyclohexylglycylproline [sic]
(6-amidino)-3-picolylamide (compound 103) was left to stand in ammonia-saturated methanol overnight. The solvent was stripped

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off and the residue was codistilled several times with ethanol/toluene.

Acetate: white crystals, melting point 87-89°C, FAB-MS (M+H⁺): 444.

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Example 108

N-(tert-Butylaminocarbonylmethylene)-(D)-cyclohexylglycylproline [sic] (6-amidino)-3-picolylamide acetate:

- 10 As in Example 68, H-(D)-Chg-Pro-NH-3-(6-CN)-pico (Example 83) was alkylated with chloroacetic acid tert-butylamide to give tBuNH-CO-CH₂-(D)-Chg-Pro-NH-3-(6-CN)-pico, and the nitrile functionality was converted via the hydroxyamidine stage into the amidine.

- 15 Purification by MPLC on an RP column and lyophilization resulted in tBuNH-CO-CH₂-(D)-Chg-Pro-NH-3-(6-am)-pico acetate as a white amorphous powder.

FAB-MS (M+H⁺): 500

Examples 109-116 were carried out by the process described above.

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Example 109

N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycylazetidine-2-carboxylic [sic] acid (6-amidino)-3-picolylamide: Acetate: white crystals, melting point 176-178°C; FAB-MS (M+H⁺): 487.6.

25

Example 110

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylglycylazetidine-2-carboxylic [sic] acid (6-amidino)-3-picolylamide:

Betaine: white crystals, melting point 162-164°C (decomposition),

- 30 FAB-MS (M+H⁺): 431.

Example 111

N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylglycylpipecolic [sic] acid (6-amidino)-3-picolylamide:

- 35 Acetate: white crystals, melting point 175-178°C (decomposition); FAB-MS (M+H⁺): 515.5.

Example 112

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylglycylpipecolic [sic] acid (6-amidino)-3-picolylamide:

- 40 Betaine: white crystals, melting point 128-130°C (decomposition); FAB-MS (M+H⁺): 459.

Example 113

- 45 N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylalanylproline [sic] (6-amidino)-3-picolylamide:

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Acetate: white crystals, melting point 83-85°C (decomposition);
FAB-MS: 515 (M+H⁺).

Example 114

- 5 N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanylproline [sic]
(6-amidino)-3-picolylamide:

Betaine: white crystals, melting point 158-162°C (decomposition);
FAB-MS: 459 (M+H⁺).

10 Example 115

N-(t-Butoxycarbonylmethylene)-(D)-cyclohexylalanylpipecolic [sic]
acid (6-amidino)-3-picolylamide:

Acetate: white crystals, melting point 161-164°C (decomposition);
FAB-MS: 529.5 (M+H⁺).

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Example 116

N-(Hydroxycarbonylmethylene)-(D)-cyclohexylalanylpipecolic [sic]
acid (6-amidino)-3-picolylamide:

Betaine: white crystals, melting point 74-76°C; FAB-MS (M+H⁺):

20 473.

Example 117

N-(Hydroxycarbonylmethylene)-(D,L)-cyclooctylglycylproline [sic]
(2-amidino)-5-pyrimidylmethanamide:

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(a) 2.72 g of Boc(D,L)-Cog-OH and 6.9 g of the crude H-Pro-5-(2-CN)-pym x 2 TFA (see above) were combined together with 9.8 ml of DIPEA and 10.1 ml of PPA (50% strength in ethyl acetate) in 40 ml [lacuna] at 0°C. The reaction mixture was allowed slowly to reach RT over the course of 18 h. The reaction solution was then diluted with 200 ml of ethyl acetate, and the resulting solution was washed with water, 5% strength citric acid and 2x with saturated NaHCO₃ solution. The organic solution was dried with MgSO₄ and then ethyl acetate was removed under reduced pressure. 4.88 g of the crude product remained and were used without further purification in the next stage.

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(b) 4.88 g of the crude Boc-(D,L)-Cog-Pro-NH-5-(2-CN)-pym were stirred in 100 ml of methylene chloride with 7.6 ml of TFA at RT for 18 h. The solution was then concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (DCM/MeOH 95:5 + 1% conc. ammonia solution). 3.3 g of H-(D)-Cog-Pro-NH-5-(2-CN)-pym remained;

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FAB-MS (M⁺) 498

- (c) 3.3 g of H-(D)-Cog-Pro-NH-5-(2-CN)-pym were introduced together with 1.5 g of KI and 1.26 g of potassium carbonate into 30 ml of acetonitrile. Then 1.24 ml of t-butyl bromoacetate were added in portions. After the reaction mixture had been stirred for 18 h it was filtered, the filter cake was washed with acetonitrile, and the combined filtrates were concentrated under reduced pressure. The residue was then taken up in ethyl acetate, the organic solution was extracted 3x with water and 1x with saturated NaCl solution and, after the solution had been dried with MgSO₄, ethyl acetate was removed under reduced pressure. 4.2 g of the crude product remained. This was purified by column chromatography (DCM/MeOH 98:2 + 1% conc. ammonia solution). 1.76 g of the product remained. FAB-MS (M⁺): 398
- (d) 1.76 g of t-BuOOC-CH₂-(D)-Cog-Pro-NH-5-(2-CN)-pym were dissolved in 35 ml of ethanol. After addition of 0.6 g of hydroxylammonium chloride and 3.2 ml of DIPEA, the solution was heated to 60°C and stirred at this temperature for 2.5 h. The heating bath was then removed, and the reaction mixture was stirred for a further 18 h. After concentration of the reaction solution, the crude product was dissolved in 60 ml of methylene chloride and the solution was extracted 3x with 5 ml of acetic acid and 1x with saturated NaCl solution and dried with Na₂SO₄, and the solvent was removed under reduced pressure. 2.0 g of the crude product remained and were used without further purification in the next stage.
- (e) 2 g of the crude N-hydroxyamidine derivative were dissolved in 35 ml of ethanol and 1.75 ml of glacial acetic acid. Addition of 2 g of Raney nickel and reduction with hydrogen (atmospheric pressure) resulted in the product tBuOOC-CH₂-(D)-Chg-Pro-NH-5-(2-am)-pym. It was purified from impurities by column chromatography (methylene chloride/MeOH/50% strength HOAc 40:10:2). Concentration of the fractions resulted in 420 mg of the required product remaining. FAB-MS (M⁺): 529
- (f) 420 mg of tBuOOC-CH₂-(D)-Cog-Pro-NH-5-(2-am)-pym were [sic] stirred in 4 ml of DCM/TFA (1:1) at RT for 18 h. The solution was then concentrated. The remaining crude product was purified by column chromatography on silica gel (MeOH/25% strength aqueous ammonia solution 100:3). The concentrated eluate was dissolved in water and stirred together with active carbon. After the active carbon had been removed by

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filtration, the filtrate was frozen and lyophilized. 166 mg of the product remained.

FAB-MS (M^+): 473.

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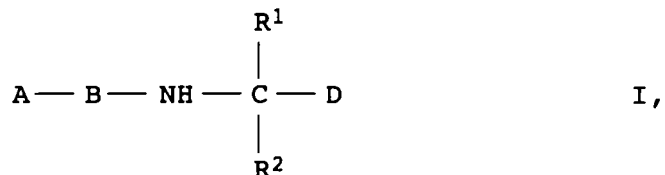
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We claim:

1. A compound of the formula I

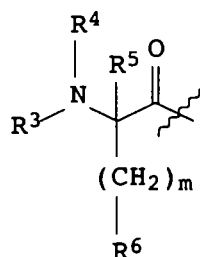


and the salts thereof with physiologically tolerated acids and the stereoisomers thereof, in which the substituents have the following meanings:

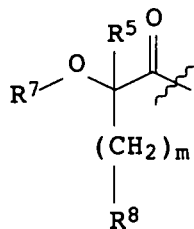
R^1 : H, C_{1-4} -alkyl;

R^2 : H, C_{1-4} -alkyl, phenyl, phenyl- C_{1-4} -alkylene [sic], $\text{R}^{18}\text{O}-\text{CH}_2-$, $\text{R}^{18}-\text{CO}-$, $\text{R}^{18}-\text{O}-\text{CH}_2-\text{CO}-$, $\text{R}^{18}\text{O}-\text{CO}-\text{CO}-$, $\text{R}^{18}-\text{NH}-\text{CO}-\text{CO}-$, where R^{18} is H, C_{1-4} -alkyl, phenyl- C_{1-4} -alkylene [sic] or phenyl, or $\text{CF}_3-\text{CO}-$, $\text{C}_2\text{F}_5-\text{CO}-$ or C_{1-4} -alkyl- $\text{O}-\text{CO}-$,

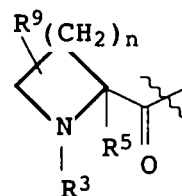
A:



IIa



IIb



IIc

in which the substituents have the following meanings:

m : 0 or 1,

n : 1, 2, 3 or 4,

R^3 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkylene [sic], $\text{R}^{19}\text{OOC}-\text{C}_{1-6}$ -alkylene [sic] (R^{19} = H, C_{1-4} -alkyl, benzyl), $\text{HO}_3\text{S}-\text{C}_{1-3}$ -alkylene [sic], C_{1-12} -alkyl- $\text{CO}-$, aryl- $\text{CO}-$, aryl- C_{1-4} -alkylene- $\text{CO}-$ [sic], $\text{R}^{19}\text{OOC}-\text{C}_{1-6}$ -alkylene- $\text{CO}-$ [sic], $\text{HO}_3\text{S}-\text{C}_{1-3}$ -alkylene- $\text{CO}-$ [sic], C_{1-7} -alkyl- $\text{OOC}-$, benzyl- $\text{OOC}-$, or

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5 $R^{20}R^{21}N-CO-$ (R^{20} and R^{21} are identical or different and are H, C_{1-6} -alkyl, aryl, aryl- C_{1-4} -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene [sic] and $R^{19}-NH-CO-C_{1-4}$ -alkylene [sic], where R^{20} and R^{21} may also together be a $-(CH_2)_{3-6}$ - group), or $R^{19}-O-$

10 R^4 : H, C_{1-12} -alkyl, aryl- C_{1-4} -alkylene [sic] or $R^{19}OOC-C_{1-4}$ -alkylene [sic] ($R^{19} = H, C_{1-4}$ -alkyl, benzyl),

R^5 : H, C_{1-4} -alkyl or benzyl,

15 R^6 : C_{3-8} -cycloalkyl, where the aliphatic rings can be provided with up to 4 C_{1-4} -alkyl and/or CH_3O groups, and one or more methylene group(s) can be replaced by $-O-$, $-S-$ or $N-C_{1-4}$ -alkyl,

20 phenyl which can be substituted by up to 3 identical or different radicals from the group of C_{1-4} -alkyl, CF_3- , C_{1-4} -alkoxy, $F-$ or $Cl-$,

$R^{25}R^{26}CH-$, where R^{25} is C_{1-6} -alkyl and R^{26} is H or C_{1-6} -alkyl,

25 adamantyl, norbornyl-, 1-decalinyl-, 1-tetralinyl-, 2-tetralinyl, 1-indanyl, 2-indanyl, dibenzosuberyl, which can be monosubstituted on one or both aromatic rings, diphenylmethyl which can be monosubstituted on one or both rings, dicyclohexylmethyl,
30 phenyl- $C(CH_3)_2-$, phenyl- $CH(CH_2-CH_2-OR^{19})-$, C_{1-4} -alkyl- $C\equiv C-$, aryl- $C\equiv C-$, $(CH_3)_3Si-$, $R^{19}-S-CH_2-$,

35 $R^{22}O-C(R^{23}R^{24})-$, where R^{22} is H, C_{1-4} -alkyl, phenyl, benzyl or C_{1-4} -alkyl- $CO-$, R^{23} is H, C_{1-4} -alkyl, $HO-C_{1-3}$ -alkylene [sic], phenyl or benzyl and R^{24} is H, C_{1-4} -alkyl, $HO-C_{1-3}$ -alkylene [sic], phenyl or benzyl,

40 R^7 : H, C_{1-12} -alkyl, C_{1-20} -alkyl- $CO-$, $R^{19}OOC-C_{1-4}$ -alkylene [sic], $R^{19}OOC-C_{1-4}$ -alkylene- $CO-$ [sic], $R^{19}NH-CO-C_{1-4}$ -alkylene [sic], $R^{20}R^{21}N-CO-$, HO_3S-C_{1-4} -alkylene [sic], HO_3S-C_{1-4} -alkylene- $CO-$ [sic], 5-(1H)-tetrazolyl- CH_2- or $(R^{19}O)_2OP-CH_2-$ or the acyl radical of a natural or unnatural bile acid,

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R⁸: phenyl which can be substituted by 1 to 3 identical or different radicals from the group of F, Cl, C₁₋₃-alkyl, C₁₋₃-alkyl-O-, HO- or CF₃-,

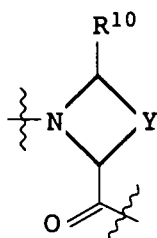
5 C₃₋₈-cycloalkyl, where the aliphatic rings can be provided with up to 4 C₁₋₄-alkyl and/or CH₃O groups, and one or more methylene group(s) can be replaced by -O-, -S- or N-C₁₋₄-alkyl,

10 R²⁵R²⁶CH- in which R²⁵ is C₁₋₆-alkyl, C₅₋₈-cycloalkyl or phenyl, which can be substituted by 1 to 3 F, Cl, C₁₋₃-alkyl, C₁₋₃-alkyl-O-, HO- or CF₃, and R²⁶ is H or has one of the meanings stated for R²⁵,

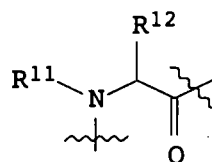
15 or R²²O-CH₂-, adamantyl, norbornyl, 1-decalinyl, 1-tetralinyl, 2-tetralinyl, 1-indanyl, 2-indanyl, C₁₋₄-alkyl-C≡C-, aryl-C≡C-, (CH₃)₃Si or dibenzosuberyl which can be monosubstituted on one or both aromatic rings,

20 R⁹: H, C₁₋₄-alkyl, aryl or C₅₋₆-cycloalkyl (R⁹ can in accordance with formula IIc be a substituent on all ring positions apart from positions 1 and 2)

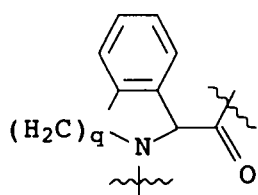
25 B:



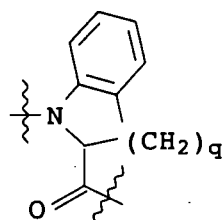
IIIa



IIIb

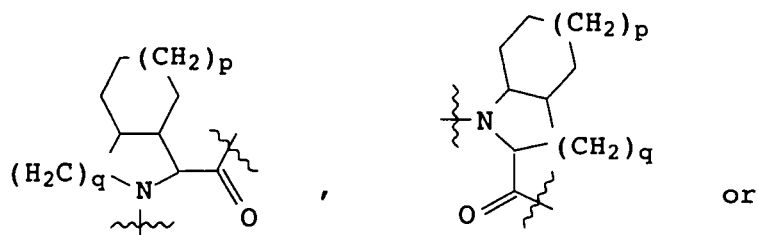


IIIc



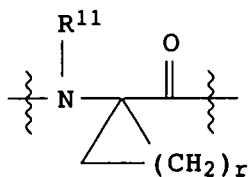
IIId

45



IIIIe

IIIIf



IIIIg

in which the substituents R^{10} , R^{11} and R^{12} , and p , q , r and Y , have the following meanings:

p : 0 or 1

q : 1 or 2

r : 1, 2, 3, 4 or 5

Y : a methylene group,
an ethylene group in which the ring resulting
therefrom can carry in position 4 a hydroxyl, oxo or
 C_{1-4} -alkoxy group,

$-CH_2-S-$, $-CH_2-SO-$, $-CH_2-O-$, $-CH=CH-$ or a propylene
group, in which the ring resulting therefrom can
carry on the carbon in position 3 and/or 4 a
 C_{1-4} -alkyl group or in which a CH_2 group can be
replaced by $-O-$, $-S-$ or $-SO-$,

R^{10} : H, C_{1-4} -alkyl or phenyl,

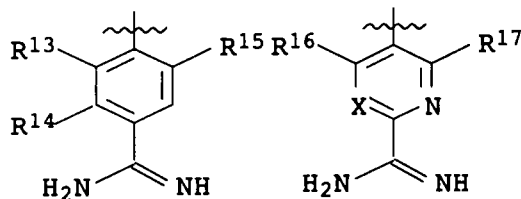
R^{11} : H, C_{1-4} -alkyl, C_{3-8} -cycloalkyl, phenyl or benzyl,

R^{12} : H, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, phenyl or benzyl,

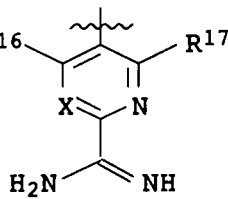
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D:

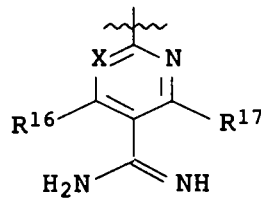
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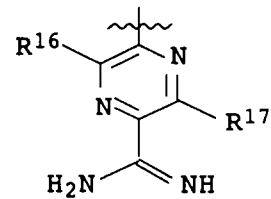
IVa



IVb

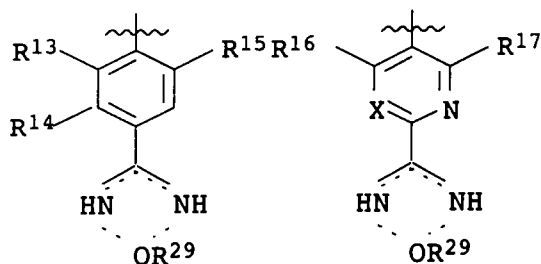


IVc

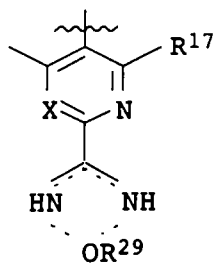


IVd

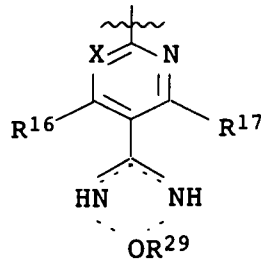
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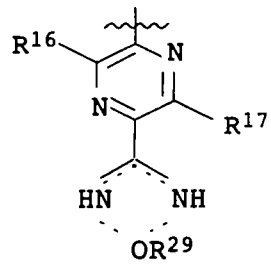
IVe



IVf



IVg



IVh

15

in which the substituents have the following meanings:

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R^{13} , R^{14} and R^{15} , which can be identical or different, are H, NO_2 , F, Cl, Br, I, C_{3-6} -cycloalkyl, $\text{R}^{30}\text{-O-}$, $\text{R}^{30}\text{OOC-}$, $\text{R}^{30}\text{-NH-}$, $\text{R}^{30}\text{-CO-NH-}$, where R^{30} is H, C_{1-6} -alkyl, C_{3-6} -cycloalkyl, benzyl or phenyl, or

25

R^{13} and R^{14} together are the chains $\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$, $\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$, $\text{-O-CH}_2\text{-O-}$ or -CH=CH-CH=CH- ,

30

R^{16} : H, F, Cl, C_{1-4} -alkyl, phenyl- C_{1-2} -alkylene [sic], phenyl, $\text{R}^{31}\text{OOC-}$ (R^{31} = H, C_{1-4} -alkyl, phenyl or benzyl), $\text{R}^{31}\text{-NH-}$, $\text{R}^{31}\text{-O-}$ or $\text{R}^{31}\text{OOC-CH}_2\text{-O-}$,

35

R^{17} : H, F, Cl, C_{1-4} -alkyl, phenyl- C_{1-2} -alkylene [sic], phenyl, $\text{R}^{31}\text{OOC-}$, $\text{R}^{31}\text{-NH-}$, $\text{R}^{31}\text{-O-}$ or $\text{R}^{31}\text{OOC-CH}_2\text{-O-}$,

R^{29} : H or C_{1-4} -alkyl, C_{1-4} -alkoxy, C_{1-4} -alkoxy-CO,

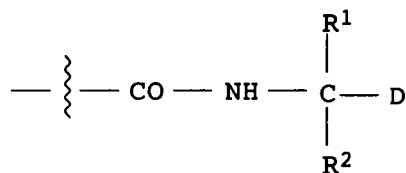
X: =CH- or =N-.

2. A compound of the formula I as claimed in claim 1 for use for controlling diseases.

3. A peptide or peptidomimetic substance which inhibits a serine protease and which contains the constituent

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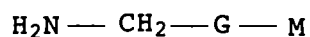
143



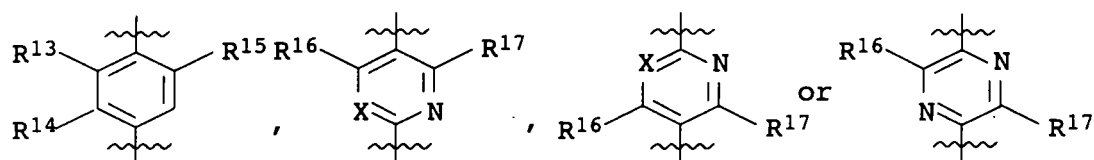
XIV

where D has the meanings stated in claim 1.

4. A compound of the formula

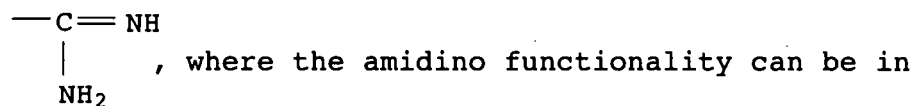


where G is one of the radicals



and

M is one of the groups $-\text{C}\equiv\text{N}$, $-\text{CO}-\text{NH}_2$ or



in mono- or diprotected form.