

Prodrugs of thrombin inhibitors

The present invention relates to prodrugs of pharmacologically active five-membered heterocyclic amidines from which are produced in vivo compounds which are competitive inhibitors of trypsin-like serine proteases, in particular thrombin, to the preparation thereof and to the use thereof as medicines. The invention also relates to pharmaceutical compositions which comprise the prodrugs of the active compounds as ingredients, and to the use of the compounds as thrombin inhibitors, anticoagulants and as antiinflammatory agents.

Thrombin belongs to the group of serine proteases and plays a central part in the blood coagulation cascade as terminal enzyme. Both the intrinsic and the extrinsic coagulation cascade lead via a plurality of amplifying stages to the production of thrombin from prothrombin. Thrombin-catalyzed cleavage of fibrinogen to fibrin then initiates blood coagulation and aggregation of platelets which, in turn, due to the binding of platelet factor 3 and coagulation factor XIII, and a large number of highly active mediators, enhance thrombin formation.

The formation and action of thrombin are central events in the development of white, arterial, and of red, venous, thrombi and are therefore potentially effective points of attack for drugs. Thrombin inhibitors are, by contrast with heparin, able independently of cofactors completely to inhibit simultaneously the effects of free thrombin and of that bound to platelets. They are able to prevent in the acute phase thromboembolic events after percutaneous transluminal coronary angioplasty (PTCA) and lysis, and to act as anticoagulants in an extracorporeal circulation (heart-lung machine, hemodialysis). They can also be used generally for the prophylaxis of thrombosis, for example after 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 Phe-Pro-Arg in which the N-terminal amino acid is in the D form have proven particularly beneficial. D-Phe-Pro-Arg-isopropyl ester is described as a competitive thrombin inhibitor (C. Mattson et al., *Folia Haematol*, 109, 43-51, 1983).

WO 94/29336, EP 0 601 459 and WO 95/23609, WO 95/35309, WO 97/23499 and WO 98/06740 represent a further development in which the agmatine residue is replaced by an arylamidine residue.

EP 0 672 658 describes not only thrombin inhibitors having an agmatine or benzamidine residue but also a thrombin inhibitor with an amidinothiophene (Example 65).

5 WO 98/06741, WO 99/37611 and WO 99/37668 describe thrombin inhibitors with five-membered heterocyclic amidines.

Although these compounds have a significant antithrombotic action, an improvement in their pharmacokinetic properties after oral or parenteral administration is advantageous. It is desirable inter alia to influence the following pharmacokinetic properties:

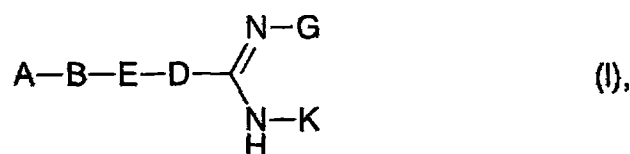
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- I. Improving the absorption from the gastrointestinal tract, aiming at high bioavailability.
- 15 II. Minimizing the inter- and intraindividual variability of the bioavailability through a constant absorption.
- III. Achieving therapeutically relevant active levels which are as constant as possible over the time course. In relation to the therapeutic index, plasma concentrations which are as constant as possible over the time course are indispensable, because
20 excessive fluctuations may lead to unwanted side effects. If the plasma concentration of the active substance is too high, hemorrhages may be expected, and if the concentration is too low there is an increased risk of thrombus formation.
- IV. Prolonging the duration of action of the active substance:
25 Active substance means the pharmacologically active substance (drug) in contrast to the substance (prodrug) which must first be converted metabolically into the active substance.

30 Another advantage of prodrugs over drugs is that no high local concentrations of the drugs occur outside the target site. In addition, side effects of less selective drugs are minimized because no other serine proteases are inhibited for example in the gastrointestinal tract if the drug is produced by metabolism of the prodrug essentially only after or during passage through the stomach and intestines.

35 The aim of this invention is to improve the pharmacokinetic properties of the thrombin inhibitors mentioned in particular in WO 98/06741 through suitable prodrugs.

The invention relates to compounds of the formula I



5 in which A, B, D, E, g and K have the following meanings:

A: $\text{R}^1\text{OOC}-\text{CH}_2-$, $\text{R}^1\text{OOC}-\text{CH}_2-\text{CH}_2-$, $\text{R}^1\text{OOC}-\text{CH}(\text{CH}_3)-$, $\text{R}^1\text{OOC}-\text{C}(\text{CH}_3)_2-$, $\text{R}^1\text{OOC}-\text{CH}(\text{C}_2\text{H}_5)-$, $\text{C}_{1-4}\text{-alkyl}-\text{SO}_2-(\text{CH}_2)_{2-6}-$, $\text{HO}_3\text{S}-(\text{CH}_2)_{2-6}-$, 5-tetrazolyl- $(\text{CH}_2)_{1-6}-$, $\text{C}_{1-4}\text{-alkyl}-\text{O}-(\text{CH}_2)_{2-6}-$, $\text{R}^2\text{R}^3\text{N}-(\text{CH}_2)_{2-6}-$, $\text{R}^2\text{S}-(\text{CH}_2)_{2-6}-$, $\text{R}^2\text{R}^3\text{NSO}_2-(\text{CH}_2)_{2-6}-$, $\text{HO}-(\text{CH}_2)_{2-6}-$,
 10 $\text{R}^{1a}\text{S}(\text{O})\text{C}-\text{CH}_2-$, $\text{R}^{1a}\text{O}(\text{S})\text{C}-\text{CH}_2-$, $\text{R}^2\text{R}^3\text{N}(\text{O})\text{C}-\text{CH}_2-$, $\text{R}^2\text{R}^3\text{N}-\text{O}-\text{CO}-\text{CH}_2-$, $\text{R}^2\text{N}(\text{OH})-\text{CO}-\text{CH}_2-$, where R^2 and R^3 are, independently of one another, h, $\text{C}_1-\text{C}_6\text{-alkyl}$, $\text{C}_{3-8}\text{-cycloalkyl}$ or $\text{C}_{3-8}\text{-cycloalkyl}-\text{C}_{1-3}\text{-alkyl}$ or R^2 and R^3 together form a $\text{C}_{4-6}\text{-alkylene}$ chain,

15 in which

R^1 : is H-, $\text{C}_1-\text{C}_{16}\text{-alkyl}$, $\text{H}_3\text{C}-[\text{O}-\text{CH}_2-\text{CH}_2]_q$ ($q = 1-4$), $\text{C}_7-\text{C}_{12}\text{-bicycloalkyl}$, $\text{C}_{10}\text{-tricycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}-\text{C}_1-\text{C}_3\text{-alkyl}$, pyranyl, piperidiny, aryl or phenyl- $\text{C}_1-\text{C}_4\text{-alkyl}$, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical or different radicals selected from $\text{C}_1-\text{C}_4\text{-alkyl}$, CF_3 , F, Cl, NO_2 , HO or $\text{C}_1-\text{C}_4\text{-alkoxy}$ radicals,
 20 or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by $\text{C}_1-\text{C}_{16}\text{-alkyl}$ or aryl,

25 R^{1a} : is H-, $\text{C}_1-\text{C}_{16}\text{-alkyl}$, $\text{H}_3\text{C}-[\text{O}-\text{CH}_2-\text{CH}_2]_q$ ($q = 1-4$), $\text{C}_7-\text{C}_{12}\text{-bicycloalkyl}$, $\text{C}_{10}\text{-tricycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}-\text{C}_1-\text{C}_3\text{-alkyl}$, aryl or phenyl- $\text{C}_1-\text{C}_3\text{-alkyl}$, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from $\text{C}_1-\text{C}_4\text{-alkyl}$, CF_3 , F, Cl, NO_2 , HO or $\text{C}_1-\text{C}_4\text{-alkoxy}$ radicals,

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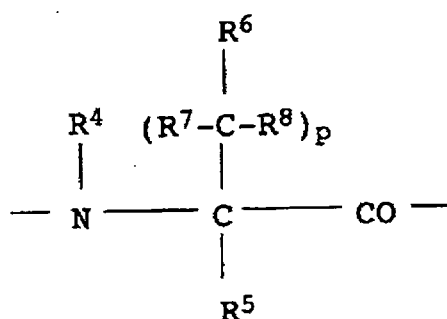
or

R^1 : is $\text{R}^{1b}-\text{C}(\text{O})\text{O}-\text{C}(\text{R}^{1c})_2-$, $\text{R}^{1b}-(\text{CO})\text{NR}^2-\text{C}(\text{R}^{1c})_2-$, where R^{1b} can be $\text{C}_1-\text{C}_4\text{-alkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}-\text{C}_1-\text{C}_3\text{-alkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}$, $\text{C}_1-\text{C}_4\text{-alkyloxy}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}-\text{C}_1-\text{C}_3\text{-}$

alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are, independently of one another, H, CH₃ or C₂H₅, and R² has the meaning stated above,

or R²OOC-C₁-C₆-alkyl, R²R³N(O)C-C₁-C₆-alkyl, R²R³N-C₂-C₆-alkyl, and in which R² and R³ have the same meanings as above or, if R¹ is R²R³N(O)C-C₁-C₆-alkyl, R² and R³ together form a C₄-C₆-alkylene chain,

B



in which

p is 0, 1,

R⁴ is H-, R⁹OOC- with R⁹ = C₁₋₁₆-alkyl, C₃₋₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, R¹⁰C(O)-O-CH₂-, R¹⁰C(O)-O-CH(CH₃)-, where R¹⁰ can be C₁-C₄-alkyl, phenyl, benzyl, C₃-C₈-cycloalkyl or cyclohexyl-CH₂-,

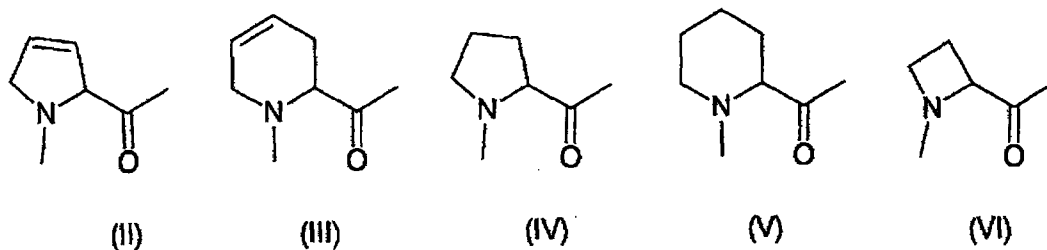
R⁵ is H-,

R⁶ is H-, C₁₋₈-alkyl, C₇-C₁₂-bicycloalkyl or C₁₀-tricycloalkyl, phenyl which may carry up to three identical or different radicals from the group of C₁₋₄-alkyl, CF₃-, C₁₋₄-alkoxy, F- or Cl-, or C₃₋₈-cycloalkyl which may carry up to four identical or different C₁₋₄-alkyl radicals, or where one or two C-C single bonds in the ring can be replaced by a C=C double bond, or a phenyl ring can be fused on,

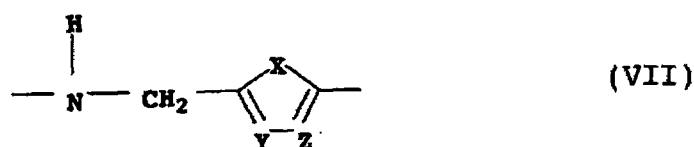
R⁷ is H-, C₁₋₈-alkyl, phenyl which may carry up to three identical or different radicals from the group of C₁₋₄-alkyl, CF₃-, C₁₋₄-alkoxy, F- or Cl-, or C₃₋₈-cycloalkyl which may carry up to four identical or different C₁₋₄-alkyl radicals,

R⁸ is H-, CH₃-,

E



D



5

with

X = S, O

Y = CH, C-CH₃, C-Cl, C-CF₃ and10 Z = CH, C-CH₃, C-Cl, C-CF₃

or X = S, O

Y = N

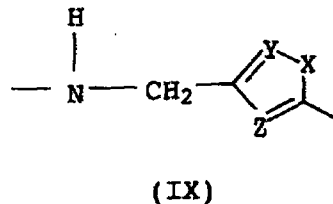
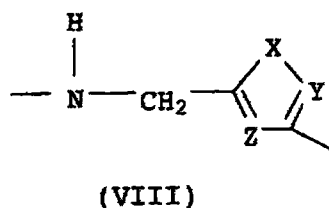
Z = CH, C-CH₃, C-CF₃

or X = S, O

Y = CH, C-CH₃, C-CF₃

Z = N,

or D is equal to



15

with

X = S, O

Y = CH, C-CH₃ und C-CF₃20 Z = CH, C-CH₃, C-Cl and C-CF₃

or X = O Y = N Z = CH, C-CH₃, C-CF₃
 or X = O, S Y = CH, C-CH₃, C-CF₃ Z = N

G : -H, -OH, -OR¹⁸, -OC(O)R¹⁹, -C(O)OR²⁰, -SR¹⁸, -C(S)SR²⁰,

in which

R¹⁸: is -C₁₋₈-alkyl, -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -aryl or -C₁-C₆-alkylphenyl, each of
 5 which may carry optionally up to three C₁-C₄-alkyl, CF₃, F, Cl, NO₂ or C₁-C₄-alkoxy
 radicals

R¹⁹: is -C₁₋₃-alkyl, -phenyl,

R²⁰: is -C₁₋₈-alkyl, -CH₂CCl₃, -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -C₃-C₈-cycloalkyl, -phenyl or
 10 C₁-C₃-alkylphenyl, each of which may carry optionally up to three identical or
 different radicals selected from the group of C₁-C₄-alkyl, CF₃, F, Cl, NO₂ or C₁-C₄-
 alkoxy radicals, or CH₂O-C(O)R^{10a}, -CH(CH₃)O-C(O)R^{10a}, where R^{10a} can be C₁-
 C₁₀-alkyl, -phenyl, benzyl, -C₃-C₈-cycloalkyl or -CH₂-cyclohexyl, or -C(R^{10b})₂-CH₂-O-
 (O)C-R^{10c}, where the two R^{10b} radicals can be, independently of one another, h,
 CH₃ or ethyl, and R^{10c} is -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -C₃-C₈-cycloalkyl or -C₁-C₄-
 15 alkyl,

K : H,

or g and K together form a -C(O)O-, -C(O)S-, -C(S)S- or
 -C(S)O- group,

20 the configurational isomers thereof, tautomers and the salts thereof with physiologically
 tolerated acids,

where the following applies, with retention of the meanings of D:

25 (i)

when E is II or III, and g and K are h, then A and B have the following meanings:

30 A: R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)-, R¹OOC-C(CH₃)₂-, R¹OOC-
 CH(C₂H₅)-, R^{1a}S(O)C-CH₂-, R^{1a}O(S)C-CH₂-, R²R³N(O)C-CH₂-, R²R³N-O-CO-CH₂-,
 R²N(OH)-CO-CH₂-, C₁₋₄-alkyl-SO₂-(CH₂)₂₋₆-, HO₃S-(CH₂)₂₋₆-, 5-tetrazolyl-(CH₂)₁₋₆-,
 C₁₋₄-alkyl-O-(CH₂)₂₋₆-, R²R³N-(CH₂)₂₋₆-, R²S-(CH₂)₂₋₆-, R²R³NSO₂-(CH₂)₂₋₆-, where
 R² and R³ are, independently of one another, h, C₁-C₆-alkyl or C₃₋₈-cycloalkyl or R²
 35 and R³ together form a C₄₋₆-alkylene chain,

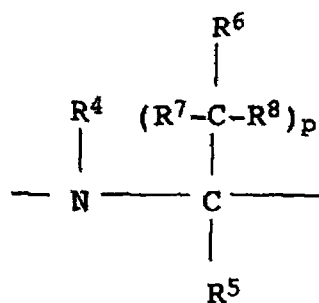
in which

R^1 : is C_7 - C_{16} -alkyl, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_7 - C_{12} -bicycloalkyl, C_{10} -tricycloalkyl, C_3 - C_8 -cycloalkyl, C_3 - C_8 -cycloalkyl- C_1 - C_3 -alkyl, pyranyl, piperidiny, it being possible
5 for all the radicals mentioned to carry optionally up to four C_1 - C_4 -alkyl, CF_3 , F, Cl, NO_2 , HO or C_1 - C_4 -alkoxy radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C_1 - C_{16} -alkyl or aryl,

R^{1a} : is H-, C_1 - C_{16} -alkyl, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_7 - C_{12} -bicycloalkyl, C_{10} -tricycloalkyl, C_3 - C_8 -cycloalkyl, C_3 - C_8 -cycloalkyl- C_1 - C_3 -alkyl, aryl- or phenyl- C_1 - C_3 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally
10 up to three C_1 - C_4 -alkyl, CF_3 , F, Cl, NO_2 , HO or C_1 - C_4 -alkoxy radicals, or

R^1 : is $R^{1b}-C(O)O-C(R^{1c})_2$, $R^{1b}-C(O)NR_2-C(R^{1c})_2$, where R^{1b} can be C_1 - C_4 -alkyl, C_3 - C_8 -cycloalkyl- C_1 - C_3 -alkyl, C_3 - C_8 -cycloalkyl, C_1 - C_4 -alkyloxy, C_3 - C_8 -cycloalkyl- C_1 - C_3 -alkyloxy, C_3 - C_8 -cycloalkoxy, aryl or phenyl- C_1 - C_6 -alkyl, the two R^{1c} radicals are,
15 independently of one another, h, CH_3 or C_2H_5 , and R^2 has the meaning stated above,
or $R^2OOC-C_1-C_6$ -alkyl, $R^2R^3N(O)C-C_1-C_6$ -alkyl, $R^2R^3N-C_2-C_6$ -alkyl, where R^2 and
20 R^3 have the same meanings as above or, if R^1 is $R^2R^3N(O)C-C_1-C_6$ -alkyl, R^2 and R^3 together form a C_4 - C_6 -alkylene chain,

B



25

in which

p is 0, 1,

R^4 is H-, R^9OOC - with $R^9 = C_{1-16}$ -alkyl, C_{3-8} -cycloalkyl, phenyl- C_1 - C_4 -alkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1 - C_4 -alkyl, phenyl, benzyl, C_3 - C_8 -cycloalkyl or cyclohexyl- CH_2 -,
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and R^5 , R^6 , R^7 and R^8 have the same meanings as above;

(ii)

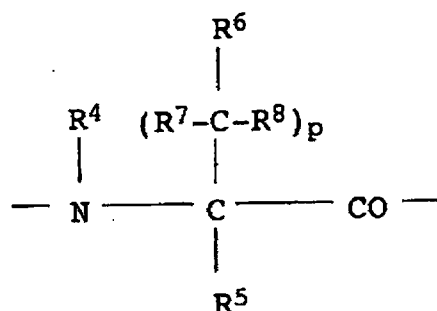
when E is II or III, and g and K are h, then A and B have the following meanings

- 5 A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^1OOC-CH(C_2H_5)-$, $HO-(CH_2)_{2-6}-$,

in which

- 10 R^1 : is H-, C_1-C_6 -alkyl, aryl or phenyl- C_1-C_4 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C_1-C_4 -alkyl, CF_3 , F, Cl, NO_2 , HO or C_1-C_4 -alkoxy radicals,

B



15

in which

p is 0, 1,

R^4 is R^9OOC- with $R^9 = C_{7-16}$ -alkyl, $R^{10}C(O)-O-CH_2-$, $R^{10}C(O)-O-CH(CH_3)-$, where R^{10}

- 20 can be C_1-C_4 -alkyl, phenyl, benzyl, C_3-C_8 -cycloalkyl or cyclohexyl- CH_2- ,
and R^5 , R^6 , R^7 and R^8 have the same meanings as above;

(iii)

- 25 when E is II or III, and g is $-OH$, $-OR^{18}$, $-OC(O)R^{19}$, $C(O)OR^{20}$, $-SR^{18}$, $-C(S)SR^{20}$, where R^{18} , R^{19} and R^{20} have the same meanings as above, and K is h, or g and K together form a $-C(O)O-$, $-C(O)S-$, $-C(S)S-$ or $-C(S)O-$ group, then A and B have the following meanings:

- 30 A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^1OOC-C(CH_3)_2-$, $R^1OOC-CH(C_2H_5)-$, C_{1-4} -alkyl- $SO_2-(CH_2)_{2-6}-$, $HO_3S-(CH_2)_{2-6}-$, 5-tetrazolyl- $(CH_2)_{1-6}-$, $C_{1-4}-$

alkyl-O-(CH₂)₂₋₆-, R²R³N-(CH₂)₂₋₆-, R²S-(CH₂)₂₋₆-, R²R³NSO₂-(CH₂)₂₋₆-,
 HO-(CH₂)₂₋₆-, R^{1a}S(O)C-CH₂-, R^{1a}O(S)C-CH₂-, R²R³N(O)C-CH₂-, R²R³N-O-CO-
 CH₂-, R²N(OH)-CO-CH₂-, where R² and R³ are, independently of one another, h,
 C₁-C₆-alkyl, or C₃₋₈-cycloalkyl or R² and R³ together form a C₄₋₆-alkylene chain,

5

in which

10 R¹: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-
 tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, pyranyl, piperidiny, aryl
 or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h
 to carry optionally up to four identical or different radicals selected from C₁-C₄-
 alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals, or R¹ is 2-oxo-1,3-dioxolen-4-
 ylmethyl which may be substituted in position 5 by C₁-C₁₆-alkyl or aryl,

15 R^{1a}: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-
 tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, aryl or phenyl-C₁-C₃-
 alkyl, it being possible for all the radicals mentioned apart from h to carry optionally
 up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂,
 HO or C₁-C₄-alkoxy radicals,

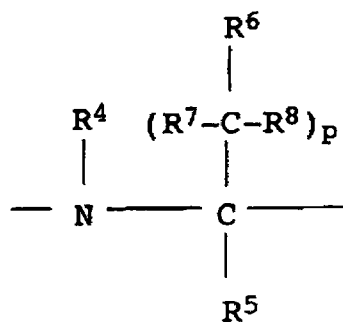
20 or

R¹: is R^{1b}-C(O)O-C(R^{1c})₂-, R^{1b}-C(O)NR₂-C(R^{1c})₂-, where R^{1b} can be C₁-C₄-alkyl, C₃-C₈-
 cycloalkyl-C₁-C₃-alkyl, C₃-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₃-C₈-cycloalkyl-C₁-C₃-
 alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are,
 independently of one another, h, CH₃ or C₂H₅ and R² has the meaning stated
 above,

25

or R²OOC-C₁-C₆-alkyl, R²R³N(O)C-C₁-C₆-alkyl, R²R³N-C₂-C₆-alkyl, and in which R² and
 R³ have the same meanings as above or, if R¹ is R²R³N(O)C-C₁-C₆-alkyl, R² and
 R³ together form a C₄-C₆-alkylene chain,

B



30

in which

p [lacuna] 0, 1,

R⁴ [lacuna] H-, R⁹OOC- with R⁹ = C₁₋₁₆-alkyl, C₃₋₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, R¹⁰C(O)-O-CH₂-, R¹⁰C(O)-O-CH(CH₃)-, where R¹⁰ can be C₁-C₄-alkyl, phenyl, benzyl, cyclohexyl or cyclohexyl-CH₂-, and R⁵, R⁶, R⁷ and R⁸ have the same meanings as above;

(iv)

10 when E is IV, V or VI, and g is h or OH, and K is h, then A and B have the following meanings:

A: R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)-, R¹OOC-C(CH₃)₂-, R¹OOC-CH(C₂H₅)-, R^{1a}S(O)C-CH₂-, R^{1a}O(S)C-CH₂-, R²R³N(O)C-CH₂-, R²R³N-O-CO-CH₂-, R²N(OH)-CO-CH₂-, where R² and R³ are, independently of one another, h, C₁-C₈-alkyl, C₃₋₈-cycloalkyl or R² and R³ together form a C₄₋₆-alkylene chain,

in which

20 R¹: is C₇-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned to carry optionally up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals, or is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C₁-C₁₆-alkyl or aryl,

25

R^{1a}: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals,

30

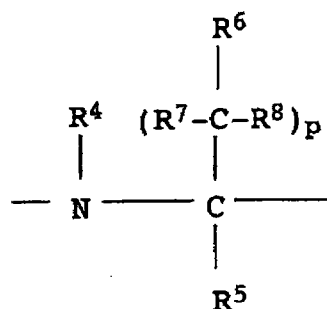
or

35 R¹: is R^{1b}-C(O)O-C(R^{1c})₂-, R^{1b}-C(O)NR²-C(R^{1c})₂-, where R^{1b} can be C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, C₃-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₃-C₈-cycloalkyl-C₁-C₃-alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are,

independently of one another, h, CH₃ or C₂H₅, and R² has the meaning stated above,

or R²OOC-C₁-C₆-alkyl, R²R³N(O)C-C₁-C₆-alkyl, R²R³N-C₂-C₆-alkyl, and in which R² and R³ have the same meanings as above or, if R¹ is R²R³N(O)C-C₁-C₆-alkyl, R² and R³ together form a C₄-C₆-alkylene chain,

B



in which

10 p [lacuna] 0, 1,

R⁴ [lacuna] H-, R⁹OOC- with R⁹ = C₁₋₁₆-alkyl, C₃₋₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, R¹⁰C(O)-O-CH₂-, R¹⁰C(O)-O-CH(CH₃)-, where R¹⁰ can be C₁-C₄-alkyl, phenyl, benzyl, C₃-C₈-cycloalkyl or cyclohexyl-CH₂-,

and

15 R⁵, R⁶, R⁷ and R⁸ have the same meanings as above;

(v)

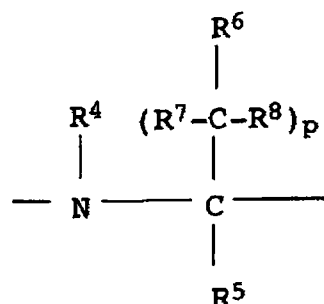
when E is IV, V or VI, and g is h or OH, and K is h, then A and B have the following meanings:

A: R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)-, R¹OOC-C(CH₃)₂-, R¹OOC-CH(C₂H₅)-, HO-(CH₂)₂₋₆-

25 in which

R¹: is H-, C₁-C₆-alkyl, aryl or phenyl-C₁-C₄-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals

30 B



in which

p is 0, 1,

- 5 R^4 is $\text{R}^9\text{OOC}-$ with $\text{R}^9 = \text{C}_{7-16}\text{-alkyl}$, $\text{R}^{10}\text{C}(\text{O})-\text{O}-\text{CH}_2-$, $\text{R}^{10}\text{C}(\text{O})-\text{O}-\text{CH}(\text{CH}_3)-$, where R^{10} can be $\text{C}_1\text{-C}_4\text{-alkyl}$, phenyl, benzyl, $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ or cyclohexyl- CH_2- ,

and

R^5 , R^6 , R^7 and R^8 have the same meanings as above;

- 10 (vi)

when E is IV, V or VI and g is $-\text{OR}^{18}$, $-\text{OC}(\text{O})\text{R}^{19}$, $-\text{C}(\text{O})\text{OR}^{20}$, $-\text{SR}^{18}$, $-\text{C}(\text{S})\text{SR}^{20}$, where R^{18} , R^{19} and R^{20} have the same meanings as above, and K is h, or g and K together form a $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{S}-$, $-\text{C}(\text{S})\text{S}-$ or $-\text{C}(\text{S})\text{O}-$ group, then A and B have the following

- 15 meanings:

- A: $\text{R}^1\text{OOC}-\text{CH}_2-$, $\text{R}^1\text{OOC}-\text{CH}_2-\text{CH}_2-$, $\text{R}^1\text{OOC}-\text{CH}(\text{CH}_3)-$, $\text{R}^1\text{OOC}-\text{C}(\text{CH}_3)_2-$, $\text{R}^1\text{OOC}-\text{CH}(\text{C}_2\text{H}_5)-$, $\text{HO}-\text{CH}_2-\text{CH}_2-$, $\text{R}^{1a}\text{S}(\text{O})\text{C}-\text{CH}_2-$, $\text{R}^{1a}\text{O}(\text{S})\text{C}-\text{CH}_2-$, $\text{R}^2\text{R}^3\text{N}(\text{O})\text{C}-\text{CH}_2-$, $\text{R}^2\text{R}^3\text{N}-\text{O}-\text{CO}-\text{CH}_2-$, $\text{R}^2\text{N}(\text{OH})-\text{CO}-\text{CH}_2-$, where R^2 and R^3 are, independently of one another, h, $\text{C}_1\text{-C}_6\text{-alkyl}$, or $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ or R^2 and R^3 together form a $\text{C}_{4-6}\text{-alkylene}$ chain,
- 20

in which

- 25 R^1 : is H-, $\text{C}_1\text{-C}_{16}\text{-alkyl}$, $\text{H}_3\text{C}-[\text{O}-\text{CH}_2-\text{CH}_2]_q$ ($q = 1-4$), $\text{C}_7\text{-C}_{12}\text{-bicycloalkyl}$, $\text{C}_{10}\text{-tricycloalkyl}$, $\text{C}_3\text{-C}_8\text{-cycloalkyl}$, $\text{C}_3\text{-C}_8\text{-cycloalkyl}-\text{C}_1\text{-C}_3\text{-alkyl}$, pyranyl, piperidinyl, aryl or phenyl- $\text{C}_1\text{-C}_3\text{-alkyl}$, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from $\text{C}_1\text{-C}_4\text{-alkyl}$, CF_3 , F, Cl, NO_2 , HO or $\text{C}_1\text{-C}_4\text{-alkoxy}$ radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by $\text{C}_1\text{-C}_{16}\text{-alkyl}$ or aryl,
- 30

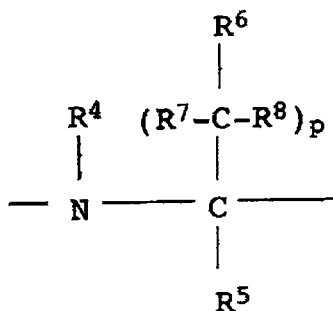
R^{1a}: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals,

or

R¹: is R^{1b}-C(O)O-C(R^{1c})₂-, R^{1b}-C(O)NR²-C(R^{1c})₂-, where R^{1b} can be C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, C₃-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₃-C₈-cycloalkyl-C₁-C₃-alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are, independently of one another, h, CH₃ or C₂H₅, and R² has the meaning stated above,

or R²OOC-C₁-C₆-alkyl, R²R³N(O)C-C₁-C₆-alkyl, R²R³N-C₂-C₆-alkyl, and in which R² and R³ have the same meanings as above or, if R¹ is R²R³N(O)C-C₁-C₆-alkyl, R² and R³ together form a C₄-C₆-alkylene chain,

B



in which

p is 0, 1,

R⁴ is H-, R⁹OOC- with R⁹ = C₁₋₁₆-alkyl, C₃₋₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, R¹⁰C(O)-O-CH₂-, R¹⁰C(O)-O-CH(CH₃)-, where R¹⁰ can be C₁-C₄-alkyl, phenyl, benzyl, C₃-C₈-cycloalkyl or cyclohexyl-CH₂-,

and

R⁵, R⁶, R⁷ and R⁸ have the same meanings as above;
and the physiologically tolerated salts thereof.

The amino acid derivatives represented by B preferably have the (D) configuration, and the amino acid derivatives represented by E preferably have the (L) configuration.

The aforementioned compounds comprise three groups of substances:

- 5 - The first group encompasses prodrugs of thrombin inhibitors (e.g. g equal to -OH-OR¹⁸, -COOR²⁰ etc.) which, as substance, have only a negligible antithrombotic effect but which, in the body, are converted into the corresponding active substance (G equal to H). These are compounds from groups (iii) and (vi), and in some cases also from groups (iv) and (v). The advantage of prodrugs is the improvement in their pharmacokinetic and pharmacodynamic behavior in the body.
- 10 - The second group encompasses prodrugs of thrombin inhibitors which have a thrombin-inhibitory effect even as prodrug (e.g. A equal to R¹OOC-CH₂-, R¹OOC-CH₂-CH₂- R¹OOC-CH(CH₃)- etc. in combination with g equal to -H). The active substance (drug; A equal to HOOC-CH₂-, HOOC-CH₂-CH₂-, HOOC-CH(CH₃)- etc., g equal to -H-)) [sic] formed in the body likewise shows a thrombin-inhibitory
- 15 effect. These are in some cases compounds from groups (i), (ii), (iv) and (v). The advantage of these prodrugs is the improvement in their pharmacokinetic and pharmacodynamic behavior in the body. Compounds with g equal to -OH, -OR¹⁸, -COOR²⁰ etc. and, at the same time, A equal to R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)- etc. are double prodrugs which are converted in the body by
- 20 transformation of the two prodrug groups into the corresponding drug (G equal to -H, A equal to HOOC-CH₂- etc.).
- 25 - The third group encompasses thrombin inhibitors which display their antithrombotic effect per se (e.g. A equal to C₁₋₄-alkyl-SO₂-(CH₂)₂₋₆-, HO₃S-(CH₂)₂₋₆-, 5-tetrazolyl-(CH₂)₁₋₆-, C₁₋₄-alkyl-O-(CH₂)₂₋₆-, R²R³N-(CH₂)₂₋₆-, R²S-(CH₂)₂₋₆-, R²R³NSO₂-(CH₂)₂₋₆- in combination with g equal to -H). Substances of this type belong in group (i).

Preferred compounds of the formula I are those in which A, B, D, E, g and K have the following meanings:

30

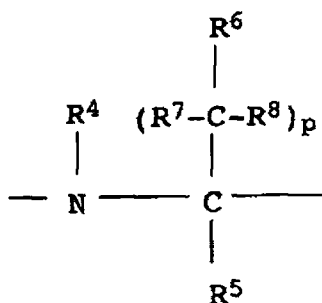
- A: R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)-, R¹OOC-C(CH₃)₂-, R^{1a}S(O)C-CH₂-, R^{1a}O(S)C-CH₂-, R²R³N(O)C-CH₂-, R²R³N-O-CO-CH₂-, R²N(OH)-CO-CH₂-, C₁₋₄-alkyl-SO₂-(CH₂)₂₋₆-, HO₃S-(CH₂)₂₋₆-, 5-tetrazolyl-(CH₂)₁₋₆-, C₁₋₄-alkyl-O-(CH₂)₂₋₆-, R²R³N-(CH₂)₂₋₆-, R²S-(CH₂)₂₋₆-, R²R³NSO₂-(CH₂)₂₋₆-, where R² and R³ are, independently of one another, h, C₁-C₆-alkyl, or C₃₋₈-cycloalkyl or R² and R³ together form a butylene or pentylene chain,

35

in which

- 5 R^1 : is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₅-C₈-cycloalkyl, C₅-C₈-cycloalkyl-C₁-C₃-alkyl, pyranyl, piperidinyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical or different radicals selected from CH₃, CF₃, F, Cl, HO or methoxy radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C₁-C₆-alkyl or aryl,
- 10 R^{1a} : is H-, C₁-C₁₆-alkyl, C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₅-C₈-cycloalkyl, C₅-C₈-cycloalkyl-C₁-C₃-alkyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical of different radicals selected from CH₃, CF₃, F, Cl, HO or methoxy radicals,
- 15 or
- R^1 : is R^{1b} -C(O)O-C(R^{1c})₂, R^{1b} -C(O)NR²-C(R^{1c})₂, where R^{1b} can be C₁-C₄-alkyl, C₅-C₈-cycloalkyl-C₁-C₃-alkyl, C₅-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₅-C₈-cycloalkyl-C₁-C₃-alkyloxy, C₅-C₈-cycloalkoxy, aryl or phenyl-C₁-C₃-alkyl, the two R^{1c} radicals are,
- 20 independently of one another, h, CH₃ or C₂H₅, and R^2 has the meaning stated above,
- or R^2 OOC-C₁-C₆-alkyl, R^2R^3 N(O)C-C₁-C₆-alkyl, R^2R^3 N-C₂-C₆-alkyl, and in which R^2 and R^3 have the same meanings as above or, if R^1 is R^2R^3 N(O)C-C₁-C₆-alkyl, R^2 and R^3 together form a butylene or pentylene chain,

25 B



in which

p is 0, 1,

R^4 is H-, R^9OOC - with $R^9 = C_{1-16}$ -alkyl, C_{3-8} -cycloalkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1-C_4 -alkyl, phenyl, benzyl, C_5-C_8 -cycloalkyl or cyclohexyl- CH_2 -,

R^5 is H-,

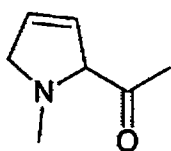
5 R^6 is C_{1-8} -alkyl, C_{5-8} -cycloalkyl, which may carry up to four methyl radicals, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl [sic] norbornyl, adamantyl, indanyl, decalyl,

R^7 is h,

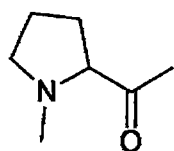
R^8 is h,

10

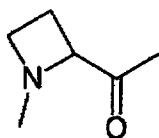
E



II

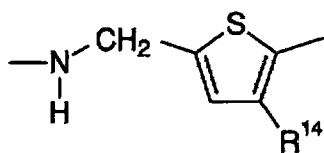


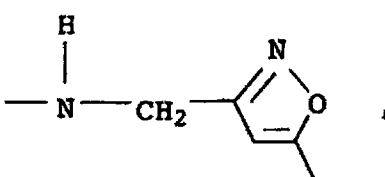
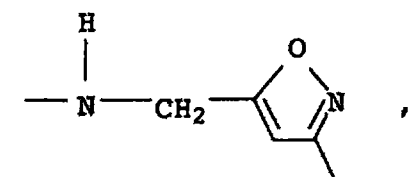
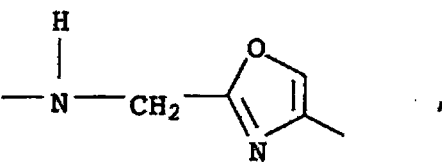
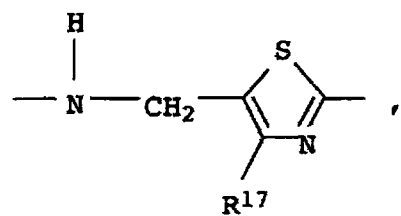
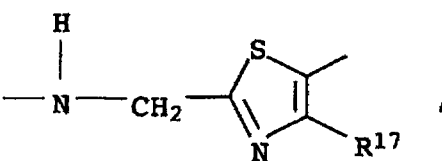
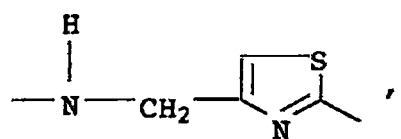
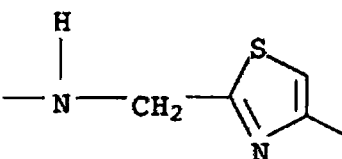
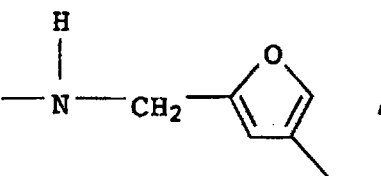
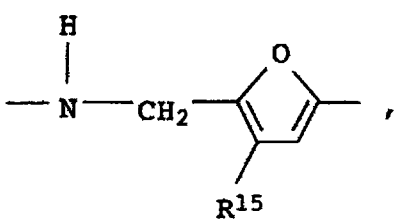
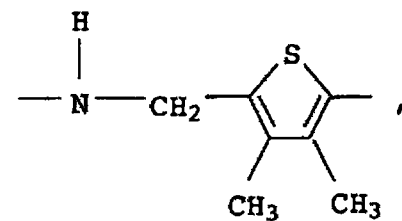
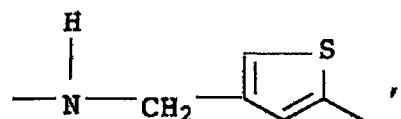
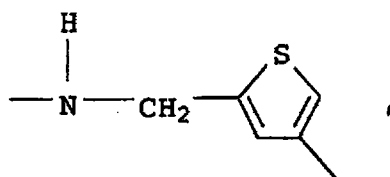
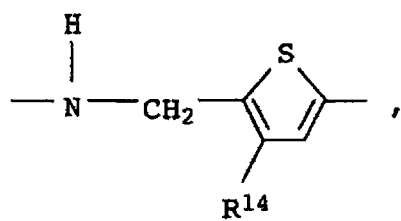
IV



VI

15 D





in which

R^{14} : is h, CH_3 , Cl

R^{15} : is h, CF_3 ,

R^{17} : is h, CH_3 , CF_3 ,

G: h, -OH, -OR¹⁸, -OC(O)R¹⁹, -C(O)OR²⁰,

5 in which

R^{18} : is -C₁₋₈-alkyl, -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -C₁-C₃-alkylphenyl which may carry optionally up to three CH_3 , CF_3 , F, Cl or methoxy radicals,

R^{19} : is -C₁₋₃-alkyl,

10 R^{20} : is -C₁₋₈-alkyl, -CH₂CCl₃, -C₁-C₃-alkyl-C₅-C₈-cycloalkyl, -C₅-C₈-cycloalkyl, -phenyl or -C₁-C₃-alkylphenyl, each of which may carry optionally up to three CH_3 , CF_3 , F, Cl or methoxy radicals, -CH₂O-C(O)R^{10a}, -CH(CH₃)O-C(O)R^{10a}, where R^{10a} can be -C₁-C₈-alkyl, -phenyl, -benzyl, -C₅-C₈-cycloalkyl or -CH₂-cyclohexyl, or -C(R^{10b})₂-CH₂-O-(O)CR^{10c}, where the R^{10b} radicals can be, independently of one another, h or CH_3 , and R^{10c} is -C₁-C₃-alkyl-C₅-C₈-cycloalkyl, -C₅-C₈-cycloalkyl or -
15 C₁-C₄-alkyl,

or

K is h or g and K together form a -C(O)O- or -C(O)S- group.

20 Particularly preferred compounds of the formula I are those in which A, B, D, E, g and K have the following meanings:

A: R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)-, R¹OOC-C(CH₃)₂-,
R²R³N(O)C-CH₂-, C₁₋₄-alkyl-SO₂-(CH₂)₂₋₆-, 5-tetrazolyl-(CH₂)₁₋₆-, C₁₋₄-alkyl-O-
(CH₂)₂₋₆-, R²R³N-(CH₂)₂₋₆-, R²S-(CH₂)₂₋₆-, R²R³NSO₂-(CH₂)₂₋₆-, where R² and R³
25 are, independently of one another, h or C₁-C₄-alkyl,

in which

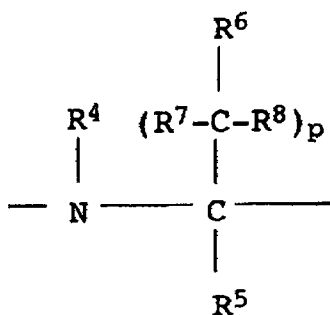
30 R^1 : is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₁₀-tricycloalkyl, C₅-C₈-cycloalkyl, C₅-C₈-cycloalkyl-C₁-C₃-alkyl, phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from CH_3 , CF_3 , F, Cl, HO or methoxy radicals, or R¹ is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C₁-C₃-alkyl or aryl,

35 or

R^1 : is $R^{1b}-C(O)O-C(R^{1c})_2$, where R^{1b} can be C_1-C_4 -alkyl, C_5-C_8 -cycloalkyl, C_1-C_4 -alkoxy, C_5-C_8 -cycloalkoxy or phenyl- C_1-C_3 -alkyl, the two R^{1c} radicals are, independently of one another, h or CH_3 ,

- 5 or $R^2OOC-C_1-C_6$ -alkyl, $R^2R^3N(O)C-C_1-C_6$ -alkyl, $R^2R^3N-C_2-C_6$ -alkyl, and in which R^2 and R^3 have the same meanings as above or, if R^1 is $R^2R^3N(O)C-C_1-C_6$ -alkyl, R^2 and R^3 together form a butylene or pentylene chain,

B



- 10 in which

p is 0, 1,

R^4 is H-, R^9OOC - with $R^9 = C_{1-16}$ -alkyl, C_{5-8} -cycloalkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1-C_4 -alkyl,

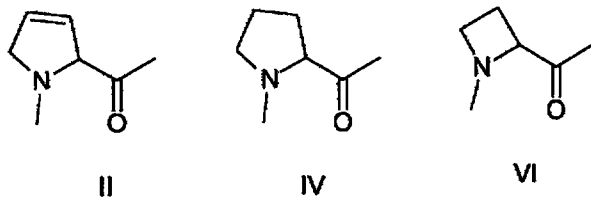
R^5 is H-,

- 15 R^6 is C_{1-8} -alkyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, norbornyl, adamantyl, indanyl, decalyl,

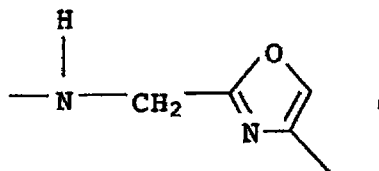
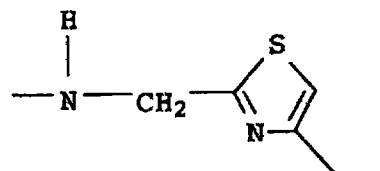
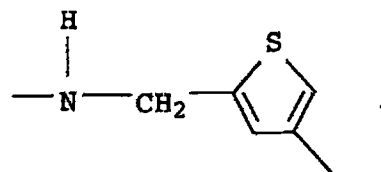
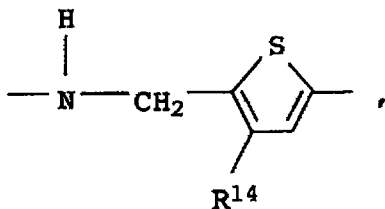
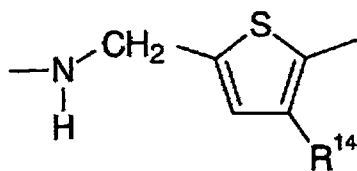
R^7 is h,

R^8 is h,

- 20 E



D



in which

R^{14} : is h, CH_3 , Cl,

5

G: H, -OH, $-OR^{18}$, $-C(O)OR^{20}$,

in which

R^{18} : is $-C_{1-8}$ -alkyl, $-C_1-C_3$ -alkyl- C_3-C_8 -cycloalkyl, $-C_1-C_3$ -alkylphenyl which may carry optionally up to three CH_3 -, CF_3 -, F-, Cl-, or methoxy radicals,

- 10 R^{20} : is $-C_{1-8}$ -alkyl, $-C_1-C_3$ -alkyl- C_5-C_8 -cycloalkyl, $-C_5-C_8$ -cycloalkyl or $-C_1-C_3$ -alkylphenyl which may carry optionally up to three CH_3 , CF_3 , F, Cl or methoxy radicals, or $-CH_2O-C(O)R^{10a}$, $-CH(CH_3)O-C(O)R^{10a}$, where R^{10a} can be $-C_1-C_4$ -alkyl, -benzyl, $-C_5-C_8$ -cycloalkyl or $-CH_2$ -cyclohexyl,

- 15 K is h,

or g and K together form a $-C(O)O-$ or $-C(O)S-$ group.

Very particularly preferred compounds of the formula I are those where A, B, D, E, g and K have the following meanings:

- 5 A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^1OOC-C(CH_3)_2-$, C_{1-4} -alkyl- $SO_2-(CH_2)_{2-4}-$, 5-tetrazolyl- $(CH_2)_{1-3}-$, C_{1-4} -alkyl-O- $(CH_2)_{2-4}-$, $H_2N-(CH_2)_{2-3}-$, $CH_3-NH-(CH_2)_{2-3}-$, $(CH_3)_2N-(CH_2)_{2-3}-$, $H_2NSO_2-(CH_2)_{2-4}-$, $CH_3-NHSO_2-(CH_2)_{2-4}-$,

in which

10

- R^1 : is H-, C_1-C_8 -alkyl, C_5-C_8 -cycloalkyl, C_5-C_8 -cycloalkyl- C_1-C_3 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical or different radicals selected from CH_3- , CF_3- , F-, Cl- or methoxy radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C_1-C_3 -alkyl or aryl,

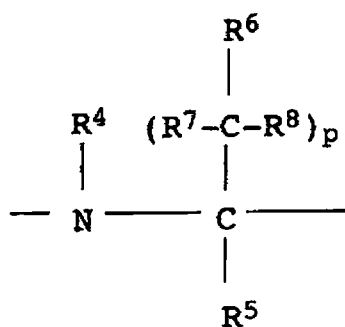
15

or

20

- R^1 : is $R^{1b}-C(O)O-CH_2-$, $R^{1b}-C(O)O-CH(CH_3)-$, where R^{1b} can be C_1-C_4 -alkyl, C_5-C_8 -cycloalkyl, C_1-C_4 -alkyloxy or C_5-C_8 -cycloalkyloxy

B



25 in which

p is 0,1,

R^4 is H-,

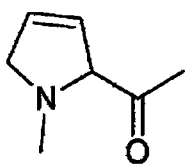
R^5 is H-,

R^6 is cyclopentyl, cyclohexyl, cycloheptyl,

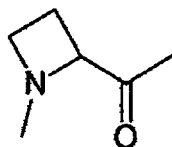
30 R^7 is h,

R^8 is h,

E



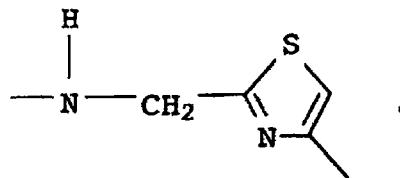
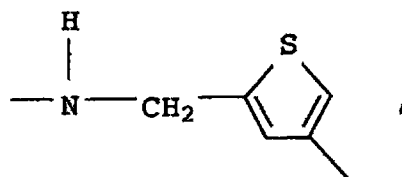
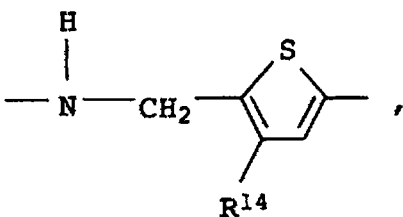
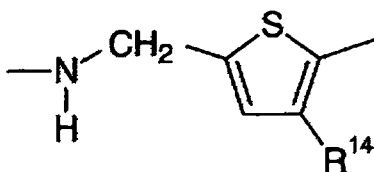
II



VI

5

D



10

in which

R^{14} : is h, CH_3 , Cl,

G: $-OH$, $-C(O)OR^{20}$,

15 in which

R^{20} : is $-C_{1-8}$ -alkyl, $-C_1-C_3$ -alkyl- C_5-C_8 -cycloalkyl, $-C_5-C_8$ -cycloalkyl,

K = is h.

Very particularly preferred compounds of the formula I are those where A, B, D, E, g and K have the following meanings:

A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^1OOC-C(CH_3)_2-$,

5

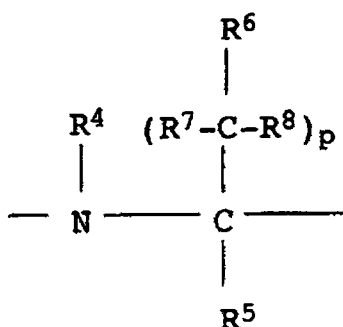
in which

R^1 : is C_1-C_8 -alkyl, C_5-C_8 -cycloalkyl, C_5-C_8 -cycloalkyl- CH_2 -alkyl, it being possible for all the radicals mentioned to carry optionally up to four identical or different radicals

10

selected from CH_3 or methoxy radicals,

B



15 in which

p is 0,1,

R^4 is H-,

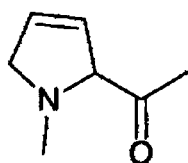
R^5 is H-,

R^6 is cyclohexyl,

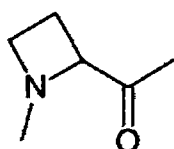
20 R^7 is h,

R^8 is h,

E



II

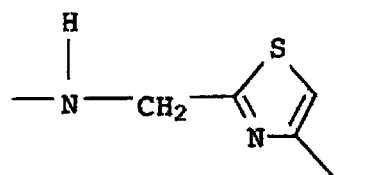
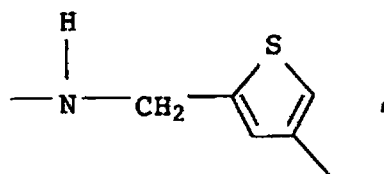
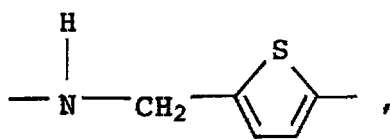


VI

,

25

D



- 5 G: -OH,
K = is h.

The following substances are very particularly preferred:

1.	CH ₃ OOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
2.	EtOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
3.	nPrOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
4.	iPrOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
5.	nBuOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
6.	tBuOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
7.	iBuOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
8.	nPentOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
9.	iPentOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
10.	neoPentOOCH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph

11.	nHexOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
12.	cHex-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
13.	nHeptOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
14.	nOctOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
15.	cOctOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
16.	BnOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
17.	AdaOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
18.	AdaOOC-CH ₂ -(D)-Chg-Dep-NH-CH ₂ -5-[2-am-(OH)]-thioph
19.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
20.	AdaOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
21.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
22.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
23.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
24.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
25.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
26.	CH ₃ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
27.	CH ₃ OOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -5-[2-am-(OH)]-thioph
28.	EtOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
29.	nPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
30.	nPrOOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -5-[2-am-(OH)]-thioph
31.	iPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
32.	nBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
33.	tBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
34.	iBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
35.	nPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
36.	iPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
37.	neoPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
38.	nHexOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
39.	cHex-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
40.	nHeptOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
41.	nOctOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
42.	cOctOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
43.	BnOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
44.	AdaOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
45.	cHex-CH ₂ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
46.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
47.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -5-[2-am-(OH)]-thioph
48.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
49.	AdaOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
50.	cHex-CH ₂ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph

51.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
52.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
53.	CH ₃ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(Ome)]-thioph
54.	CH ₃ OOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -5-[2-am-(Ome)]-thioph
55.	EtOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(Ome)]-thioph
56.	nPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(Ome)]-thioph
57.	CH ₃ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
58.	nPrOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
59.	iPrOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
60.	nBuOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
61.	nBuOOC-CH ₂ -(D)-Chg-Dep-NH-CH ₂ -5-[3-am-(OH)]-thioph
62.	iBuOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
63.	nPentOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
64.	iPentOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
65.	neoPentOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
66.	nHeptOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
67.	nOctOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
68.	nOctOOC-CH ₂ -(D)-Chg-Dep-NH-CH ₂ -5-[3-am-(OH)]-thioph
69.	cOctOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
70.	BnOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
71.	AdaOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
72.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
73.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
74.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
75.	AdaOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
76.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
77.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
78.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
79.	EtOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(Ome)]-thioph
80.	tBuOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(Ome)]-thioph
81.	CH ₃ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
82.	CH ₃ OOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -5-[3-am-(OH)]-thioph
83.	EtOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
84.	nPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
85.	iPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
86.	nBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
87.	tBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
88.	iBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
89.	nPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
90.	nPentOOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -5-[3-am-(OH)]-thioph

91.	iPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
92.	neoPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
93.	nHexOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
94.	cHex-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
95.	nHeptOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
96.	nOctOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
97.	cOctOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
98.	BnOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
99.	BnOOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -5-[3-am-(OH)]-thioph
100.	AdaOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
101.	cHex-CH ₂ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
102.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
103.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
104.	AdaOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
105.	cHex-CH ₂ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
106.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
107.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
108.	CH ₃ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
109.	EtOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
110.	EtOOC-CH ₂ -(D)-Chg-Dep-NH-CH ₂ -2-[4-am-(OH)]-thiaz
111.	nPrOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
112.	iPrOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
113.	nBuOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
114.	tBuOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
115.	tBuOOC-CH ₂ -(D)-Chg-Dep-NH-CH ₂ -2-[4-am-(OH)]-thiaz
116.	iBuOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
117.	nPentOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
118.	iPentOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
119.	nHexOOC-CH ₂ -(D)-Chg-Dep-NH-CH ₂ -2-[4-am-(OH)]-thiaz
120.	neoPentOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
121.	nHexOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
122.	cHex-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
123.	nHeptOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
124.	nOctOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
125.	cOctOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
126.	BnOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
127.	AdaOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
128.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
129.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
130.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz

131.	AdaOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(H)]-thiaz
132.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(H)]-thiaz
133.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(H)]-thiaz
134.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(H)]-thiaz
135.	CH ₃ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
136.	nPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
137.	nPrOOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -2-[4-am-(OH)]-thiaz
138.	nBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
139.	iBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
140.	nPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
141.	nPentOOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -2-[4-am-(OH)]-thiaz
142.	iPentOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
143.	nHeptOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
144.	nOctOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
145.	cOctOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
146.	BnOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
147.	BnOOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -2-[4-am-(OH)]-thiaz
148.	cHex-CH ₂ OOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -2-[4-am-(H)]-thiaz
149.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -2-[4-am-(H)]-thiaz
150.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -2-[4-am-(H)]-thiaz
151.	CH ₃ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OMe)]-thiaz
152.	nPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OMe)]-thiaz
153.	EtOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OMe)]-thiaz
154.	nBuOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OMe)]-thiaz
155.	HOOC-CH ₂ -N-(CO ₂ CH ₂ ^c Hex)-(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(H)]-thiaz
156.	HOOC-CH ₂ -N-(CO ₂ ^c Oct)-(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(H)]-thiaz
157.	HOOC-CH ₂ -N-(CO ₂ ^c Hex)-(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
158.	HOOC-CH ₂ -N-(CO ₂ CH ₂ ^c Hex)-(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
159.	HOOC-CH ₂ -N-(CO ₂ ^c Oct)-(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(H)]-thioph
160.	HOOC-CH ₂ -N-(CO ₂ ^c Hex)-(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
161.	HOOC-CH ₂ -N-(CO ₂ CH ₂ ^c Hex)-(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
162.	HOOC-CH ₂ -N-(CO ₂ ^c Oct)-(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(H)]-thioph
163.	CH ₃ OOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[5-am-(OH)]-thiaz
164.	EtOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[5-am-(OH)]-thiaz
165.	nPrOOC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[5-am-(OH)]-thiaz
166.	nPrOOC-CH ₂ -(D)-Cha-Dep-NH-CH ₂ -2-[5-am-(OH)]-thiaz
167.	CH ₃ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-3-Me-[2-am-(OH)]-thioph
168.	EtOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-3-Me-[2-am-(OH)]-thioph

169.	nPrOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-3-Me-[2-am-(OH)]-thioph
170.	CH ₃ OOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-4-Me-[3-am-(OH)]-thioph
171.	EtOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-4-Me-[3-am-(OH)]-thioph
172.	nPrOOC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-4-Me-[3-am-(OH)]-thioph
173.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
174.	AdaOOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(H)]-thioph
175.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(H)]-thioph
176.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
177.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
178.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(H)]-thioph
179.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(H)]-thioph
180.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
181.	AdaOOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(H)]-thioph
182.	cHex-CH ₂ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(H)]-thioph
183.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
184.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
185.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(H)]-thioph
186.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(H)]-thioph
187.	cHex-CH ₂ OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
188.	AdaOOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(H)]-thiaz
189.	cHex-CH ₂ OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(H)]-thiaz
190.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
191.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
192.	CH ₃ -(CH ₂) ₁₀ OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(H)]-thiaz
193.	CH ₃ -(CH ₂) ₁₅ OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(H)]-thiaz
194.	cPent-OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
195.	cPent-CH ₂ -OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
196.	cHex-OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
197.	cPent-OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
198.	cPent-CH ₂ -OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
199.	cHex-OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
200.	cHex-CH ₂ -OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[2-am-(OH)]-thioph
201.	cPent-OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
202.	cPent-CH ₂ -OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
203.	cHex-OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
204.	cPent-OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
205.	cPent-CH ₂ -OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
206.	cHex-OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
207.	cHex-CH ₂ -OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -5-[3-am-(OH)]-thioph
208.	cPent-OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
209.	cPent-CH ₂ -OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
210.	cHex-OOC-CH ₂ -(D)-Chg-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz

211.	cPent-OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
212.	cPent-CH ₂ -OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
213.	cHex-OOC-CH ₂ -(D)-Cha-Pro-NH-CH ₂ -2-[4-am-(OH)]-thiaz
214.	cHN ₄ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
215.	cHN ₄ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
216.	cHN ₄ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
217.	cHN ₄ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
218.	cHN ₄ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
219.	cHN ₄ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
220.	HONH-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
221.	HONH-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
222.	HONH-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
223.	HONH-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
224.	HONH-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
225.	cHex-N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
226.	cHex-N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
227.	cHex-N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
228.	cHex-N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
229.	cHex-N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
230.	cHex-N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
231.	iPr-N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
232.	iPr-N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
233.	iPr-N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
234.	iPr-N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
235.	iPr-N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
236.	iPr-N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
237.	CH ₃ -N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
238.	CH ₃ -N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
239.	CH ₃ -N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
240.	CH ₃ -N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
241.	CH ₃ -N(OH)-OC-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
242.	CH ₃ -N(OH)-OC-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
243.	NH ₂ -O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
244.	NH ₂ -O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
245.	NH ₂ -O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
246.	NH ₂ -O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
247.	NH ₂ -O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
248.	NH ₂ -O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
249.	c(CH ₂) ₅ N-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
250.	c(CH ₂) ₅ N-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
251.	c(CH ₂) ₅ N-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
252.	c(CH ₂) ₅ N-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
253.	c(CH ₂) ₅ N-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
254.	c(CH ₂) ₅ N-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
255.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz

256.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
257.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
258.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
259.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
260.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
261.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
262.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
263.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
264.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
265.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
266.	N-Me-4-Pip-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
267.	NH ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
268.	NH ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
269.	NH ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
270.	NH ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
271.	NH ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
272.	NH ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
273.	(CH ₃) ₂ N-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
274.	(CH ₃) ₂ N-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
275.	(CH ₃) ₂ N-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
276.	(CH ₃) ₂ N-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
277.	(CH ₃) ₂ N-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
278.	(CH ₃) ₂ N-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
279.	CH ₃ -NH-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
280.	CH ₃ -NH-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
281.	CH ₃ -NH-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
282.	CH ₃ -NH-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
283.	CH ₃ -NH-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
284.	CH ₃ -NH-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
285.	CH ₃ -SO ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
286.	CH ₃ -SO ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
287.	CH ₃ -SO ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
288.	CH ₃ -SO ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
289.	CH ₃ -SO ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
290.	CH ₃ -SO ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
291.	CH ₃ -O-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
292.	CH ₃ -O-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
293.	CH ₃ -O-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
294.	CH ₃ -O-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
295.	CH ₃ -O-CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
296.	CH ₃ -O-CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
297.	CH ₃ -NH-SO ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
298.	CH ₃ -NH-SO ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
299.	CH ₃ -NH-SO ₂ -CH ₂ -CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
300.	CH ₃ -NH-SO ₂ -CH ₂ -CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph

301.	$\text{CH}_3\text{-NH-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
302.	$\text{CH}_3\text{-NH-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
303.	$\text{H}_2\text{N-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
304.	$\text{H}_2\text{N-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
305.	$\text{H}_2\text{N-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
306.	$\text{H}_2\text{N-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
307.	$\text{H}_2\text{N-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
308.	$\text{H}_2\text{N-SO}_2\text{-CH}_2\text{-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
309.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
310.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
311.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
312.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
313.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
314.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
315.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
316.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
317.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
318.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
319.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
320.	$(\text{CH}_3)_3\text{C-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
321.	$\text{cHex-O-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
322.	$\text{cHex-O-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
323.	$\text{cHex-O-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
324.	$\text{cHex-O-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$
325.	$\text{cHex-O-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
326.	$\text{cHex-O-CO}_2\text{-CH}_2\text{-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-[3-am-(OH)]-thioph}$
327.	$\text{cHex-O-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
328.	$\text{cHex-O-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-2-[4-am-(OH)]-thiaz}$
329.	$\text{cHex-O-CO}_2\text{-CH(CH}_3\text{)-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-5-[2-am-(OH)]-thioph}$

330.	cHex-O-CO ₂ -CH(CH ₃)-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
331.	cHex-O-CO ₂ -CH(CH ₃)-O ₂ C-CH ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
332.	cHex-O-CO ₂ -CH(CH ₃)-O ₂ C-CH ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
333.	cHex-OCO-C(CH ₃) ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
334.	cHex-OCO-C(CH ₃) ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
335.	cHex-OCO-C(CH ₃) ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
336.	cHex-OCO-C(CH ₃) ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
337.	cHex-OCO-C(CH ₃) ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
338.	cHex-OCO-C(CH ₃) ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
339.	C ₂ H ₅ -O-CO-C(CH ₃) ₂ -(D)-Cha-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
340.	C ₂ H ₅ -O-CO-C(CH ₃) ₂ -(D)-Chg-Pyr-NH-CH ₂ -2-[4-am-(OH)]-thiaz
341.	C ₂ H ₅ -O-CO-C(CH ₃) ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
342.	C ₂ H ₅ -O-CO-C(CH ₃) ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[2-am-(OH)]-thioph
343.	C ₂ H ₅ -O-CO-C(CH ₃) ₂ -(D)-Cha-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph
344.	C ₂ H ₅ -O-CO-C(CH ₃) ₂ -(D)-Chg-Pyr-NH-CH ₂ -5-[3-am-(OH)]-thioph

List of abbreviations:

5	Adaala:	adamantylalanine
	Adagly:	adamantylglycine
	AIBN:	azobisisobutyronitrile
	Ac:	acetyl
	Ala:	alanine
10	am:	amidino
	Asp:	aspartic acid
	Aze:	azetidinecarboxylic acid
	Bn:	benzyl
	Boc:	tert-butyloxycarbonyl
15	Bu:	butyl
	c-pent:	cyclopentyl
	Cbz:	benzyloxycarbonyl
	c(CH ₂) ₅ N-:	N-piperidiny
	Cha:	cyclohexylalanine
20	Chea:	cycloheptylalanine
	Cheg:	cycloheptylglycine
	CHN ₄ C-:	tetrazolyl- (3-tetrazolyl- or 5 tetrazolyl)
	Chg:	cyclohexylglycine

	Cog:	cyclooctylglycine
	Cpa:	cyclopentylalanine
	Cpg:	cyclopentylglycine
	TLC:	thin layer chromatography
5	DCC:	dicyclohexylcarbodiimide
	Dch:	dicyclohexylalanine
	Dcha:	dicyclohexylamine
	DCM:	dichloromethane
	Dep:	4,5-dehydropipecolic acid
10	DMF:	dimethylformamide
	DIPEA:	diisopropylethylamine
	Dpa:	diphenylalanine
	Et:	ethyl
	Eq:	equivalents
15	Gly:	glycine
	fur:	furan
	ham:	hydroxyamidino
	HOSucc:	hydroxysuccinimide
	HPLC:	high performance liquid chromatography
20	iPr:	isopropyl
	Me:	methyl
	MPLC:	medium pressure liquid chromatography
	MTBE:	methyl tert-butyl ether
	NBS:	N-bromosuccinimide
25	N-Me-4-Pip-OH:	N-methyl-4-piperidiny alcohol
	Nog:	norbornylglycine
	Oxaz:	oxazole
	Ph:	phenyl
	Phe:	phenylalanine
30	Pic:	pipecolic acid
	PPA:	propylphosphonic anhydride
	Pro:	proline
	Py:	pyridine
	Pyr:	3,4-dehydropipecolic acid
35	pyraz:	pyrazole
	pyrr:	pyrrole
	RT:	room temperature

	RP-18	reversed phase C-18
	t:	tertiary
	tBu:	tertiary butyl
	tert:	tertiary
5	TBAB:	tetrabutylammonium bromide
	TEA:	triethylamine
	TFA:	trifluoroacetic acid
	TFAA:	trifluoroacetic anhydride
	thiaz:	thiazole
10	thioph:	thiophene
	TOTU:	O-[cyano(ethoxycarbonyl)methyleneamino]- N,N,N',N'-tetramethyluronium tetrafluoroborate
	Z:	benzyloxycarbonyl
	ⁿ Pent:	n-pentyl
15	neoPent:	neopentyl (2,2-dimethyl-1-propyl)
	nHex:	n-hexyl
	cHex:	cyclohexyl
	nOct:	n-octyl
	O-p-Me-Bn:	p-methylbenzyloxy
20	MeO-tetraethoxy:	[lacuna] tetraethylene glycol monomethyl ether

The definitions for the individual substituents in the description and the claims are as follows:

- 25 The term "cycloalkyl" as such or as part of another substituent comprises saturated, cyclic hydrocarbon groups which contain the stated number of carbon atoms and in which up to two CH₂ groups may be replaced by oxygen, sulfur or nitrogen atoms. C₃₋₈-Cycloalkyl refers to saturated alicyclic rings having 3 to 8 C atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl,
- 30 cyclohexylmethylene [sic], cycloheptyl or cyclooctyl, pyrrolidine [sic], piperidine [sic], morpholine [sic]. Saturated cyclic hydrocarbons without heteroatoms are preferred.

- The term "alkyl" as such or as part of another substituent means a linear or branched alkyl chain radical of the length stated in each case, which may be saturated or
- 35 unsaturated and in which up to five CH₂ groups may be replaced by oxygen, sulfur or nitrogen atoms. In the latter case, the heteroatoms are separated from one another by at least two carbon atoms. Thus, C₁₋₄-alkyl means, for example, methyl, ethyl, 1-propyl, 2-

propyl, 2-methyl-2-propyl, 2-methyl-1-propyl, 1-butyl, 1-but-2-enyl, 2-butyl, C₁₋₆-alkyl for example C₁₋₄-alkyl, pentyl, [sic] 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl or 3,3-dimethylbutyl. C₁₋₈-Alkyl means in addition to the radicals stated for C₁₋₄-alkyl for example C₁₋₆-alkyl, heptyl, 2-(2-methoxyethoxy)ethyl or octyl. Linear or
5 branched saturated alkyl radicals without heteroatoms are preferred.

The term "alkoxy" as such or as part of another substituent means a linear or branched alkyl chain radical of the length stated in each case, which may be saturated or unsaturated and is linked via an oxygen atom to the parent compound in each case.

10 Thus, C₁₋₄-alkoxy means, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy, 2-methyl-2-propoxy, 2-methyl-1-propoxy, 1-butoxy, 2-butoxy.

The term "aryl" as such or as part of another substituent comprises mono-, bi- or tricyclic aromatic hydrocarbons [sic] such as phenyl, naphthyl, tetralinyl, indenyl, fluorenyl,
15 indanyl, anthracenyl, phenanthrenyl.

The compounds of the formula I may exist as such or in the form 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,
20 maleic acid, fumaric acid, succinic acid, hydroxysuccinic acid, sulfuric acid, glutaric acid, aspartic acid, pyruvic acid, benzoic acid, glucuronic acid, oxalic acid, ascorbic acid and acetylglycine.

The novel compounds of the formula I can be employed for the following indications:

- 25
- disorders whose pathomechanism is based directly or indirectly on the proteolytic effect of thrombin,
 - disorders whose pathomechanism is based on the thrombin-dependent activation
30 of receptors and signal transductions,
 - disorders associated with stimulation [e.g. by PAI-1, PDGF (platelet derived growth factor), P-selectin, ICAM-1, tissue factor] or inhibition (e.g. NO synthesis in smooth muscle cells) of the expression of genes in body cells,
35
 - disorders based on the mitogenic effect of thrombin,

- disorders based on a thrombin-dependent change in the contractility and permeability of epithelial cells (e.g. vascular endothelial cells),
- 5 - thrombin-dependent thromboembolic events such as deep vein thrombosis, pulmonary embolism, myocardial or cerebral infarction, atrial fibrillation, bypass occlusion,
- disseminated intravascular coagulation (DIC),
- 10 - reocclusion and for reducing the reperfusion time on comedication with thrombolytics such as streptokinase, urokinase, prourokinase, t-PA, APSAC, plasminogen activators from the salivary glands of animals, and the recombinant and mutated forms of all these substances,
- 15 - the occurrence of early reocclusion and late restenosis after PTCA,
- thrombin-dependent proliferation of smooth muscle cells,
- accumulation of active thrombin in the CNS (e.g. in Alzheimer's disease),
- 20 - tumor growth, and to counter the adhesion and metastasis of tumor cells.

The novel compounds can be employed in particular for the therapy and prophylaxis of thrombin-dependent thromboembolic events such as deep vein thromboses, pulmonary
25 embolisms, myocardial or cerebral infarctions and unstable angina, also for the therapy of disseminated intravascular coagulation (DIC). They are further suitable for combination therapy with thrombolytics such as streptokinase, urokinase, prourokinase, t-PA, APSAC and other plasminogen activators for reducing the reperfusion time and increasing the reocclusion time.

30 Further preferred areas of use are to prevent thrombin-dependent early reocclusion and late restenosis after percutaneous transluminal coronary angioplasty [sic], to prevent thrombin-induced proliferation of smooth muscle cells, to prevent the accumulation of active thrombin in the CNS (e.g. in Alzheimer's diseases), to control tumors and to
35 prevent mechanisms which lead to adhesion and metastasis of tumor cells.

The novel compounds can be administered orally in a conventional way. Administration can also take place with vapors or sprays through the nasopharyngeal space.

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

10 The novel compounds can be used in conventional solid or liquid pharmaceutical forms, for example as uncoated or (film-)coated tablets, capsules, powders, granules, solutions or sprays. These are produced in a conventional way. The active substances can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or
15 propellant gases (cf. h. Sucker et al.: Pharmazeutische Technologie, Thieme-Verlag, Stuttgart, 1978). The administration forms obtained in this way normally contain from 0.1 to 99% by weight of the active substance.

Experimental part

20

Pharmacological tests

The rate of absorption of medicines administered orally from the gastrointestinal tract (GIT) is an essential factor in relation to the bioavailability of the medicine. A good rate
25 of absorption is a precondition for high bioavailability.

Several in vitro models are available for studying intestinal absorption. Thus, the human colon adenocarcinoma cell lines HT-29, Caco-2 and T84 are routinely employed to investigate various intestinal transport processes (Madara et al., *Am. J. Physiol.* **1988**,
30 254: G416-G423; K. I. Audus et al., *Pharm. Res.* **1990**, 7, 435-451). The IEC-18 cell line has also shown itself to be a suitable model for investigating the permeability of hydrophilic substances through the intestinal membrane (Ma et al., *J. Lab. Clin. Med.* **1992** [lacuna]; Duizer et al., *J. Contr. Rel.* **1997** [lacuna]).

35 For the transport experiments (for materials and methods, see R.T. Borchardt, P.L. Smith, g. Wilson, *Models for Assessing Drug Absorption and Metabolism*, 1st edition, Plenum Press New York and London, **1996**, chapter 2), the cells are cultivated on

Transwell polycarbonate membranes for 17-24 days. The test chamber is arranged so that the membrane divides the apical from the basolateral compartment. Transport of the test substances from the apical side through the cell layer onto the basolateral side can be measured as a function of the pH gradient, for example

5 apical (pH 6.0) → basolateral (pH 8.0).

After incubation of the cells with the test substance, samples are taken from the apical and basolateral sides after a defined time interval (e.g. 24 h). The content of test substance employed and any metabolites in each of the two compartments is
10 determined by HPLC (comparison of retention times) and HPLC-MS (elucidation of metabolites) analyses. The transport rate is calculated.

It is possible on the basis of the results of these tests to divide test substances into the following categories:

15

+++ : very good transport

++ : good transport

+ : moderate transport

20 The division of selected samples into said categories has been undertaken in the following table:

Ex. No.	Transport
2	+
10	+
11	+++
21	++
25	++
29	++
33	+++

Pharmacokinetics and coagulation parameters in rats

25

The test substances are dissolved in isotonic saline immediately before administration to conscious Sprague Dawley rats. The volumes administered are 1 ml/kg for intravenous bolus injection into the tail vein and 10 ml/kg for oral administration, which takes place

by gavage. Blood samples are taken, unless otherwise mentioned, 1 h after oral administration of $21.5 \text{ mg} \cdot \text{kg}^{-1}$ or intravenous administration of $1.0 \text{ mg} \cdot \text{kg}^{-1}$ of the test substance or the corresponding vehicle (control). Five minutes before taking blood, the animals are anesthetized by i.p. administration of 25% strength urethane solution (dose 5 $1 \text{ g} \cdot \text{kg}^{-1}$ i.p.) in physiological saline. The carotid artery is dissected and catheterized for taking blood samples (2 ml) in citrate tubes (1.5 parts of citrate plus 8.5 parts of blood). Immediately after taking a sample, the ecarin time (ECT = ecarin clotting time) is determined on whole blood. After preparation of the plasma by centrifugation, the plasma thrombin time and the activated partial thromboplastin time (APTT) are 10 determined using a coagulometer.

Coagulation parameters:

Ecarin time (ECT = ecarin clotting time): 100 ml of citrated blood are incubated in a 15 coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG) at 37°C for 2 min. After addition of 100 ml of prewarmed (37°C) ecarin reagent (Pentapharm), the time until a fibrin clot forms is determined.

Activated thromboplastin time (APTT = activated thromboplastin time): 50 μl of citrated 20 plasma and 50 μl of the PTT reagent (Pathrombin, Behring) are mixed and incubated in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG) at 37°C for 2 min. After addition of 50 μl of prewarmed (37°C) calcium chloride, the time until a fibrin clot forms is determined.

25 Thrombin time (TT): 100 μl of citrate-treated plasma are incubated in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG) at 37°C for 2 min. After addition of 100 μl of prewarmed (37°C) thrombin reagent (Boehringer Mannheim), the time until a fibrin clot forms is determined.

30 Pharmacokinetics and coagulation parameters in dogs

The test substances are dissolved in isotonic saline immediately before administration to conscious mongrel dogs. The volumes administered are 0.1 ml/kg for intravenous bolus injection and 1 ml/kg for oral administration, which takes place by gavage. Samples of 35 venous blood (2 ml) are taken in citrated tubes before and 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min (if required after 420 or 480 min and 24 h) after intravenous administration of 1.0 mg/kg and before and 10, 20, 30, 60, 120, 180, 240, 300, 360,

480 min and 24 h after oral administration of 4.64 mg/kg. Immediately after taking a sample, the ecarin time (ECT = ecarin clotting time) is determined on whole blood. After preparation of the plasma by centrifugation, the plasma thrombin time and the activated partial thromboplastin time (APTT) are determined using a coagulometer.

5

In addition, the anti-F IIa activity (ATU/ml) is determined, and the concentration of the substance is determined through its anti-F IIa activity in plasma by a chromogenic (S-2238) thrombin assay, employing calibration plots with r-hirudin and the test substance. The plasma concentration of the test substance is the basis for calculating the pharmacokinetic parameters: time of maximum plasma concentration (T max), maximum plasma concentration; plasma half-life, $t_{0.5}$; area under the curve (AUC); absorbed portion of the test substance (F).

10

Coagulation parameters:

15

Ecarin time (ECT = ecarin clotting time): 100 μ l of citrate-treated blood are incubated in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG) at 37°C for 2 min. After addition of 100 μ l of prewarmed (37°C) ecarin reagent (Pentapharm), the time until a fibrin clot forms is determined.

20

Activated thromboplastin time (APTT = activated thromboplastin time): 50 μ l of citrate-treated plasma and 50 μ l of the PTT reagent (Pathrombin, Behring) are mixed and incubated in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG) at 37°C for 2 min. After addition of 50 μ l of prewarmed (37°C) calcium chloride, the time until a fibrin clot forms is determined.

25

Thrombin time (TT): 100 μ l of citrate-treated plasma are incubated in a coagulometer (CL 8, ball type, Bender & Hobein, Munich, FRG) at 37°C for 2 min. After addition of 100 μ l of prewarmed (37°C) thrombin reagent (Boehringer Mannheim), the time until a fibrin clot forms is determined.

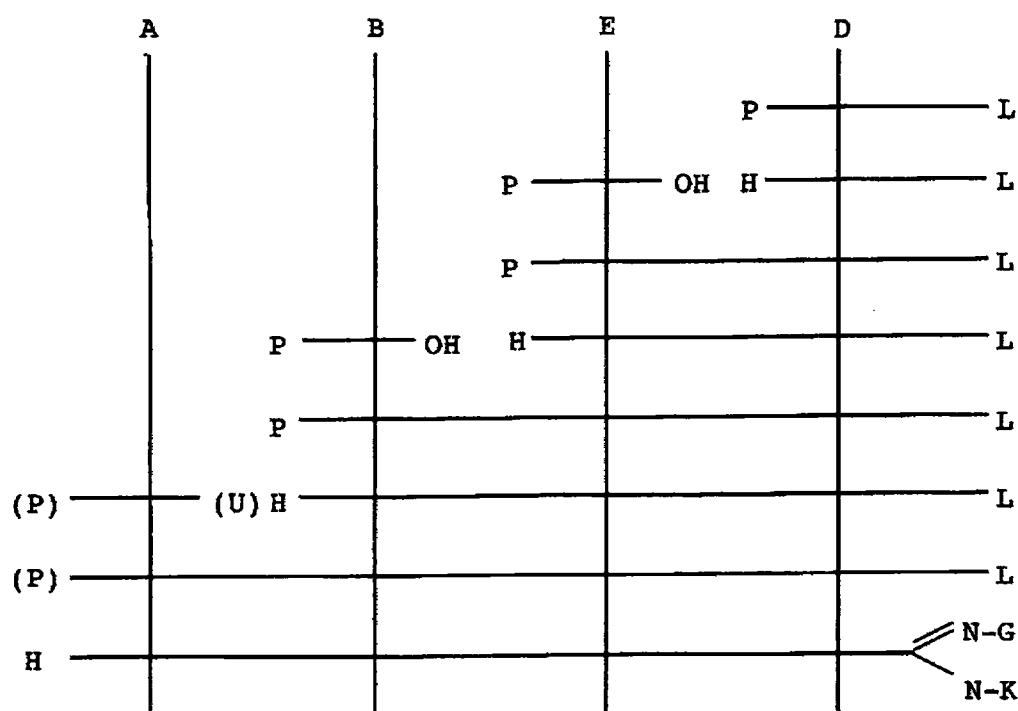
30

The compounds of the formula I can be prepared as shown in schemes I-III.

The building blocks A, B, E and D are preferably assembled separately and employed in suitably protected form (see schemes I-III) using protective groups which are orthogonal in each case and are compatible with the synthetic method used (P or P*).

35

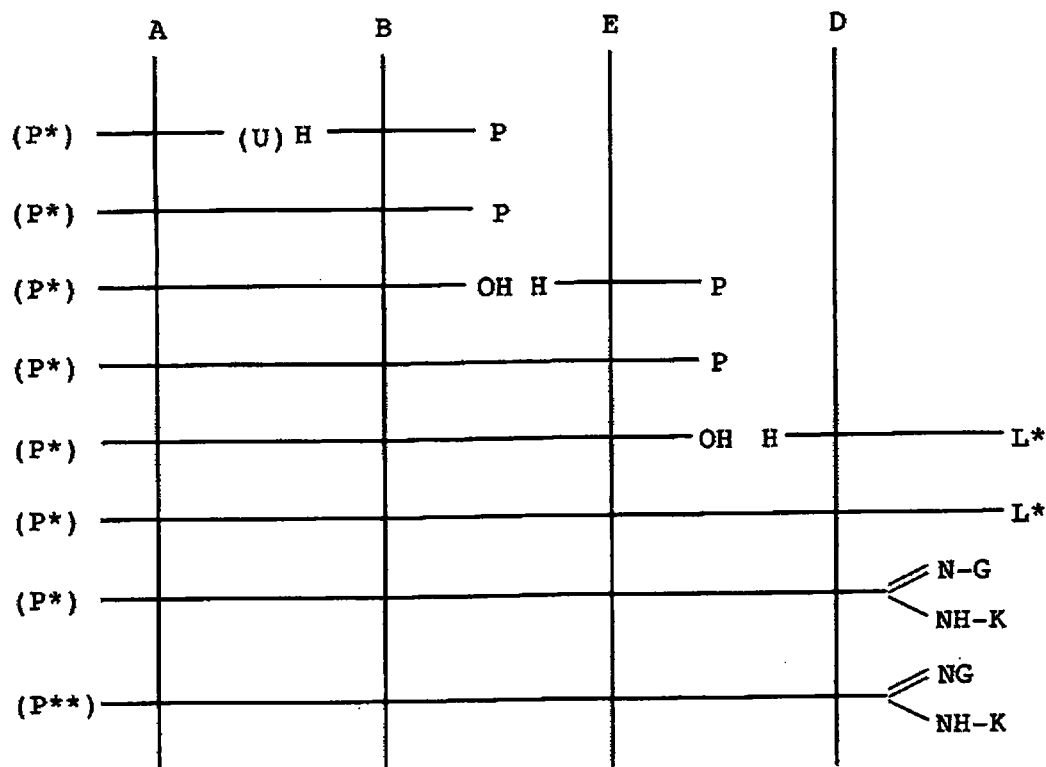
Scheme I



5 (P = protective group, (P) = protective group or H)

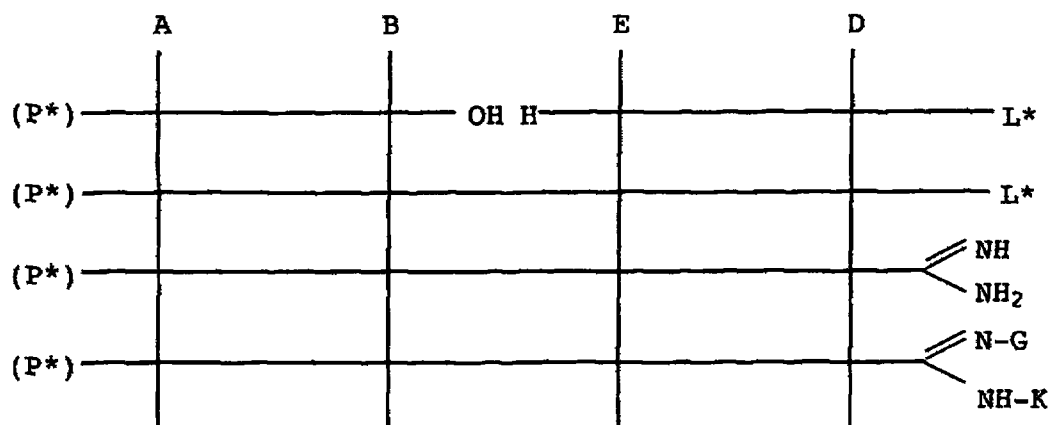
Scheme I describes the linear assembly of molecule I by elimination of protective groups from P-D-L (L equal to CONH_2 , CSNH_2 , CN), coupling of the amine H-D-L to the N-protected amino acid P-E-OH to give P-E-D-L, elimination of the N-terminal protective group to give H-E-D-L, coupling to the N-protected amino acid P-B-OH to give P-B-E-D-L, elimination of the protective group P to give H-B-E-D-L, subsequent coupling or alkylation with the optionally protected (P)-A-U building block (U = leaving group) or reductive alkylation with (P)-A'-U (U = aldehyde, ketone) or Michael addition with a suitable (P)-A''-C=C derivative to give (P)-A-B-E-D-L. If I is an amide function, this can be converted, at the protected stages in each case, by dehydration with trifluoroacetic anhydride into the corresponding nitrile function. Amidine syntheses for thienylamidine, furylamidine and thiazolylamidine compounds of structural type I starting from the corresponding carboxamides, nitriles, thiocarboxamides and hydroxyamidines are described in a number of patent applications (see, for example, WO 95/35309, WO 96/178860, WO 96/24609, WO 96/25426, WO 98/06741, WO 98/09950). Any protective groups still present are then eliminated.

Scheme II



- 5 Scheme II describes the linear assembly of molecule I by coupling, alkylation, reductive amination or Michael addition of H-B-P onto appropriately suitable, optionally protected (P*)-A building blocks [(P*)-A-U (U = leaving group) or (P*)-A'-U (U = aldehyde, ketone) or (P*)-A''-C=C derivative] to give (P*)-A-B-P. Elimination of the C-terminal protective group to give (P*)-A-B-OH is followed by coupling to H-E-P to give (P*)-A-B-E-P,
- 10 renewed elimination of the C-terminal protective group to give (P*)-A-B-E-OH and coupling to H-D-L* (L* equal to CONH₂, CSNH₂, CN, C(=NH)NH-R*; R* equal to hydrogen atom or protective group) to give (P*)-A-B-E-D-L*. Reaction of this intermediate to give the final product takes place in analogy to scheme I. Synthesis of the hydroxy-, alkoxy- or aryloxyamidines (G=OH, OR) takes place by reacting the
- 15 appropriate nitriles or imino thioester salts with hydroxylamine hydrochloride or O-substituted hydroxylamine derivatives. (P**) is then introduced by transesterification or starting from the free acid. To synthesize the oxadiazolones (G and K together form a COO group), in particular the 3-substituted 1,2,4-oxadiazol-5-ones, the appropriate amide oximes are reacted with carbonic acid derivatives such as, for example,
- 20 phosgene, di- and triphosgene, carbonyldiimidazole or chloroformic esters with addition of bases (e.g. NaOH, pyridine, tertiary amines) (R.E. Bolton et al., Tetrahedron Lett. 1995, 36, 4471; K. Rehse, F. Brehme, Arch. Pharm. Med. Chem. 1998, 331, 375).

Scheme III



5

Scheme III describes a very efficient way for preparing the compounds I by a convergent synthesis. The appropriately protected building blocks (P*)-A-B-OH and H-E-D-L* are coupled together and the resulting intermediates (P*)-A-B-E-D-L* are reacted analogously to scheme I and scheme II to give the final product.

10

The N-terminal protective groups employed are Boc, Cbz or Fmoc, and C-terminal protective groups are methyl, tert-butyl and benzyl esters. Amidine protective groups are preferably BOC [sic] and Cbz. If the intermediates contain olefinic double bonds, protective groups eliminated by hydrogenolysis are unsuitable.

15

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

20

Boc protective groups are eliminated using dioxane/HCl, diethyl ether/HCl, dichloromethane/HCl or TFA/DCM, Cbz protective groups are eliminated by hydrogenolysis or with HF, Fmoc protective groups are eliminated with piperidine. Ester functions are hydrolyzed with LiOH in an alcoholic solvent or in dioxane/water. TFA or

25

dioxane/HCl is used to cleave t-butyl esters.

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

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

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

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

15

The starting compounds can be prepared by the following methods:

- The building blocks A employed for the alkylation are, for example, tert-butyl α -bromoacetate, adamantyl α -bromoacetate, tert-butyl b-bromopropionate [sic], tert-butyl α -bromopropionate, tert-butyl α -bromobutyrate, 2,3-dimethyl-2-butyl α -bromoacetate, THP-protected bromoethanol, N-tert-butyl- α -bromoacetamide and N,N-diethyl- α -bromoacetamide. The tert-butyl esters mentioned are prepared in analogy to g. Uray, W. Lindner, Tetrahedron 1988, 44, 4357-4362, unless they can be purchased. The bromoacetic esters not commercially available were prepared by reacting bromoacetyl bromide with the appropriate alcohols, adding pyridine as base.
- 20
- 25

B building blocks:

- A wide variety of possibilities for the general and specific synthesis of amino acids are available in the literature. A review thereof is to be found, inter alia, in volume E16d/part 1 of Houben-Weyl, pp. 406 et seq.
- 30

Precursors which are frequently employed were diphenylmethyleneglycine ethyl ester, diethyl acetamidomalonate and ethyl isocyanoacetate.

35

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

- 5 The syntheses of cyclooctylglycine, 2-norbonylglycine [sic], adamantylalanine, 4-isopropylcyclohex-1-ylalanine, 4-methylcyclohex-1-ylalanine and 4-methylcyclohex-1-ylglycine were carried out via the corresponding ethyl 2-formylaminoacrylates (U. Schöllkopf and R. Meyer, Liebigs Ann. Chem. 1977, 1174) starting from ethyl isocyanoacetate with the relevant carbonyl compounds cyclooctanone, 2-norbornanone, 10 1-formyladamantane, 1-formyl-1-methylcyclohexane, 1-formyl-4-isopropylcyclohexane, 1-formyl-4-methylcyclohexane and 4-methylcyclohexanone by the following general methods:

General method for synthesizing ethyl 2-formylaminoacrylates

15

- A solution of 100 mmol of ethyl isocyanoacetate in 50 ml of THF was 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 appropriate carbonyl compound in 50 ml of THF were added at the same temperature, the reaction mixture was allowed slowly to rise to RT, and the solvent 20 was stripped off in a rotary evaporator. The residue was mixed with 50 ml of water, 100 ml of acetic acid and 100 ml of DCM, and the product was extracted with DCM. The DCM phase was dried over Na₂SO₄, and the solvent was stripped off in a rotary evaporator. The resulting products were almost pure but could, if necessary, be purified further by column chromatography on silica gel (mobile phases: ether/petroleum ether 25 mixtures).

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

- 30 100 mmol of the ethyl 2-formylaminoacrylates were hydrogenated with Pd/C (10%) and hydrogen in 200 ml of glacial acetic acid until the reaction was complete. The catalyst was then filtered off, the acetic acid was stripped off as far as possible in a rotary evaporator, and the residue was refluxed in 200 ml of 50% concentrated hydrochloric acid for 5 h. The hydrochloric acid was stripped off in a rotary evaporator, and the 35 product was dried at 50°C in vacuo and then washed several times with ether. The hydrochlorides resulted as pale-colored crystals.

25.0 g of cyclooctylglycine hydrochloride were obtained starting from 18.9 g (150 mmol) of cyclooctanone. 26.6 g of 2-norbornylglycine [sic] hydrochloride were obtained starting from 16.5 g (150 mmol) of 2-norbornanone. 26.0 g of adamantylalanine hydrochloride were obtained starting from 19.7 g (120 mmol) of 1-formyladamantane. 16.6 g of g-
5 methylcyclohexylalanine hydrochloride 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. 18 g of trans-4-methylcyclohex-1-ylalanine hydrochloride were obtained starting from 15 g of trans-1-formyl-4-methylcyclohexane. 10 g of 3,3-dimethylcyclohex-1-ylalanine hydrochloride
10 were obtained starting from 9 g of 3,3-dimethyl-1-formylcyclohexane.

The aldehyde 1-formyl-3,3-dimethylcyclohexane required for the synthesis was prepared by a method based on that of Moskal and Lensen (Rec. Trav. Chim. Pays-Bas 1987, 106, 137-141):

15 A solution of n-butyllithium in n-hexane (72 ml, 115 mmol) was added dropwise over the course of 10 min to a stirred solution of diethyl isocyanomethylphosphonate (17 ml, 105 mmol) in 280 ml of anhydrous diethyl [sic] ether at -60°C. The resulting suspension was then stirred at -60°C for 15 min and, over the course of 10 min, a solution of 3,3-
20 dimethylcyclohexanone (13 g, 105 mmol) in 100 ml of anhydrous diethyl ether was added, keeping the temperature below -45°C. The reaction mixture was allowed to reach 0°C and, after stirring at this temperature for 90 min, 150-200 ml of 38% strength aqueous hydrochloric acid were cautiously added. The mixture was vigorously stirred at
25 room temperature for 15 h to complete the hydrolysis. The organic phase was separated off and washed with 200 ml each of water, saturated sodium bicarbonate solution and saturated sodium chloride solution. It was dried over magnesium sulfate, filtered and concentrated in a rotary evaporator in order to remove the solvent. The resulting residue was employed without further purification as starting material for synthesizing the amino
30 acid.

Boc-(D)- α -Methylcyclohexylalanine

3.4 g (12.2 mmol) of Boc-(D)- α -methyl-Phe-OH were hydrogenated in 100 ml of MeOH in the presence of 250 mg of 5% Rh on Al₂O₃ under 10 bar of hydrogen at 50°C for 24 h. Filtration and stripping off the solvent resulted in 2.8 g of Boc-(D)- α -methyl-Cha-OH.

35 ¹H-NMR (DMSO-d₆, d [sic] in ppm): 12 (very broad signal, COOH); 1.7-0.8 (25 H; 1.35 (s, Boc), 1.30 (s, Me))

Boc-(3-Ph)-Pro-OH was synthesized in analogy to a method of J.Y.L. Chung et al. (J.Y.L. Chung et al. J. Org. Chem. 1990, 55, 270).

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

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

10 Preparation of cycloheptylglycine, cyclopentylglycine, 4-isopropylcyclohexylglycine and 3,3-dimethylcyclohexylglycine

These amino acids were prepared by reacting cycloheptanone, cyclopentanone, 4-isopropylcyclohexanone and 3,3-dimethylcyclohexanone, respectively, with ethyl

15 isocyanoacetate by a method of h.-J. Prätorius (H.-J. Prätorius, J. Flossdorf, M. Kula, Chem. Ber. 1985, 108, 3079)

Preparation of H-D,L-Chea-OH

20 4.0 g of cycloheptylmethyl methanesulfonate (19.39 mmol), prepared from cycloheptylmethanol and methanesulfonyl chloride, were refluxed together with 4.9 g of diphenylmethyleneglycine 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
25 potassium carbonate was then filtered off, the filtrate was evaporated to dryness, and the crude product was hydrolyzed directly with 20 ml of 2N hydrochloric acid in 40 ml of ethanol, stirring at RT for 1.5 h. The reaction solution was diluted and then benzophenone was extracted with ethyl acetate in the acidic range, and subsequently H-D,L-Chea-OEt was extracted with DCM in the alkaline range (pH = 9), and the solution
30 was dried over magnesium sulfate and concentrated in a rotary evaporator. Yield 3.7 g $\triangle$ 95% of theory.

Said amino acids were converted with di-tert-butyl dicarbonate in water/dioxane by conventional methods into the Boc-protected form in each case and subsequently
35 recrystallized from ethyl acetate/hexane mixtures or purified by column chromatography on silica gsel (mobile phases: ethyl acetate/petroleum ether mixtures).

The Boc-protected amino acids were employed as B building blocks as shown in scheme I.

Said amino acids as B building blocks were also in some cases converted into the corresponding benzyl esters and linked to the appropriately protected A building blocks. In the case of compounds with an N-H function which was still free, this was subsequently protected with a Boc group, the benzyl ester group was removed by hydrogenation and the building block A-B-OH was purified by crystallization, salt precipitation or column chromatography. This route is described by way of example for tBuOOC-CH₂-(Boc)(D)Cha-OH below.

Synthesis of D-cyclohexylalanine benzyl ester

A suspension of 100 g (481 mmol) of D-cyclohexylalanine hydrochloride, 104 g (962 mmol) of benzyl alcohol and 109.7 g (577 mmol) of p-toluenesulfonic acid monohydrate in 2200 ml of toluene was slowly heated to reflux with a water trap. Evolution of hydrogen chloride and dissolving of the suspension to give a clear solution were observed in the temperature range 80-90°C. When no further water separated out (about 4 h), 500 ml of toluene were distilled out, the reaction mixture was allowed to cool overnight, and the resulting residue was filtered off and washed twice with 1000 ml of hexane each time. The resulting residue (195 g) was then suspended in 2000 ml of dichloromethane and, after addition of 1000 ml of water, adjusted to pH 9-9.5 by gradual addition of 50% strength sodium hydroxide solution while stirring. The organic phase was separated off, washed twice with 500 ml of water each time, dried over sodium sulfate and filtered to remove desiccant, and the filtrate was concentrated, resulting in 115 g (94%) of the title product as a pale oil.

N-(tert-Butyloxycarbonylmethylene)-D-cyclohexylalanine [sic] benzyl ester

115 g (440 mmol) of D-cyclohexylalanine benzyl ester were dissolved in 2000 ml of acetonitrile and, at room temperature, 607.5 g (4.40 mol) of potassium carbonate and 94.3 g (484 mmol) of tert-butyl bromoacetate were added, and the mixture was stirred at this temperature for 3 days. Carbonate was filtered off, washing with acetonitrile, the mother liquor was concentrated (30°C, 20 mbar), the residue was taken up in 1000 ml of methyl tert-butyl ether, and the organic phase was extracted with 5% strength citric acid and saturated sodium bicarbonate solution. The organic phase was dried over sodium

sulfate, filtered to remove desiccant and concentrated, and the resulting oil (168 g) was employed directly in the following reaction.

N-Boc-N-(tert-Butyloxycarbonylmethylene)-D-cyclohexylalanine [sic] benzyl ester

5

The oil (168 g, 447 mmol) obtained in the previous synthesis was dissolved in 1400 ml of acetonitrile and, after addition of 618 g (4.47 mol) of potassium carbonate powder and 107.3 g (492 mmol) of di-tert-butyl dicarbonate, stirred at room temperature for 6 days. The potassium carbonate was filtered off with suction, washing with about 1000 ml of
10 acetonitrile, and the filtrate was concentrated. 230 g of the required product were obtained.

N-Boc-N-(tert-Butyloxycarbonylmethylene)-D-cyclohexylalanine [sic]
cyclohexylammonium salt

15

115 g of N-Boc-N-(tert-butyloxycarbonylmethylene)-D-cyclohexylalanine [sic] benzyl ester were dissolved in 1000 ml of pure ethanol and hydrogenated in the presence of 9 g of 10% Pd on active carbon with hydrogen under atmospheric pressure at 25-30°C for 2 h. Filtration and removal of the solvent in a rotary evaporator resulted in 100 g
20 (260 mmol) of a yellow oil which was taken up in 1600 ml of acetone and heated to reflux. The heating bath was removed, and a solution of 27 g (273 mmol) of cyclohexylamine in acetone was quickly added through a dropping funnel. The required salt crystallized out on cooling the reaction mixture to room temperature. The solid was filtered off, washed with 200 ml of acetone and, for final purification, recrystallized once
25 more from acetone. Drying of the residue in a vacuum oven at 30°C resulted in 70.2 g of the required salt as a white powder.

N-Boc-N-(tert-Butyloxycarbonylmethylene)-D-cyclohexylglycine [sic]
cyclohexylammonium salt was prepared in an analogous way from cyclohexylglycine as
30 precursor.

N-Boc-N-(tert-Butyloxycarbonylethylene)-D-cyclohexylalanine [sic] cyclohexylammonium salt

35 a) tert-Butyl 3-bromopropionate

16.64 g (109 mmol) of bromopropionic acid, 150 ml of condensed 2-methylpropene and 2 ml of concentrated sulfuric acid were placed at -30°C under a countercurrent of nitrogen in a glass vessel suitable for an autoclave, tightly closed and stirred at room temperature for 72 h. For workup, the reaction vessel was again cooled to -30°C, and the reaction solution was cautiously poured into 200 ml of ice-cold saturated sodium bicarbonate solution. Excess 2-methylpropene was allowed to evaporate off with stirring, the residue was extracted three times with 50 ml of dichloromethane each time, the combined organic phases were dried over sodium sulfate, the desiccant was filtered off, and the solution was concentrated under waterpump vacuum. The oily residue was purified by column chromatography (mobile phase n-hexane, later n-hexane/diethyl ether 9:1). 18.86 g of the title compound were obtained.

b) N-(tert-Butyloxycarbonylethylene)-D-cyclohexylalanine [sic] benzyl ester

49.4 g (189 mmol) of D-cyclohexylalanine benzyl ester were dissolved in 250 ml of acetonitrile and, after addition of 31.6 g (151 mmol) of tert-butyl bromopropionate at room temperature, refluxed for 5 days. The resulting precipitate was filtered off and washed several times with acetonitrile, the filtrate was concentrated under waterpump vacuum, the residue was taken up in 350 ml of dichloromethane, and the organic phase was extracted with 5% strength citric acid and saturated sodium bicarbonate solution. The organic phase was dried over sodium sulfate, filtered to remove desiccant and concentrated. The oily residue was purified by column chromatography (mobile phase dichloromethane, later dichloromethane/methanol 95:5). A slightly impure oil was obtained and was employed directly in the next reaction.

c) N-Boc-N-(tert-Butyloxycarbonylethylene)-D-cyclohexylalanine [sic] benzyl ester

The oil obtained in the previous synthesis (30 g, max. 70 mmol) was dissolved in 150 ml of acetonitrile and, after addition of 28 ml (160 mmol) of diisopropylethylamine and 19.2 g (88 mmol) of di-tert-butyl dicarbonate, stirred at room temperature for 3 days. The reaction mixture was concentrated in a rotary evaporator under waterpump vacuum, the residue was taken up in n-hexane and washed five times with 3 ml of a 5% strength citric acid solution each time, the combined organic phases were dried over sodium sulfate, the desiccant was filtered off, and the residue after concentration was subjected to separation by

column chromatography (mobile phase hexane/ethyl acetate 95:5). 32.66 g (64 mmol) of the required product were obtained.

- d) N-Boc-N-(tert-Butyloxycarbonylethylene)-D-cyclohexylalanine [sic]
cyclohexylammonium salt

32.66 g (64 mmol) of N-Boc-N-(tert-butyloxycarbonylethylene)-D-cyclohexylalanine [sic] benzyl ester were dissolved in 325 ml of pure ethanol and hydrogenated with hydrogen under atmospheric pressure at 25 - 30°C in the presence of 3 g of 10% Pd on active carbon for 14 h. Filtration of the solution through Celite®, washing with ethanol and removal of the solvent in a rotary evaporator resulted in 26.7 g of a yellow oil, which was taken up in acetone and heated to reflux. The heating bath was removed, and a solution of 7 g (70 mmol) of cyclohexylamine in acetone was quickly added through a dropping funnel. The required salt crystallized out on cooling the reaction mixture to room temperature. The solid was filtered off, washed with 25 ml of acetone and, for final purification, recrystallized once more from acetone. Drying of the residue in a vacuum oven at 30°C resulted in 26.6 g (54 mmol) of the required salt as a white powder.

- 20 N-Boc-N-(tert-Butyloxycarbonylmethylene)-(D)-cyclohexylalanyl-3,4-dehydroproline [sic]:

- a) N-Boc-Pyr-OH (5 g, 23.45 mmol) was dissolved in MeOH (50 ml), and HCl in dioxane (4N, 30 ml) was added. After refluxing for 12 h, the solvent was removed in a rotary evaporator and H-Pyr-OMe hydrochloride was obtained as product. Yield: 3.84 g (100%).

- b) N-(t-BuO₂C-CH₂)-N-Boc-(D)-Cha-OH (8 g, 20.75 mmol) was dissolved in dichloromethane (75 ml) and, at -10°C, ethyldiisopropylamine (15.5 ml, 89.24 mmol) was added. After stirring at this temperature for 5 min, a solution of H-Pyr-OMe hydrochloride (3.4 g, 20.75 mmol) in dichloromethane (25 ml) was added dropwise. A solution of propanephosphonic anhydride in ethyl acetate (50% strength, 20 ml, 26.96 mmol) was then added dropwise, and the mixture was stirred at -10 to 0°C for 2 h. The mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution (2 x 80 ml), 5% strength citric acid solution (2 x 15 ml) and saturated sodium chloride solution (1 x 20 ml). The organic phase was dried over sodium sulfate, and the solvent was removed in a

rotary evaporator. The crude product was purified by flash chromatography (silica gel, dichloromethane/methanol ?? [sic] 95/5). Yield: 6.2 g (60%).

- 5 c) N-(t-BuO₂C-CH₂)-N-Boc-(D)-Cha-Pyr-OMe (5.5 g, 11.12 mmol) was dissolved in dioxane (40 ml) and, after addition of sodium hydroxide solution (1N, 22.2 ml, 22.24 mmol), stirred at room temperature for 2 h. The dioxane was removed in a rotary evaporator, and the aqueous phase was washed with ethyl acetate and acidified to pH 1-2 with potassium bisulfate solution (20% strength). The aqueous phase was extracted with dichloromethane, and the combined organic phases were
10 dried over sodium sulfate. Yield: 5 g (94%), colorless foam. Recrystallization from n-hexane saturated with water afforded colorless crystals (m.p. = 158 - 160°C).

N-Boc-N-(tert-Butyloxycarbonylmethylene)-(D)-cyclohexylglycyl-
3,4-dehydroproline [sic]

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This compound was prepared in an analogous manner from N-Boc-N-(tert-butyloxycarbonylmethylene)-(D)-cyclohexylglycine [sic] and 3,4-dehydroproline [sic] methyl ester.

- 20 (L)3,4-Dehydroproline employed as E building block can be purchased, and (D,L)-4,5-dehydropipecolic acid can be prepared by the method of A. Burgstahler, C.E. Aiman J. Org. Chem. 25 (1960), 489 or C. Herdeis, W. Engel Arch. Pharm 326 (1993), 297 and subsequently converted with (Boc)₂O into Boc-(D,L)-Dep-OH.

- 25 The D building blocks were synthesized as follows:

5-Aminomethyl-2-cyanothiophene

This building block was prepared as described in WO 95/23609

30

4-Aminomethyl-2-cyanothiophene

- a) 2-Bromo-4-formylthiophene

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36 g (320 mmol) of 3-formylthiophene were dissolved in 600 ml of methylene chloride and cooled to 5°C, 100 g (750 mmol) of aluminum trichloride were added in portions, and the reaction mixture was then refluxed. A solution of 59 g (19 ml,

360 mmol) of bromine in 40 ml of methylene chloride was added dropwise over the course of 45 min, and the reaction was allowed to continue under reflux for 4 h.

After cooling, the reaction solution was poured into 600 g of ice-water and extracted with methylene chloride, and the organic phase was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and concentrated in a rotary evaporator. 64.5 g of crude product were obtained and were purified by column chromatography (silica gel, methylene chloride/petroleum ether) to result in a total of 56.5 g of slightly impure product.

10 b) 2-Cyano-4-formylthiophene

7.6 g (85 mmol) of copper(I) cyanide were added to a solution of 13.53 g (70.82 mmol) of 2-bromo-4-formylthiophene in 25 ml of DMF, and the reaction mixture was refluxed for 3.5 h, during which the originally pale green suspension changed into a black solution. After addition of water, the reaction mixture was extracted several times with ethyl acetate, and the organic phases were combined, washed with saturated brine, dried over sodium sulfate and concentrated in a rotary evaporator under gentle vacuum. Addition of ether to the residue (7 g) resulted in 1.6 g of pure product. The mother liquor was purified together with the crude products from other batches by chromatography (silica gel, methylene chloride/petroleum ether 1:1). A total of 56.5 g of 2-bromo-4-formylthiophene was reacted to give 12.6 g of pure 2-cyano-4-formylthiophene (31% yield).

25 c) 2-Cyano-4-hydroxymethylthiophene

3.47 g (91.8 mmol) of sodium borohydride were added in portions to a suspension of 12.6 g (91.8 mmol) of 2-cyano-4-formylthiophene in 200 ml of ethanol, and the reaction mixture was stirred at room temperature for 2 h, during which it slowly formed a clear solution. The residue after concentration in vacuo was taken up in ethyl acetate and washed successively with saturated brine, 5% strength citric acid and saturated brine, and the organic phase was dried with sodium sulfate and concentrated in vacuo to result in 11.7 g of almost pure product (yield 91.5%).

35 d) 4-Bromomethyl-2-cyanothiophene

11.7 g (84.07 mmol) of 2-cyano-4-hydroxymethylthiophene were dissolved together with 24.1 g (91.87 mmol) of triphenylphosphine in 100 ml of THF at room

temperature and, while cooling (ice bath), 30.47 g (91.87 mmol) of tetrabromomethane were added in portions. Stirring at room temperature for 3 hours was followed by concentration in vacuo and purification by chromatography over silica gel (methylene chloride/petroleum ether) to result in 18.8 g of pale yellow crystalline product still containing petroleum ether.

e) 4-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-2-cyanothiophene

18.81 g of 4-bromomethyl-2-cyanothiophene (crude product, maximum 84.07 mmol) were dissolved in 160 ml of THF and cooled to 5°C, and 3.07 g (102.4 mmol) of 80% sodium hydride suspension were added in portions. Subsequently, 22.25 g (102.4 mmol) of di-tert-butyl iminodicarboxylate dissolved in 160 ml of THF were added dropwise at 5°C, and the mixture was then stirred at room temperature overnight. Since conversion was incomplete according to TLC, the mixture was heated at 30-35°C for 4.5 h. After cooling to 0 - 5°C, 33 ml of saturated ammonium chloride solution were slowly added dropwise, THF was distilled off in vacuo, the residue was extracted several times with ethyl acetate, and the ethyl acetate phases were washed with saturated brine, dried over sodium sulfate and concentrated in a rotary evaporator. The viscous red residue (34.61 g) was employed as crude product in the next reaction.

f) 4-Aminomethyl-2-cyanothiophene hydrochloride

34.61 g of 4-[N,N-bis(tert-butoxycarbonyl)aminomethyl]-2-cyanothiophene (crude product, maximum 84.07 mmol) were dissolved in 600 ml of ethyl acetate, cooled to 0-5°C, saturated with HCl gas and warmed to room temperature. After 3 h, the resulting suspension was concentrated in a rotary evaporator and codistilled several times with methylene chloride, and the residue was extracted by stirring with ether and dried in vacuo. 13.85 g of product were obtained as a pale powder. Yield over two stages 94.3%.

5-Aminomethyl-3-cyanothiophene [sic]

a) 4-Cyanothiophene-2-carbaldehyde

49.3 g (258.05 mmol) of 4-bromothiophene-2-carbaldehyde and 27.8 g (310.41 mmol) of copper(I) cyanide were suspended in 130 ml of absolute DMF

and refluxed for 8 h. The solvent was removed in a rotary evaporator at 40°C, and the residue was suspended in ethyl acetate and transferred into a Soxhlet [sic] apparatus. The residue was extracted overnight, the yellow solution was dried over sodium sulfate and concentrated in a rotary evaporator, and the resulting yellow solid was recrystallized from ether to result in 25.3 g of product (80% of theory).

b) 4-Cyanothiophene-2-carbaldehyde oxime

11.6 g (84.6 mmol) of 4-cyanothiophene-2-carbaldehyde were dissolved in 140 ml of methanol, and 12.3 g (116.1 mmol) of sodium carbonate were added. Then 6.5 g (93.5 mmol) of hydroxylamine hydrochloride were added in portions while cooling at 15°C, and the mixture was stirred at 10°C for 2 h. After addition of 80 ml of water, the reaction mixture was extracted five times with 50 ml of diethyl ether each time, the organic phase was dried over sodium sulfate, and the solvent was removed in vacuo to result in 12.5 g of the required product as a yellow crystalline powder (96% of theory).

c) 5-Aminomethyl-3-cyanothiophene [sic] hydrochloride

11.22 g (171.64 mmol) of fine zinc dust were added cautiously in several small portions to a solution of 4.65 g (30.60 mmol) of 4-cyanothiophene-2-carbaldehyde oxime in 50 ml of trifluoroacetic acid cooled to 0-5°C in such a way that the temperature did not exceed 15°C. After stirring at room temperature for 3 h and decantation from excess zinc, the trifluoroacetic acid was substantially removed in vacuo (oil pump), the remaining oil was cooled to 0°C, and a mixture of 150 ml of 3N sodium hydroxide solution and 2 l of methylene chloride which had been cooled to 0°C was added in portions. Insolubles were removed by filtration and then the organic phase was separated off, the aqueous phase was extracted eight times with 20 ml of methylene chloride, the collected organic phases were dried over sodium sulfate and then, while cooling in ice, 20 ml of 6M methanolic hydrochloric acid were added. The product precipitated in the form of the hydrochloride as a white solid, crystallization was completed by cooling the suspension at 4°C overnight. 2.2 g of product were obtained as colorless needles (50% of theory).

5-Aminomethyl-3,4-dimethylthiophene-2-carboxamide hydrochloride:

19 g (105.42 mmol) of 5-cyano-3,4-dimethylthiophene-2-carboxamide were suspended in 760 ml of methanol and 110 ml of 2N hydrochloric acid solution and, after addition of 9.5 g of Pd on carbon (10%), hydrogenated at room temperature. After uptake of 4.7 l of hydrogen (4 h), methanol was distilled out in vacuo, and the aqueous phase was
5 extracted three times with ethyl acetate and then freeze dried. 16.3 g of the required product were obtained as a white solid (70.4% of theory).

5-Aminomethylisoxazole-3-carboxamide:

10 a) Ethyl 5-chloromethylisoxazole-3-carboxylate

21.2 g (210 mmol) of triethylamine were added dropwise to a stirred mixture of 30 g (198 mmol) of ethyl 2-chloro-2-hydroxyiminoacetate and 150 ml of propargyl chloride cooled to 10-15°C and, after stirring at room temperature for 1 h, water
15 was added, the mixture was extracted with ether, and the organic phase was dried over magnesium sulfate and concentrated in a rotary evaporator. The residue was distilled under 0.5 Torr, the product distilling over at 116-122°C.

20 b) 5-Chloromethylisoxazole-3-carboxylic acid

47.3 g (250 mmol) of 5-chloromethylisoxazole-3-carboxylate in 150 ml of ethanol were mixed with 14 g (250 mmol) of potassium hydroxide, and the reaction mixture was stirred at 60 - 70°C for 6 h. After cooling and concentration in vacuo, the residue was taken up in water and extracted with ether, the aqueous phase was
25 acidified with hydrochloric acid and then extracted several times with ether, and the ether phase was dried over sodium sulfate and concentrated in vacuo (oil pump, 50°C). 31 g of the required product were obtained (77% of theory).

30 c) 5-Chloromethylisoxazole-3-carbonyl chloride

120 g (743 mmol) of 5-chloromethylisoxazole-3-carboxylic acid were refluxed together with 500 ml of thionyl chloride and 2 drops of pyridine for 10 h, then concentrated in vacuo and subsequently distilled under 20 Torr. The product distilled at 125-133°C. 78 g (58% of theory) were obtained.

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d) 5-Chloromethylisoxazole-3-carboxamide

Ammonia was passed into a solution of 10 g (55.56 mmol) of 5-chloromethylisoxazole-3-carbonyl chloride in 100 ml of methylene chloride at 10-15°C for 1 h, and the mixture was then stirred at room temperature for 1 h. After the solution had been cooled to 0°C, the precipitate was filtered off with suction and washed with a little cold methylene chloride, and the residue was extracted by stirring with water twice to remove ammonium salts. Drying in vacuo resulted in 6.58 g of pure product as a pale powder (74% of theory).

e) 5-Aminomethylisoxazole-3-carboxamide hydrochloride

2.44 g (15.2 mmol) of 5-chloromethylisoxazole-3-carboxamide were added to a mixture of 100 ml of concentrated ammonia solution and 72 ml of methanol, the reaction solution was warmed to 40°C and, during this, continuously saturated with ammonia gas. The precursor had reacted after 6 h. The methanol was removed in vacuo, the aqueous phase was extracted twice with methylene chloride, and then the aqueous phase was carefully evaporated to dryness in vacuo. The solid white residue was employed as crude product in the couplings.

2-Aminomethylisoxazole-4-thiocarboxamide and 2-aminomethylthiazole-4-thiocarboxamide were prepared as described by g. Videnov, D. Kaier, C. Kempter and g. Jung *Angew. Chemie* (1996) 108, 1604, deprotecting the N-Boc-protected compounds described therein with ethereal hydrochloric acid in methylene chloride.

4-Aminomethylthiazole-2-thiocarboxamide:

a) Monothiooxamide

Monothiooxamide was prepared starting from ethyl thiooxamate by the method of W. Walter, K.-D. Bode *Liebigs Ann. Chem.* 660 (1962), 74-84.

b) 2-Carbamoyl-4-chloromethylthiazole

10 g (96 mmol) of ethyl thiooxamate were introduced into 170 ml of n-butanol and, after addition of 26 g (204 mmol) of 1,3-dichloroacetone, heated at 112°C under nitrogen for 90 min. The reaction mixture was then concentrated in vacuo, and the residue was extracted by stirring with n-hexane (120 ml). This resulted in 10 g of pure product.

c) 4-Boc-Aminomethyl-2-carbamoylthiazole

10 g (56.6 mmol) of 2-carbamoyl-4-chloromethylthiazole were introduced into an ammonia-saturated solution of 350 ml of methanol and 80 ml of 25% strength aqueous ammonia solution. The reaction mixture was heated at 40 - 42°C, while continuing to saturate with ammonia, for 6 h, and was then concentrated in vacuo and codistilled with methanol, and the residue was then extracted by stirring firstly with ether and then with acetone. 7.6 g of crude product which still contained a little ammonium chloride were thus isolated. To remove this byproduct, the crude product was reacted with (Boc)₂O in aqueous dioxane solution and the protected compound was purified by column chromatography. This resulted in 4.95 g of pure product.

d) 4-Boc-Aminomethyl-2-cyanothiazole

4.95 g (19.24 mmol) of 4-Boc-aminomethyl-2-carbamoylthiazole were introduced into 90 ml of methylene chloride and 16.7 ml (97.44 mmol) of diisopropylethylamine and, after cooling to 0°C, a solution of 6.35 ml of trifluoroacetic anhydride in 10 ml of methylene chloride was added dropwise at 0 to 5°C, and the mixture was then warmed to room temperature (TLC check). Then 25 ml of water were added and, after stirring at room temperature for 30 min and adjustment to pH 2.5 with 10% strength citric acid solution, the organic phase was washed several times, dried with magnesium sulfate and concentrated in vacuo. 5.4 g of pale brownish viscous crude product were obtained and were employed without further purification in the next stage.

e) 4-Boc-Aminomethyl-2-thiocarbamoylthiazole

The crude product (max 19.24 mmol) obtained from d) was dissolved in 65 ml of pyridine and 5 ml of triethylamine, saturated with hydrogen sulfide and left to stand at room temperature over the weekend. The reaction mixture was then concentrated in vacuo, taken up in a mixture of ether and ethyl acetate, washed with 10% strength citric acid solution and water, dried over magnesium sulfate and concentrated in vacuo. This resulted in 6.0 g as a pale yellow solid foam.

f) 4-Aminomethyl-2-thiocarbamoylthiazole hydrochloride

The product obtained from the preceding experiment was taken up in 100 ml of methylene chloride and, after addition of 30 ml of approx. 5 molar ethereal hydrochloric acid solution, stirred at room temperature overnight. The reaction mixture was then evaporated to dryness in vacuo, codistilled with ether several times and then extracted by stirring with methylene chloride. 4.15 g of the required product were obtained as a pale yellow amorphous substance.

4-Amidino-2-(*N*-Boc-aminomethyl)-5-methylthiazole x HOAc

a) α -Acetylglycine [sic] methyl ester hydrochloride

Potassium tertiary butoxide (17.8 g, 157.9 mmol) was introduced into THF (120 ml) and, at -70°C, a solution of *N*-(diphenylmethylidene)glycine methyl ester (40 g, 157.9 mmol) in THF (60 ml) was added. After stirring at this temperature for 30 min, the yellowish solution was added dropwise to a solution of acetyl chloride (12.4 g, 157.9 mmol) in THF (70 ml) at -70°C. After stirring at this temperature for 1.75 h, 3N HCl (160 ml) was added and the yellowish suspension was then stirred at room temperature for 10 min. The THF was removed in a rotary evaporator at room temperature, and the remaining aqueous phase was washed 3x with diethyl ether. The aqueous phase was freeze dried and the residue was extracted by stirring with methanol. The methanolic solution of the product was evaporated in a rotary evaporator at 35°C. Yield: 26.4 g (157.9 mmol, quant., yellowish solid).

b) BOC-Gly-(α -Acetyl-Gly)-OMe [sic].

BOC-Gly-OH [sic] (24.05 g, 137.27 mmol) was introduced into THF (400 ml) and triethylamine (13.87 g, 137.19 mmol) was added. The colorless solution was cooled to -20°C and, at this temperature, a solution of isobutyl chloroformate (18.75 g, 137.28 mmol) in THF (20 ml) was added dropwise. The colorless suspension was stirred at -20°C for 30 min and then α -acetylglycine methyl ester hydrochloride (23.0 g, 137.3 mmol) was added in portions. After stirring at -20°C for 30 min, a solution of triethylamine (13.87 g, 137.19 mmol) in THF (20 ml) was added dropwise over the course of 45 min. Stirring at -20°C for 4 h was followed by stirring at RT for 12 h. The residue was filtered off with suction and washed with THF, and the combined THF phases were concentrated in a rotary evaporator. Yield: 44.1 g (pale brownish oil).

$^1\text{H-NMR}$ (270 MHz, CDCl_3) δ = 1.45 (s, 9H), 2.40 (s, 3H), 3.85 (s, 3H), 3.90 (d, J = 6.5 Hz, 2H), 5.25 (d, J = 6.5 Hz, 1H), 7.30 (sbr, 1H).

c) Methyl 2-(N-Boc-aminomethyl)-5-methylthiazole-4-carboxylate

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BOC-Gly-(α -Acetyl-Gly)-OMe [sic] (39.8 g, 138.2 mmol) was introduced into THF (400 ml) and, at room temperature, Lawesson's reagent (96.6 g, 238.8 mmol) was added in portions. The yellowish solution was then refluxed for 1.5 h. The THF was removed in a rotary evaporator. The residue (reddish brown oil) was extracted by stirring with diethyl ether (600 ml). The ether phase was decanted off the undissolved brownish oil and washed successively with 5% strength citric acid (2x), saturated NaHCO_3 solution (9x) and water (2x). After drying (MgSO_4), the solvent was removed in a rotary evaporator. Yield: 22.0 g (77 mmol, 56%, pale brownish solid).

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$^1\text{H-NMR}$ (270 MHz, CDCl_3) δ = 1.50 (s, 9H), 2.75 (s, 3H), 3.95 (s, 3H), 4.55 (d, J = 6.5 Hz, 2H), 5.45 (t, J = 6.5 Hz, 1H). (Main rotamer in relation to BOC [sic] group)

d) 2-(N-Boc-Aminomethyl)-5-methylthiazole-4-carboxylic acid

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Methyl 2-(N-Boc-aminomethyl)-5-methylthiazole-4-carboxylate (22.0 g, 77 mmol) was dissolved in ethanol (100 ml), and a solution of LiOH (2.2 g, 92 mmol) in water (50 ml) was added. After stirring at room temperature for 30 min, the ethanol was removed in a rotary evaporator, and the remaining solution was diluted with water (70 ml). The aqueous phase was washed with ethyl acetate (3x) and adjusted to pH 2 with 20% strength NaHSO_4 solution, whereupon a pale brownish oil separated out. The aqueous phase was extracted with dichloromethane, and the combined organic extracts were dried (MgSO_4) and concentrated in vacuo. The pale brownish residue was extracted by stirring in diisopropyl ether. The remaining colorless precipitate was filtered off with suction and washed with diisopropyl ether. Yield: 6.9 g (25.4 mmol, 33%, colorless solid).

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$^1\text{H-NMR}$ (270 MHz, DMSO-d_6) δ = 1.40 (s, 9H), 2.65 (s, 3H), 4.30 (d, J = 6.5 Hz, 2H), 7.80 (t, J = 6.5 Hz, 1H).

e) 2-(N-Boc-Aminomethyl)-5-methylthiazole-4-carboxamide

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2-(N-Boc-Aminomethyl)-5-methylthiazole-4-carboxylic acid

(6.8 g, 25 mmol) was dissolved in THF (100 ml), and triethylamine (2.53 g, 25 mmol) was added. After cooling to -20°C , a solution of isobutyl chloroformate (3.41 g, 25 mmol) in THF (10 ml) was added dropwise. After stirring at -20°C for 30 min, gaseous ammonia was passed into the pale brownish suspension for 45 min. It was then warmed to room temperature. The residue was filtered off with suction and extracted with THF, and the filtrates were concentrated. Yield: 6.9 g (25 mmol, quant.).

$^1\text{H-NMR}$ (270 MHz, DMSO-d_6) δ = 1.40 (s, 9H), 2.65 (s, 3H), 4.30 (m, 2H), 7.40 (sbr, 1H), 7.50 (sbr, 1H), 7.80 (t, J = 6.5 Hz, 1H).

f) 4-Cyano-2-(N-Boc-aminomethyl)-5-methylthiazole

2-(N-Boc-Aminomethyl)-5-methylthiazole-4-carboxamide (6.8 g, 25 mmol) was introduced into dichloromethane (120 ml). After cooling to 0°C , diisopropylethylamine (15.84 g, 122.8 mmol) was added dropwise. Then, at -5°C , a solution of trifluoroacetic anhydride (8.25 g, 39.3 mmol) in dichloromethane (20 ml) was added dropwise over the course of 30 min. After stirring at 0°C for 30 min, the reaction mixture was warmed to room temperature and then stirred for 12 h. It was diluted with dichloromethane (100 ml) and washed with 20% strength citric acid, saturated NaHCO_3 [sic] solution and saturated NaCl solution. The organic phase was dried (MgSO_4) and concentrated in vacuo. Yield: 6.3 g (25 mmol, quant.).

g) 4-Amidino-2-(N-Boc-aminomethyl)-5-methylthiazole $\times$ CH_3COOH

4-Cyano-2-(N-Boc-aminomethyl)-5-methylthiazole (5.5 g, 21.74 mmol) was dissolved in methanol (15 ml) and N-acetylcysteine (4.1 g, 25.12 mmol) was added. The mixture was then heated to 60°C , and ammonia was passed in for 22 h. The mixture was diluted with methanol and passed over an acetate ion exchanger. The methanol was removed in a rotary evaporator, and the residue was extracted by stirring with acetone. The colorless residue was filtered off with suction and dried in vacuo. Yield: 4.75 g (14.4 mmol, 66%, colorless solid). $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ = 1.40 (s, 9H), 1.80 (s, 3H), 2.60 (s, 3H), 4.35 (d, J = 6.5 Hz, 2H), 7.90 (t, J = 6.5 Hz, 1H).

2-Aminomethyl-5-amidino-4-methylthiazole $\times$ 2 HCl

a) N-BOC-Glycinethioamide [sic].

N-BOC-Glycinonitrile [sic] (12.0 g, 76.8 mmol) and diethylamine (0.16 ml, 2.1 mmol) were dissolved in toluene (100 ml). The solution was cooled to -10°C, saturated with hydrogen sulfide and then stirred at room temperature overnight. The precipitate which formed was filtered off with suction and washed with toluene.

5 The product was dried in vacuo at 45°C. Yield: 13.2 g (69.4 mmol, 90.3%, yellowish solid).

¹H-NMR (270 MHz, DMSO-d₆) δ = 1.40 (s, 9H), 3.80 (d, J = 7 Hz, 2H), 7.05 (t, J = 7 Hz, 1H), 9.0 (sbr, 1H), 9.65 (sbr, 1H).

10 b) Methyl 2-(N-BOC-aminomethyl)-4-methylthiazole-5-carboxylate [sic].

N-Boc-Glycinethioamide (10.0 g, 52.6 mmol) was introduced into methanol (70 ml) and methyl 2-chloroacetate (7.9 g, 52.6 mmol) was added. The mixture was heated at 60°C for 2 h and then stirred at room temperature for 48 h. The methanol was removed in a rotary evaporator, and the residue was extracted by stirring with acetone/diethyl ether. The remaining precipitate was filtered off with suction and the filtrate was concentrated. The solid obtained from the filtrate was the product (pure according to TLC and HPLC). Yield: 8.7 g (30.4 mmol, 57.8%). ESI-MS: 287 (M+H⁺).

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c) 2-(N-BOC-Aminomethyl)-4-methylthiazole-5-carboxylic [sic] acid

Methyl 2-(N-BOC-aminomethyl)-4-methylthiazole-5-carboxylate [sic] (2.8 g, 9.74 mmol) was dissolved in 1,4-dioxane (30 ml), and 1N sodium hydroxide solution (19 ml) was added. After stirring at room temperature for 4 h, the 1,4-dioxane was removed in a rotary evaporator. The residue was diluted with water and washed with ethyl acetate. The aqueous phase was acidified with 20% strength potassium bisulfate solution, and the resulting precipitate was filtered off with suction and washed with water. The product obtained in this way was dried in a vacuum oven at 40°C. Yield: 2.5 g.

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d) 2-(N-BOC-Aminomethyl)-4-methylthiazole-5-carboxamide [sic].

2-(N-BOC-Aminomethyl)-4-methylthiazole-5-carboxylic [sic] acid (12.6 g, 46.27 mmol) was dissolved in dichloromethane (460 ml) and dimethylformamide (0.4 ml). After cooling to 0°C, a solution of oxalyl chloride (6.46 g, 50.90 mmol) in dichloromethane (40 ml) was added dropwise over

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the course of 30 min. After stirring at 0°C for 2 h, the mixture was cooled to -20°C and, at this temperature, ammonia was passed in until the reaction was complete. It was then warmed to room temperature and washed with water. The resulting precipitate was filtered off with suction. The organic phase was washed with 5% strength citric acid solution, dried (MgSO₄) and concentrated in a rotary evaporator. The resulting solid was combined with the previously filtered precipitate and dried in a vacuum oven at 50°C. Yield: 9.8 g (36.12 mmol, 78%).

e) 2-(*N*-BOC-Aminomethyl)-5-cyano-4-methylthiazole [sic].

2-(*N*-BOC-Aminomethyl)-4-methylthiazole-5-carboxamide [sic] (11.13 g, 41.02 mmol) was suspended in dichloromethane (75 ml) and cooled to 0°C. At this temperature, firstly ethyldiisopropylamine (17.86 ml, 102.55 mmol) and then slowly a solution of trifluoroacetic anhydride (6.56 ml, 47.17 mmol) in dichloromethane (20 ml) were added. After stirring for 1 h, the mixture was diluted with dichloromethane and washed with 5% strength citric acid solution. After drying (MgSO₄) and removal of the solvent in a rotary evaporator, the crude product was purified by flash chromatography. Yield: 6.5 g (25.66 mmol, 63%).

f) 2-(*N*-BOC-Aminomethyl)-4-methylthiazole-5-thioamide [sic]

2-(*N*-BOC-Aminomethyl)-5-cyano-4-methylthiazole [sic] (7.5 g, 29.61 mmol) was dissolved in pyridine (30 ml), and triethylamine (27 ml) was added. The solution was saturated with hydrogen sulfide at 0°C and then left to stand at room temperature for 48 h. The solvent was then removed in a rotary evaporator, and the residue was taken up in ethyl acetate, washed with 20% strength potassium bisulfate solution and dried over magnesium sulfate. The solvent was removed in a rotary evaporator, and the crude product was dissolved in dichloromethane and precipitated with petroleum ether. The precipitated product was filtered off with suction and dried in a vacuum oven at 40°C. Yield: 7.1 g (24.7 mmol, 83%).

g) 5-Amidino-2-(*N*-BOC-aminomethyl)-4-methylthiazole [sic] x HOAc

2-(*N*-BOC-Aminomethyl)-4-methylthiazole-5-thioamide [sic] (7.1 g, 24.70 mmol) was dissolved in dichloromethane (40 ml), and iodomethane (17.5 g, 123.52 mmol) was added. After stirring at room temperature for 56 h, the solvent was removed in a rotary evaporator. The residue was dissolved in 10%

strength methanolic ammonium acetate solution (29 ml) and stirred at 40°C until the reaction was complete. The solvent was removed in a rotary evaporator, the residue was extracted by stirring with dichloromethane, and the resulting solid was filtered off with suction and washed with dichloromethane. The residue was dissolved in methanol and converted into the corresponding acetate using an acetate-loaded ion exchanger. The solvent was removed in a rotary evaporator and the resulting reddish brown oil was extracted by stirring with dichloromethane. This resulted in the product as a colorless solid which was dried in vacuo at 40°C. Yield: 5.3 g (16.04 mmol, 65%).

h) 5-Amidino-2-aminomethyl-4-methylthiazole x 2 HCl

5-Amidino-2-(*N*-BOC-aminomethyl)-4-methylthiazole [sic] x HOAc (1.6 g, 4.84 mmol) was suspended in dichloromethane (20 ml) and, at room temperature, 4M hydrochloric acid in 1,4-dioxane (4.84 ml, 19.37 mmol) was added and the mixture was stirred at this temperature for 3 h. The product was filtered off and washed with dichloromethane, and dried in vacuo at 40°C. Yield: 0.73 g (3.00 mmol, 62%).

2-Aminomethyl-5-amidino-4-trifluoromethylthiazole x 2 HCl

a) Ethyl 2-(*N*-BOC-aminomethyl)-4-trifluoromethylthiazole-5-carboxylate [sic]

N-BOC-Glycinethioamide [sic] (5.0 g, 26.28 mmol) was dissolved in acetonitrile (60 ml) and, at 5 to 10°C, a solution of ethyl 2-chloro-4,4,4-trifluoroacetoacetate (6.38 g, 26.28 mmol) was added dropwise. The mixture was then stirred at 5°C for 30 min and at room temperature for 12 h. It was then cooled to 0°C and triethylamine (12 ml, 86.77 mmol) was added dropwise. After stirring at 0°C for 20 min, the yellowish suspension had changed to a clear reddish brown solution. Then thionyl chloride (2.1 ml, 28.89 mmol) was slowly added dropwise at 0°C. Stirring at 0°C for 20 min was followed by warming to room temperature in 1 h. The solvent was removed in a rotary evaporator, and the residue was taken up in water (100 ml) and extracted several times with ethyl acetate. The combined organic phases were dried (Na₂SO₄) and concentrated. The crude product was purified by chromatography (silica gel, MeOH:DCM = 2:98). Yield: 2.2 g (6.4 mmol, 24.5%).

¹H-NMR (270 MHz, DMSO-d₆) δ = 1.30 (t, J = 6.5 Hz, 3H), 1.45 (s, 9H), 4.35 (q, J = 6.5 Hz, 2H), 4.45 (d, J = 6.5 Hz, 2H), 7.95 (t, J = 6.5 Hz, 1H).

b) 2-(*N*-BOC-Aminomethyl)-4-trifluoromethylthiazole-5-carboxamide [sic].

5 Ethyl 2-(*N*-BOC-aminomethyl)-4-trifluoromethylthiazole-5-carboxylate [sic] (15 g, 42.33 mmol) was dissolved in methanol. Ammonia was passed through the solution at room temperature until the ester was completely converted into the carboxamide. The solvent was removed in a rotary evaporator, and the crude product was purified by flash chromatography. Yield: 4.6 g (14.14 mmol, 33%).

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c) 2-(*N*-BOC-Aminomethyl)-5-cyano-4-trifluoromethylthiazole [sic]

2-(*N*-BOC-Aminomethyl)-4-trifluoromethylthiazole-5-carboxamide [sic] (4.6 g, 14.14 mmol) was dissolved in dichloromethane (30 ml) and cooled to -5°C. At this
15 temperature, ethyldiisopropylamine (4.6 g, 35.35 mmol) and a solution of trifluoroacetic anhydride (3.4 g, 16.26 mmol) in dichloromethane (10 ml) were added. The mixture was then stirred at 0°C for 2 h. It was washed successively with saturated sodium bicarbonate solution and 5% strength citric acid solution. After drying (MgSO₄) the solvent was removed in a rotary evaporator. The crude
20 product was extracted by stirring with diethyl ether/petroleum ether. The supernatant was separated from the oil and concentrated in a rotary evaporator. Yield: 1.9 g (6.18 mmol, 44%).

d) 2-(*N*-BOC-Aminomethyl)-4-trifluoromethylthiazole-5-
25 thioamide [sic].

2-(*N*-BOC-Aminomethyl)-5-cyano-4-trifluoromethylthiazole [sic] (4.6 g, 14.97 mmol) was dissolved in pyridine (20 ml) and, after addition of triethylamine (24 ml), the solution was saturated with hydrogen sulfide. After two days at room
30 temperature, the solvent was removed in a rotary evaporator. The crude product was taken up in ethyl acetate and washed successively with 20% strength sodium bisulfate solution and water. After drying (MgSO₄), the solvent was removed in a rotary evaporator. The crude product was purified by flash chromatography. Yield: 2.5 g (7.32 mmol, 49%).

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e) 5-Amidino-2-(*N*-BOC-aminomethyl)-4-trifluoromethylthiazole [sic].

2-(*N*-BOC-Aminomethyl)-4-trifluoromethylthiazole-5-thioamide [sic] (2.5 g, 7.32 mmol) was dissolved in dichloromethane (10 ml), and iodomethane (10.4 g, 73.24 mmol) was added. The mixture was then stirred at room temperature for 48 h. The solvent was removed in a rotary evaporator and the residue was taken up in methanol (5 ml), and 10% strength methanolic ammonium acetate solution (8.5 ml, 10.98 mmol) was added. After stirring at room temperature for 4 days, the solution of the crude product was passed over an acetate-loaded ion exchanger, and the solvent was removed in a rotary evaporator. The crude product was purified by flash chromatography. Yield: 0.8 g (2.08 mmol, 28%).

f) 5-Amidino-2-aminomethyl-4-trifluoromethylthiazole x 2 HCl

5-Amidino-2-(*N*-BOC-aminomethyl)-4-trifluoromethylthiazole [sic] (0.8 g, 2.08 mmol) was dissolved in dichloromethane, and a 4M solution of hydrochloric acid in 1,4-dioxane (2.1 ml, 4.2 mmol) was added. After stirring at room temperature for 1 h, the solvent was removed in a rotary evaporator. The crude product obtained in this way was employed without further purification in the following reactions. Yield: 0.6 g (2.0 mmol, 97%).
ESI-MS: 225 ($M+H^+$).

5-Aminomethyl-3-methylthiophene-2-carbonitrile

a) 5-Formyl-3-methylthiophene-2-carbonitrile:

112 ml (179 mmol) of a 1.6 molar solution of *n*-butyllithium in *n*-hexane were added over the course of 20 min to a solution, cooled to -78°C , of 25.1 ml (179 mmol) of diisopropylamine in 400 ml of tetrahydrofuran. The solution was allowed to reach -35°C and was cooled again to -78°C , and a solution of 20.0 g (162 mmol) of 2-cyano-3-methylthiophene in 80 ml of tetrahydrofuran was slowly added dropwise at this temperature. The solution became dark red in color. After stirring for 45 min, 63 ml (811 mmol) of dimethylformamide were slowly added dropwise, and stirring was continued for 30 min. For workup, a solution of 27 g of citric acid in 160 ml of water was added at -70°C . Concentration in a rotary evaporator and addition of 540 ml of saturated sodium chloride solution were followed by extraction three times with 250 ml of diethyl ether each time. The combined organic extracts were dried over magnesium sulfate. After filtering off the desiccant, the solvent was distilled off under waterpump vacuum and the

residue was purified by column chromatography (mobile phase hexane/ethyl acetate 4/1). 23 g (94%) of the title compound were obtained.

¹H-NMR (270 MHz, DMSO-d₆): δ = 2.4 (s, 3H), 8.0 (s, 1H), 9.8 (s, 1H).

5 b) 5-Hydroxymethyl-3-methylthiophene-2-carbonitrile:

5.75 g (152 mmol) of sodium borohydride were added in portions to a solution of 23 g (152 mmol) of 5-formyl-3-methylthiophene-2-carbonitrile in 300 ml of absolute ethanol at room temperature. The reaction mixture was stirred for 5 minutes, concentrated under waterpump vacuum, taken up in ethyl acetate and extracted with 5% strength citric acid solution and with saturated sodium chloride solution, the organic phase was dried over magnesium sulfate, the desiccant was filtered off and the solvent was distilled off under waterpump vacuum at room temperature. This resulted in 24 g of the title compound as a dark red oil which still contained solvent and was employed without further purification in the following reactions. ¹H-NMR (270 MHz, DMSO-d₆): δ = 2.4 (s, 3H), 4.7 (m, 2H), 5.9 (m, 1H), 7.0 (s, 1H).

20 c) 5-Bromomethyl-3-methylthiophene-2-carbonitrile:

44 g (167 mmol) of triphenylphosphine were added to a solution of 24 g (152 mmol) of 5-hydroxymethyl-3-methylthiophene-2-carbonitrile in 180 ml of tetrahydrofuran. A solution of 55 g (167 mmol) of tetrabromomethane in 100 ml of tetrahydrofuran was then added. The reaction mixture was stirred at room temperature for 90 min. It was then concentrated in a rotary evaporator under waterpump vacuum, and the residue was purified by column chromatography (mobile phase hexane: ethyl acetate 8:2). 34 g of the title compound which still contained a little solvent were obtained. ¹H-NMR (270 MHz, DMSO-d₆): δ = 2.4 (s, 3H), 5.0 (s, 2H), 7.3 (s, 1H).

30 d) 5-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-3-methylthiophene-2-carbonitrile:

5.0 g (167 mmol) of sodium hydride (80% suspension in mineral oil) were added in portions to a solution, cooled to 0°C, of 33.8 g (152 mmol) of 5-bromomethyl-3-methylthiophene-2-carbonitrile in 255 ml of tetrahydrofuran. Then a solution of 36.4 g (167 mmol) of di-tert-butyl iminodicarboxylate in 255 ml of tetrahydrofuran was added dropwise, during which the temperature did not exceed 5°C. The

mixture was allowed to reach room temperature and was stirred overnight. It was then heated at 35°C for 3 hours to complete the reaction and, after cooling to room temperature, 510 ml of a saturated ammonium chloride solution were slowly added. The solvent was distilled off under waterpump vacuum, the residue was extracted several times with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated in a rotary evaporator. 57.6 g of an oily residue which still contained di-tert-butyl iminodicarboxylate were obtained and were employed as crude product in the following reaction.

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.45 (s, 18H), 2.35 (s, 3H), 4.85 (s, 2H), 7.05 (s, 1H).

e) 5-Aminomethyl-3-methylthiophene-2-carbonitrile hydrochloride:

52.6 g of 5-[N,N-bis(tert-butoxycarbonyl)aminomethyl]-3-methylthiophene-2-carbonitrile (crude product from d), maximum 139 mmol) were dissolved in 950 ml of ethyl acetate and cooled to 0°C. On saturation with gaseous hydrogen chloride a white precipitate separated out after 10 min. After stirring at room temperature for two hours and at 30°C for one hour, the resulting suspension was concentrated in a rotary evaporator, the residue was extracted by stirring with diethyl ether, the solvent was removed by filtration, and the solid residue was dried in vacuo at room temperature. 24.7 g (94%) of the title compound were obtained as a white powder. ¹H-NMR (270 MHz, DMSO-d₆): δ = 2.4 (s, 3H), 4.25 (s, 2H), 7.3 (s, 1H), 8.8-9.0 (bs, 3H). ¹³C-NMR (DMSO-d₆): 15.0 (CH₃), 36.4 (CH₂), 104.8 (C-2), 113.8 (CN), 131.5 (C-4), 142.8 (C-5), 149.6 (C-3).

5-Aminomethyl-3-chlorothiophene-2-carbonitrile hydrochloride

This compound was prepared in analogy to 5-aminomethyl-3-methylthiophene-2-carbonitrile, preparing the 3-chloro-2-cyanothiophene used by dehydration of 3-chlorothiophene-2-carboxamide with trifluoroacetic anhydride.

5-Aminomethyl-4-methylthiophene-3-thiocarboxamide [sic]

a) Ethyl 2-amino-3-cyano-4-methylthiophene-5-carboxylate

Ethyl 2-amino-3-cyano-4-methylthiophene-5-carboxylate was synthesized in accordance with "Organikum", 19th edition, Dt. Verlag der Wissenschaften, Leipzig, Heidelberg, Berlin, 1993, chapter 6, pages 374-375, starting from 130 g (1.0 mol) of ethyl acetoacetate, 66 g (1.0 mol) of malononitrile, 32 g (1.0 mol) of sulfur and 80 g (0.92 mol) of morpholine.

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.25 (t, 3H), 2.3 (s, 3H), 4.2 (q, 2H), 7.9 (bs, 2H).

b) Ethyl 4-cyano-3-methylthiophene-2-carboxylate

A solution of 20.5 g (97.5 mmol) of ethyl 2-amino-3-cyano-4-methylthiophene-5-carboxylate in 600 ml of a 1:1 mixture of acetonitrile and dimethylformamide was cooled to 5°C, and 15.7 g (146 mmol) of tert-butyl nitrite were added dropwise, during which the reaction mixture became hot and vigorous evolution of gas started. After stirring at room temperature for seven hours and concentrating in a rotary evaporator and under high vacuum, the residue was purified by column chromatography (mobile phase dichloromethane) to result in 9.1 g (48%) of the required compound as a yellow oil.

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.3 (t, 3H), 2.55 (s, 3H), 4.3 (q, 2H), 8.8 (s, 1H).

c) 5-Hydroxymethyl-4-methylthiophene-3-carbonitrile [sic]:

2.44 g (64 mmol) of lithium aluminum hydride were added in portions to a solution of 25.1 g (129 mmol) of ethyl 3-cyano-4-methylthiophene-5-carboxylate [sic] in 400 ml of tetrahydrofuran at 0°C. The mixture was stirred at room temperature for five hours, excess reducing agent was destroyed by adding 0.5N hydrochloric acid, and the reaction mixture was concentrated under waterpump vacuum, diluted with water and extracted three times with ethyl acetate. The combined organic phases were then washed once each with 0.5N hydrochloric acid and saturated sodium chloride solution. The organic phase was dried over magnesium sulfate, the desiccant was filtered off, and the solvent was distilled off under waterpump vacuum at room temperature. The residue was purified by column chromatography (mobile phase dichloromethane/methanol 95:5) to result in 16.1 g (83%) of the required compound as a pale yellow oil.

¹H-NMR (270 MHz, DMSO-d₆): δ = 2.2 (s, 3H), 4.6 (d, 2H), 5.7 (m, 1H), 8.35 (s, 1H).

d) 5-Bromomethyl-4-methylthiophene-3-carbonitrile [sic]:

30 g (115 mmol) of triphenylphosphine were added to a solution of 16 g (104 mmol) of 5-hydroxymethyl-4-methylthiophene-3-carbonitrile [sic] in 300 ml of tetrahydrofuran at 5°C. A solution of 38 g (115 mmol) of tetrabromomethane in 100 ml of tetrahydrofuran was then added. The reaction mixture was stirred at room temperature overnight. It was then concentrated in a rotary evaporator under waterpump vacuum, and the residue was purified by column chromatography (mobile phase petroleum ether: dichloromethane 1:1). 17 g (76%) of the title compound were obtained as a yellow oil.

¹H-NMR (270 MHz, DMSO-d₆): δ = 2.25 (s, 3H), 5.0 (s, 2H), 8.5 (s, 1H).

e) 5-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-4-methylthiophene-3-carbonitrile [sic]:

3.5 g (103 mmol) of sodium hydride (oil-free) were added in portions to a solution, cooled to 0°C, of 17.2 g (79.5 mmol) of 2-bromomethyl-3-methylthiophene-4-carbonitrile in 250 ml of tetrahydrofuran. A solution of 22.5 g (103 mmol) of di-tert-butyl iminodicarboxylate in 100 ml of tetrahydrofuran was then added dropwise, during which the temperature did not exceed 5°C. The mixture was allowed to warm to room temperature and was stirred for two hours. 400 ml of a saturated ammonium chloride solution were slowly added. The solvent was distilled off under waterpump vacuum, and the residue was diluted with a little water and extracted three times with ethyl acetate. The combined organic phases were washed with saturated ammonium chloride solution and with saturated sodium chloride solution, dried over magnesium sulfate and concentrated in a rotary evaporator. 28 g of an oil which still contained di-tert-butyl iminodicarboxylate were obtained and were employed as crude product in the following reaction.

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.4 (s, 9H), 1.45 (s, 9H), 2.3 (s, 3H), 4.8 (s, 2H), 8.4 (s, 1H).

f) 5-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-4-methylthiophene-3-thiocarboxamide [sic].

The crude product (max. 79 mmol) obtained from e) was dissolved in 280 ml of pyridine and 140 ml of triethylamine and saturated with hydrogen sulfide at room temperature. The previously yellow solution became green. It was stirred at room temperature overnight. To complete the reaction, hydrogen sulfide was passed in

for a further 15 min, and the mixture was stirred at room temperature for two hours. A stream of nitrogen was used to drive out excess hydrogen sulfide through a scrubbing tower. The reaction mixture was then concentrated in a rotary evaporator, taken up in ethyl acetate, washed several times with 20% strength sodium bisulfate solution, dried over magnesium sulfate and concentrated in a rotary evaporator. This resulted in 27 g of a pale yellow solid foam which was employed without further purification in the following reaction.

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.4 (s, 18H), 2.15 (s, 3H), 4.8 (s, 2H), 7.5 (s, 1H), 9.3 (bs, 1H), 9.75 (bs, 1H).

g) 5-Aminomethyl-4-methylthiophene-3-thiocarboxamide [sic] hydrochloride

27 g of 5-[N,N-bis(tert-butoxycarbonyl)aminomethyl]-4-methylthiophene-3-thiocarboxamide [sic] (crude product from f), maximum 70 mmol) were dissolved in 400 ml of ethyl acetate and cooled to 0°C. On saturation with gaseous hydrogen chloride, a white precipitate separated out after 10 min. After stirring at room temperature for two hours, the precipitate was filtered off and washed with ethyl acetate, and the solid residue was dried at room temperature in vacuo. 13.6 g (87%) of the title compound were obtained as a white powder.

EI-MS: M⁺ = 186.

5-Aminomethyl-4-chlorothiophene-3-thiocarboxamide [sic].

a) 5-Formyl-4-chlorothiophene-3-carbonitrile [sic]:.

35 g (325 mmol) of tert-butyl nitrite were added dropwise to a solution of 53.0 g (250 mmol) of 2-amino-4-chloro-5-formylthiophene-3-carbonitrile (the preparation of this compound is described in the patent DB 3738910) in 600 ml of a 1:1 mixture of acetonitrile and dimethylformamide at room temperature, during which the reaction mixture warmed from 20°C to 37°C and vigorous evolution of gas started. After cooling to 25°C and stirring at room temperature for seven hours, the black solution was concentrated in a rotary evaporator and under high vacuum, and the residue was purified by column chromatography (mobile phase dichloromethane) to result in 29 g (68%) of the required compound as a yellow oil.

¹H-NMR (270 MHz, DMSO-d₆): δ = 9.1 (s, 1H), 10.0 (s, 1H).

b) 5-Hydroxymethyl-4-chlorothiophene-3-carbonitrile [sic]:

6.3 g (166 mmol) of sodium borohydride were added in portions to a solution of 28.5 g (166 mmol) of 5-formyl-4-chlorothiophene-3-carbonitrile [sic] in 400 ml of absolute methanol at 5°C. The reaction mixture became slightly warm and dark red in color. Vigorous evolution of gas was observed. After ten minutes, the reaction mixture was concentrated under waterpump vacuum, taken up in 200 ml of ethyl acetate, extracted with 200 ml of 1M hydrochloric acid, and washed twice with 250 ml of water each time and with saturated sodium chloride solution, the organic phase was dried over magnesium sulfate, the desiccant was filtered off, and the solvent was distilled off under waterpump vacuum at room temperature. 22 g (76%) of the title compound were obtained as a dark red oil which was employed without further purification in the following reactions.

$^1\text{H-NMR}$ (270 MHz, DMSO- d_6): δ = 4.65 (bs, 1H), 5.95 (t, 2H), 8.6 (s, 1H).

c) 5-Bromomethyl-4-chlorothiophene-3-carbonitrile [sic]:

36.1 g (137 mmol) of triphenylphosphine were added to a solution of 21.7 g (125 mmol) of 5-hydroxymethyl-4-chlorothiophene-3-carbonitrile [sic] in 250 ml of tetrahydrofuran at 5°C. A solution of 45.6 g (137 mmol) of tetrabromomethane in 100 ml of tetrahydrofuran was then added. The mixture was stirred at room temperature overnight. The precipitate was filtered off, the filtrate was concentrated in a rotary evaporator under waterpump vacuum, and the residue was purified by column chromatography (mobile phase petroleum ether: dichloromethane 1:1).

26.0 g (88%) of the title compound were obtained as an oil.

$^1\text{H-NMR}$ (270 MHz, DMSO- d_6): δ = 4.95 (s, 2H), 8.8 (s, 1H).

d) 5-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-4-chlorothiophene-3-carbonitrile [sic]:.

6.9 g (159 mmol) of sodium hydride (oil-free) were added in portions to a solution, cooled to 0°C, of 25.0 g (106 mmol) of 5-bromomethyl-4-chlorothiophene-3-carbonitrile [sic] in 300 ml of tetrahydrofuran. A solution of 34.4 g (159 mmol) of di-tert-butyl iminodicarboxylate in 100 ml of tetrahydrofuran was then added dropwise, during which the temperature did not exceed 5°C. The mixture was allowed to warm to room temperature and was stirred for two hours. 300 ml of a saturated ammonium chloride solution were slowly added. The solvent was distilled off under waterpump vacuum, and the residue was diluted with a little water and

extracted three times with ethyl acetate. The combined organic phases were washed with saturated ammonium chloride solution and with saturated sodium chloride solution, dried over magnesium sulfate and concentrated in a rotary evaporator. 51.3 g of an oil which still contained di-tert-butyl iminodicarboxylate and solvent residue were obtained and were employed as crude product in the following reaction.

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.4 (s, 9H), 1.45 (s, 9H), 4.8 (s, 2H), 8.65 (s, 1H).

- 10 e) 5-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-4-methylthiophene-3-thiocarboxamide [sic].

Part of the crude product obtained from d) (39.4 g, max. 106 mmol) was dissolved in 400 ml of pyridine and 40 ml of triethylamine and, at room temperature, saturated with hydrogen sulfide. The previously yellow solution became green. It was stirred at room temperature overnight. A stream of nitrogen was used to drive out excess hydrogen sulfide through a scrubbing tower. The reaction mixture was then poured into ice-cold, 20% strength sodium bisulfate solution and extracted three times with ethyl acetate. The organic phase was subsequently washed several times with 20% strength sodium bisulfate solution, dried over magnesium sulfate and concentrated in a rotary evaporator. This resulted in 49.0 g of a solvent-containing residue which was employed without further purification in the following reaction.

¹H-NMR (270 MHz, DMSO-d₆): δ = 1.4, 1.45 (s, 18H), 4.8 (s, 2H), 7.75 (s, 1H), 9.4 (bs, 1H), 10.0 (bs, 1H).

- f) 5-Aminomethyl-4-chlorothiophene-3-thiocarboxamide [sic] hydrochloride

38.0 g of the crude product from e), maximum 93 mmol, were dissolved in 400 ml of ethyl acetate and cooled to 0°C. On saturation with hydrogen chloride gas a white precipitate separated out after 10 min. Since conversion was still incomplete, 200 ml of ethyl acetate were added and the solution was saturated again with hydrogen chloride gas and stirred at room temperature overnight. The precipitate was filtered off, washed with petroleum ether and dried at room temperature in vacuo. 21.1 g of the title compound were obtained as a white powder which contained ammonium chloride as impurity.

EI-MS: M⁺ = 206.

5-Aminomethyl-2-cyanofuran

a) 5-Cyanofuran-2-carbaldehyde:

5 165 ml (264 mmol) of a 1.6 molar solution of n-butyllithium in n-hexane were
added over the course of 20 min to a solution of 26.7 g (264 mmol) of
diisopropylamine in 600 ml of tetrahydrofuran cooled to -78°C . The solution was
allowed to reach -20°C , again cooled to -75°C and, at this temperature a solution of
22.3 g (240 mmol) of 2-cyanofuran in 100 ml of tetrahydrofuran was slowly added
10 dropwise. After stirring for 30 min, 93 ml of dimethylformamide were slowly added
dropwise, and the mixture was stirred for a further 30 min. For workup, a solution
of 40 g of citric acid in 200 ml of water was added at -70°C . After concentration in a
rotary evaporator, 600 ml of saturated sodium chloride solution were added, and
the mixture was extracted three times with 200 ml of diethyl ether each time. The
15 combined organic extracts were dried over magnesium sulfate. The desiccant was
filtered off and then the solvent was distilled off under waterpump vacuum, and the
residue was purified by column chromatography (mobile phase dichloromethane).
The eluate was concentrated and the residue was subjected to steam distillation
(boiling range of the azeotrope with water: 60 to 65°C at $p = 0.1$ mm Hg).
20 Extraction of the distillate with diethyl ether, drying of the organic phase and
concentration of the solution resulted in 10.6 g (88 mmol, 36%) of the title
compound.
 $^1\text{H-NMR}$ (270 MHz, d_6 -DMSO): ? [sic] = 7.7 (d, 1H), 7.8 (d, 1H), 9.75 (s, 1H).

25 b) 5-Hydroxymethyl-2-cyanofuran:

2.34 g (62 mmol) of sodium borohydride were added in portions to a solution of
30 g (0.25 mol) of 5-cyanofuran-2-carbaldehyde in 500 ml of absolute ethanol at
 -30°C . The solution was stirred at -30°C for two hours and, while cooling, was
30 adjusted to pH 7 with a 5% strength citric acid solution in water. The reaction
mixture was concentrated under waterpump vacuum, saturated sodium chloride
solution was added to the residue, the mixture was extracted several times with
150 ml of diethyl ether each time, the combined organic phases were dried over
magnesium sulfate, the desiccant was filtered off, and the solvent was distilled off
35 under waterpump vacuum at room temperature. This resulted in 27 g (22 mmol,
88%) of the title compound as a dark red oil, which was employed without further
purification in the following reactions.

¹H-NMR (250 MHz, d₆-DMSO): ? [sic] = 4.4 (m, 2H), 5.6 (bs, 1H), 6.6 (d, 1H), 7.5 (d, 1H).

c) 5-Bromomethyl-2-cyanofuran:

38 g (145 mmol) of triphenylphosphine were added to a solution of 15 g (121 mol) of 5-hydroxymethyl-2-cyanofuran in 250 ml of tetrahydrofuran. The mixture was cooled to -10°C, and a solution of 48 g (145 mmol) of tetrabromomethane in 100 ml of tetrahydrofuran was added. The mixture was allowed to warm to room temperature and was stirred at this temperature for three hours. The reaction mixture was concentrated in a rotary evaporator under waterpump vacuum, and the residue was purified by column chromatography (mobile phase petroleum ether: dichloromethane 1:1, R_f = 0.5). 11.5 g of the title compound were obtained. ¹H-NMR (250 MHz, d₆-DMSO): ? [sic] = 4.8 (m, 2H), 6.7 (d, 1H), 7.7 (d, 1H).

d) 5-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-2-cyanofuran:

4.0 g (135 mmol) of sodium hydride (80% suspension in mineral oil) were added in portions to a solution of 22.9 g (123 mmol) of 5-bromomethyl-2-cyanofuran in 400 ml of tetrahydrofuran cooled to 0°C. Then a solution of 29.4 g (135 mmol) of di-tert-butyl iminodicarboxylate in 200 ml of tetrahydrofuran was added dropwise, during which the temperature did not exceed 5°C. The mixture was allowed to warm to room temperature and was stirred overnight. Since conversion was incomplete (TLC check), a total of 1.2 g of sodium hydride was added in three portions over a period of 9 hours. To complete the conversion, the mixture was then heated at 35°C for three hours and, after allowing to cool to room temperature, 600 ml of a saturated ammonium chloride solution were slowly added. The solvent was distilled off under waterpump vacuum, the residue was extracted several times with ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated in a rotary evaporator. 37.3 g of an oily residue which still contained di-tert-butyl iminodicarboxylate were obtained and were employed as crude product in the following reaction.

¹H-NMR (250 MHz, d₆-DMSO): ? [sic] = 1.40, 1.45 (s, 18H), 4.75 (s, 2H), 6.55 (d, 1H), 7.55 (d, 1H).

e) 5-Aminomethyl-2-cyanofuran hydrochloride:

37.3 g of 5-[N,N-bis(tert-butoxycarbonyl)aminomethyl]-2-cyanofuran (crude product from d), maximum 123 mmol) were dissolved in 600 ml of ethyl acetate and cooled to 0°C. The solution was saturated with hydrogen chloride gas, a white precipitate separating out after 30 min. The mixture was allowed to reach room temperature and was stirred overnight, and then the resulting suspension was concentrated in a rotary evaporator, the residue was extracted by stirring with diethyl ether, the solvent was removed by filtration, and the solid residue was dried at room temperature in vacuo. 15.1 g (77% yield over two stages) of the title compound were obtained as a pale ocher powder.

¹H-NMR (250 MHz, d₆-DMSO): ? [sic] = 4.15 (bs, 2H), 6.85 (d, 1H), 7.65 (d, 1H), 8.8-9.0 (bs, 3H).

15 5-Aminomethyl-3-cyanofuran [sic] hydrochloride:

a) 5-[N,N-Bis(tert-butoxycarbonyl)aminomethyl]-3-cyanofuran [sic]

A solution, cooled to 0°C, of 20.5 g (0.11 mol) of 5-bromomethyl-3-cyanofuran (L. M. Pevzner, V. M. Ignat'ev, B.I. Ionin, Russ. J. of Gen. Chem. 1994, 64, 2, 125-128) in 50 ml of tetrahydrofuran was added over the course of 30 min to a stirred suspension of 4.8 g (0.12 mol) of sodium hydride (60% dispersion in mineral oil) in 30 ml of tetrahydrofuran at 0°C. A solution of 26.2 g (121 mmol) of di-tert-butyl iminodicarboxylate in 50 ml of tetrahydrofuran was then added dropwise, during which the temperature did not exceed 5°C. The mixture was stirred at 5 to 10°C for three hours, allowed to warm to room temperature and stirred overnight. 150 ml of a saturated ammonium chloride solution were slowly added. The solvent was distilled off under waterpump vacuum, the residue was extracted four times with 60 ml of ethyl acetate each time, and the combined organic phases were washed twice with saturated sodium chloride solution, dried over magnesium sulfate and concentrated in a rotary evaporator. Drying at room temperature in vacuo (1 mm Hg) for three hours resulted in 33.2 g of a dark syrup which still contained di-tert-butyl iminodicarboxylate and was employed as crude product in the following reaction.

¹H-NMR (250 MHz, d₆-DMSO): δ = 1.40, 1.45 (s, 18H), 4.70 (s, 2H), 6.70 (s, 1H), 8.6 (s, 1H).

b) 5-Aminomethyl-3-cyanofuran [sic] hydrochloride

12.89 g of 2-[N,N-bis(tert-butoxycarbonyl)aminomethyl]-4-cyanofuran (crude product from a) were dissolved in 80 ml of ethyl acetate and cooled to -10°C. On saturation with hydrogen chloride gas a white precipitate separated out after 15 min. The mixture was allowed to reach room temperature and was stirred for two hours, the resulting suspension was then concentrated in a rotary evaporator, the residue (7 g) was extracted by stirring with diethyl ether, the solvent was removed by filtration, and the solid residue was dried at room temperature in vacuo. 5 g (79%) of the title compound were obtained as a pale ocher powder. ¹H-NMR (250 MHz, d₆-DMSO): δ = 4.15 (bs, 2H), 7.0 (s, 1H), 8.6-8.9 (m, 4H).

5-Aminomethyl-3-cyano-1,2,4-oxadiazole hydrochloride:

a) N-Boc-5-Aminomethyl-3-cyano-1,2,4-oxadiazole

Ethyl N-Boc-5-aminomethyl-1,2,4-oxadiazole-2-carboxylate [sic] (S. Borg et al. J. Org. Chem. 1995, 60, 3112-20) was dissolved in methanol (50 ml). Ammonia was passed into this solution at -10°C to RT until reaction was complete. The solvent was removed in a rotary evaporator. The crude product obtained in this way was dissolved in dichloromethane (70 ml) and, at -5°C, diisopropylethylamine (2.9 ml, 16.55 mmol) was added. Then trifluoroacetic anhydride (1.06 ml, 7.61 mmol) dissolved in dichloromethane (10 ml), was added dropwise. The mixture was stirred at 0°C for 1.5 h and then diluted with dichloromethane, washed 2x with saturated sodium bicarbonate solution, 2x with 5% strength citric acid solution and 1x with saturated sodium chloride solution and then dried over sodium sulfate. The solvent was removed in a rotary evaporator and the crude product was purified by chromatography (silica gel, dichloromethane: methanol = 97.5:2.5). Yield: 1.2 g (80%).

b) 5-Aminomethyl-3-cyano-1,2,4-oxadiazole hydrochloride

The product obtained in a) (0.9 g, 4.0 mmol) was dissolved in dichloromethane (45 ml) and, at RT, 4 M hydrochloric acid in dioxane (3.9 ml, 15.61 mmol) was added. After stirring at RT for 16 h, the solvent was removed in a rotary evaporator. Yield: 645 mg (100%). ¹H-NMR (DMSO-d₆) δ = 4.6 (s, 2H), 9.2 (s, 3H).

Example 1:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxycarbonyl)amidino-5-thienylmethanamide hydrochloride:

5 a) 3,4-Dehydroproline 2-cyano-5-thienylmethanamide

10 Boc-3,4-Dehydroproline (5 g, 23.4 mmol) and 5-aminomethyl-2-cyanothiophene hydrochloride (4.5 g, 25.8 mmol; WO 95/23609) were dissolved in dichloromethane (25 ml) and, at 0°C, ethyldiisopropylamine (28 ml, 163.8 mmol) [lacuna] a 50% strength solution of propanephosphonic anhydride in ethyl acetate (24.8 ml, 117 mmol) were added. The mixture was stirred at 0°C for 1 h and then warmed to RT and stirred at RT for 12 h. The reaction mixture was diluted with dichloromethane [lacuna] washed with sodium bisulfate solution (4x), sodium bicarbonate solution (3x) and saturated sodium chloride solution (1x). After drying
15 over sodium sulfate and removal of the desiccant by filtration, the solvent was distilled off under waterpump vacuum. To eliminate the Boc group, the residue was mixed [lacuna] in dichloromethane (95 ml), stirred at RT, evaporated to dryness, codistilled twice with dichloromethane, again concentrated and purified by column chromatography. 6.6 g of the required product, which still contained a small
20 amount of solvent, were obtained.

b) N-(tert-butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-cyano-5-thienylmethanamide

25 t-BuO₂C-CH₂-(Boc)-(D)-Chg-OH (6.5 g, 17.5 mmol; WO 9806741) and H-Pyr-NH-CH₂-5-(2-CN)-thioph hydrochloride (4.72 g, 17.5 mmol) were suspended in dichloromethane (90 ml), and ethyldiisopropylamine (11.3 g, 87.5 mmol) was added, resulting in a clear, pale reddish solution. The reaction mixture was cooled to about 5°C and a 50% strength solution of propanephosphonic anhydride in ethyl
30 acetate (18 ml) was added dropwise. Stirring at RT overnight was followed by dilution with dichloromethane (100 ml) and washing with dilute sodium bisulfate solution (3x), saturated sodium bicarbonate solution (2x) and water (1x). Drying over sodium sulfate and removal of the desiccant was followed by removal of the solvent by distillation under waterpump vacuum.
35 11.15 g of a pale reddish brown oil were obtained.

- c) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-aminothiocarbonyl-5-thienylmethylamide

The product obtained in b), t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-CN)-thioph, was dissolved in pyridine (68 ml) and triethylamine (11.5 ml). The reaction mixture was cooled to 0°C and saturated with hydrogen sulfide (the solution became green). The reaction solution was left to stand at RT overnight. The excess hydrogen sulfide was displaced by nitrogen, and the solvent was distilled off under waterpump vacuum. The residue was dissolved in diethyl ether (500 ml) and washed with dilute sodium bisulfate solution (3x), saturated sodium bicarbonate solution (2x) and water (1x). After drying over sodium sulfate, the solvent was distilled off under waterpump vacuum. The viscous yellow crude product (10.92 g) was employed without further purification in the next stage.

- d) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-methylthio(imino)methyl-5-thienylmethylamide hydroiodide

The crude product obtained in c), t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-CSNH₂)-thioph, was dissolved in dichloromethane (115 ml), and methyl iodide (14.99 g, 105.6 mmol) was added. After stirring at RT over the weekend, the solvent was removed by distillation under waterpump vacuum. 12.6 g of a yellowish solid foam were obtained.

- e) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-amidino-5-thienylmethylamide acetate

The crude product obtained in d), t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-C=NH(SCH₃))-thioph x HI, was mixed with 25.5 ml of a 10% strength solution of ammonium acetate in methanol (2.55 g of ammonium acetate, 38.12 mmol). Since precursor was still present according to TLC after stirring at RT overnight, a further 3.0 ml of a 10% strength solution of ammonium acetate in methanol was added and the mixture was stirred at RT overnight. The solvent was then removed by distillation under waterpump vacuum, the residue was taken up in dichloromethane, the salts were filtered off with suction, and the filtrate was concentrated, resulting in 13.3 g of crude product in the form of a yellow solid foam. The product was dissolved in methanol and converted into the

corresponding acetate salt on an ion exchanger (Fluka: acetate on polymeric support, 3.0 mmol of acetate per g).

- 5 f) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-amidino-5-thienylmethylamide

10 The crude product obtained in e), $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(NH}_2\text{))-thioph x HJ [sic] x CH}_3\text{COOH}$, was dissolved in methylene chloride, concentrated ammonia solution was added (PH [sic] 11), the aqueous phase was extracted several times with methylene chloride, and the combined organic phases were dried over magnesium sulfate and concentrated in vacuo. The product was obtained as a white solid.

- 15 g) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxycarbonyl)amidino-5-thienylmethylamide

20 The crude product obtained in f), $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(NH}_2\text{))-thioph}$ (1.4 g, 2.32 mmol), were dissolved in 50 ml of methylene chloride and, after addition of diisopropylamine (3.0 g, 23.2 [sic] mmol) and then, while cooling with a waterbath, dropwise methyl chloroformate (0.24 g, 2.55 mmol) in 5 ml of methylene chloride, the mixture was stirred at room temperature for 1 h. The residue after concentration in vacuo was mixed with ether, water and 5% strength citric acid (pH 5) and extracted, and the ether phase once again washed with acid (pH 3), dried over magnesium sulfate and concentrated in vacuo. 1.7 g of
25 the product were obtained as a colorless foam.

- h) N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxycarbonyl)amidino-5-thienylmethylamide hydrochloride

30 The crude product obtained in g), $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(NH-COOCH}_3\text{))-thioph}$ (1.7 g, max. 2.3 mmol), was dissolved in a mixture of 45 ml of methylene chloride, 20 ml of dioxane and 45 ml of 4N hydrochloric acid in dioxane and stirred overnight with exclusion of moisture. The reaction solution was concentrated in vacuo, and the residue was codistilled with ether several times and subsequently
35 extracted by stirring with ether. After drying in vacuo, 1.3 g of the title compound were obtained as a white solid product. Neutral aqueous solutions of the product

are distinctly more stable than acidic solutions because the acylated amidine function is hydrolyzed under these conditions.

FAB-MS ($M+H^+$): 506

5 Example 2:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-isobutyloxycarbonyl)amidino-5-thienylmethanamide hydrochloride: FAB-MS ($M+H^+$): 548

10 Preparation took place in analogy to Example 1 by reacting t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-C=NH(NH₂))-thioph with isobutyl chloroformate and subsequently eliminating protective groups.

Example 3:

15 N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-hexyloxycarbonyl)amidino-5-thienylmethanamide hydrochloride: FAB-MS ($M+H^+$): 576

Preparation took place in analogy to Example 1 by reacting t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-C=NH(NH₂))-thioph with hexyl chloroformate and subsequently eliminating protective groups.

20

Example 4:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-allyloxycarbonyl)amidino-5-thienylmethanamide hydrochloride: FAB-MS ($M+H^+$): 532

25 Preparation took place in analogy to Example 1 by reacting t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-C=NH(NH₂))-thioph with allyl chloroformate and subsequently eliminating protective groups.

Example 5:

30 N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-benzyloxycarbonyl)amidino-5-thienylmethanamide hydrochloride: FAB-MS ($M+H^+$): 582

35 Preparation took place in analogy to Example 1 by reacting t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-C=NH(NH₂))-thioph with benzyl chloroformate and subsequently eliminating protective groups.

Example 6:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxyethoxycarbonyl)amidino-5-thienylmethanamide hydrochloride: FAB-MS ($M+H^+$): 550

- 5 Preparation took place in analogy to Example 1 by reacting $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(NH}_2\text{))-thioph}$ with methoxyethyl chloroformate and subsequently eliminating protective groups.

Example 7:

- 10 N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxyethoxyethoxycarbonyl)amidino-5-thienylmethanamide hydrochloride: FAB-MS ($M+H^+$): 594

- 15 Preparation took place in analogy to Example 1 by reacting $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(NH}_2\text{))-thioph}$ with methoxyethoxyethyl chloroformate and subsequently eliminating protective groups.

Example 8:

- 20 N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxyamidino)-5-thienylmethanamide hydrochloride:

- a) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxyamidino)-5-thienylmethanamide

- 25 Methoxylamine hydrochloride (0.7 g, 8.38 mmol) was dissolved in 50 ml of methanol and converted into the corresponding acetate salt on an ion exchanger (Fluka: acetate on polymeric support, 3.0 mmol of acetate per g). $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(SCH}_3\text{))-thioph} \times \text{HI}$ (3.0 g, 4.0 mmol; see Example 1d) was added to this methanolic solution, and the reaction mixture was
- 30 stirred at 50°C for 15 min (TLC check (methylene chloride/acetone:9/1)). The residue after concentration in vacuo was purified by chromatography on silica gel, it being possible to isolate 1.0 g of the required product as a pale yellow solid.

- b) N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 2-(N-methoxyamidino)-5-thienylmethanamide hydrochloride:
- 35

The product obtained in a), $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(NHOCH}_3\text{))-thioph}$ (0.9 g, 1.42 mmol), was stirred in a mixture of 10 ml of methylene chloride and 5 ml of 5 N hydrochloric acid solution in ether at room temperature with exclusion of moisture for 24 h, and then 60 ml of ether were added and the precipitated solid was filtered off. The latter was dissolved in 20 ml of water, and the aqueous phase was extracted 3 times with ethyl acetate and freeze dried. 0.7 g of the title compound was obtained as a white powder.

FAB-MS ($\text{M}+\text{H}^+$): 478

10 Example 9:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3.4-dehydroproline 2-(N-isobutyloxyamidino)-5-thienylmethylamide hydrochloride: FAB-MS ($\text{M}+\text{H}^+$): 520

Preparation took place in analogy to Example 8 by reacting $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(SCH}_3\text{))-thioph}$ x HI with O-isobutylhydroxylamine and subsequently eliminating protective groups.

Example 10:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3.4-dehydroproline 2-(N-(p-methylbenzyloxy)amidino)-5-thienylmethylamide hydrochloride: FAB-MS ($\text{M}+\text{H}^+$): 568

Preparation took place in analogy to Example 8 by reacting $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(SCH}_3\text{))-thioph}$ x HI with O-(p-methylbenzyl)hydroxylamine and subsequently eliminating protective groups.

Example 11:

N-(Ethoxycarbonylmethyl)-(D)-cyclohexylglycyl-3.4-dehydroproline 2-(N-(p-methylbenzyloxy)amidino)-5-thienylmethylamide hydrochloride: FAB-MS ($\text{M}+\text{H}^+$): 596

Preparation took place in analogy to Example 8 by reacting $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Chg-Pyr-NH-CH}_2\text{-5-(2-C=NH(SCH}_3\text{))-thioph}$ x HI with O-(p-methylbenzyl)hydroxylamine and subsequently eliminating protective groups in ethanol, there being simultaneous esterification to give the ethyl ester.

Example 12:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3.4-dehydroproline 2-hydroxyamidino-5-thienylmethylamide hydrochloride:

FAB-MS ($M+H^+$): 464

Preparation took place in analogy to Example 8 by reacting t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(2-C=NH(SCH₃))-thioph x HI with hydroxylamine hydrochloride in
5 methylene chloride with the aid of diisopropylethylamine as base. The protective groups were eliminated in 2N aqueous hydrochloric acid at 60°C within 35 min.

Example 13:

10 N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thienylmethanamide hydrochloride:

a) 3,4-Dehydroproline 4-cyano-2-thienylmethanamide hydrochloride

15 This compound was prepared in analogy to Example 1a), employing 2-aminomethyl-4-cyanothiophene (WO 98/06741).

b) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-cyano-2-thienylmethanamide

20 This compound was prepared in analogy to Example 1b).

c) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-methylthioiminomethyl-2-thienylmethanamide hydroiodide

25 This compound was prepared in analogy to Example 1c) and d).

d) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thienylmethanamide

30 This compound was prepared in analogy to Example 8a).

e) N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thienylmethanamide hydrochloride

35 The protective groups were eliminated with dioxane/HCl

f) FAB-MS ($M+H^+$): 478

Example 14:

N-(Cyclohexyloxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thienylmethanamide hydrochloride:

- 5 This compound was synthesized by reacting the compound detailed in Example 13d) with cyclohexanol in 5M hydrochloric acid in dioxane at 50°C, which achieved elimination of the protective groups and transesterification/esterification of the carboxyl function to give the cyclohexyl ester.

FAB-MS (M+H⁺): 560

10

Example 15:

N-(Methoxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thienylmethanamide hydrochloride:

- 15 The [lacuna] took place in analogy to Example 14.

FAB-MS (M+H⁺): 492

Example 16:

- 20 N-(Isopropylloxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thienylmethanamide hydrochloride:

The [lacuna] took place in analogy to Example 14.

FAB-MS (M+H⁺): 520

- 25 Example 17:

N-(tert-Butoxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-hydroxyamidino-2-thienylmethanamide

- 30 a) (D)-cyclohexylglycyl-3,4-dehydroproline 4-cyano-2-thienylmethanamide hydrochloride

- 35 H-Pyr-NH-CH₂-5-(3-CN)-thioph hydrochloride (Example 13a) and Boc-(D)Chg-OH were reacted in analogy to Example 1b) to give Boc-(D)-Chg-Pyr-NH-CH₂-5-(3-CN)-thioph and the Boc protective group was then eliminated with hydrochloric acid in ether/ethyl acetate, resulting in H-(D)-Chg-Pyr-NH-CH₂-5-(3-CN)-thioph hydrochloride as a white solid.

- b) N-(tert-Butoxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-de- hydroproline 4-cyano-2-thienylmethanamide

The product obtained in a), H-(D)-Chg-Pyr-NH-CH₂-5-(3-CN)-thioph hydrochloride (4.8 g, 11.7 mmol), was suspended in 10 ml of methylene chloride and, after addition of 40 ml of ammonia-saturated methylene chloride solution, stirred for 20 min, and then magnesium sulfate was added and the solids were filtered off. Evaporation of the filtrate in vacuo was followed by codistillation with methylene chloride several times until ammonia was completely removed. H-(D)-Chg-Pyr-NH-CH₂-5-(3-CN)-thioph as base was dissolved in 60 ml of methylene chloride, followed by addition of diisopropylethylamine (6.1 g, 8.0 ml, 47 mmol) and then, while cooling, dropwise tert-butyl bromoacetate (2.3 g, 11.7 mmol) in 10 ml of methylene chloride. After 24 h, TLC (methylene chloride/methanol: 9/1) showed 90% of the precursor had reacted. The reaction solution was adjusted to pH 3 with aqueous hydrochloric acid and extracted with methylene chloride, with unreacted precursor remaining in the aqueous phase. The residue after drying of the organic phase and evaporation in vacuo was dissolved in a little methylene chloride and precipitated with n-hexane and the solid was filtered off. 5.2 g of the title compound were obtained as a white solid.

- b)[sic] N-(tert-Butoxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-hydroxyamidino-2-thienylmethanamide

The product obtained in b), t-BuO₂C-CH₂-(D)-Chg-Pyr-NH-CH₂-5-(3-CN)-thioph (5.2 g, 10.7 mmol), was dissolved in 60 ml of methanol and, after addition of hydroxylamine hydrochloride (1.86 g, 26.7 mmol) and diisopropylethylamine ((6.9 g, 9.15 ml, 53.4 mmol), stirred at room temperature overnight. The reaction solution was evaporated in vacuo and then the residue was taken up in aqueous hydrochloric acid at pH 3 and extracted with ethyl acetate, the aqueous phase was adjusted to pH 8 with sodium bicarbonate and again extracted several times with ethyl acetate, and this organic phase was dried over magnesium sulfate and concentrated in vacuo. The resulting product was dissolved in the minimum amount of methylene chloride and reprecipitated with ether. 2.9 g of the title compound were obtained as a white solid.

FAB-MS (M+H⁺): 520

Example 18:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(1,2,4-oxadiazol-5-on-3-yl)-2-thienylmethanamide hydrochloride

- 5 a) N-(tert-Butoxycarbonylmethyl)-N-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-hydroxyamidino-2-thienylmethanamide

10 A solution of 5.0 g (8.5 mmol) of the product obtained in Example 13b), t-BuO₂C-CH₂-N-Boc-(D)-Chg-Pyr-NH-CH₂-5-(3-CN)-thioph, 1.3 g (17 mmol) of hydroxylamine hydrochloride and 1.98 g (15.3 mmol) of diisopropylethylamine in 50 ml of ethanol was heated at 55 to 60°C for five hours. The solution was then concentrated in vacuo, and the residue was taken up in 50 ml of ethyl acetate and washed twice with saturated brine. Drying over magnesium sulfate was followed by removal of the solvent by distillation. 4.6 g (87%) of a pale yellowish amorphous residue were obtained.

15

- b) N-(tert-Butyloxycarbonylmethyl)-N-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(1,2,4-oxadiazol-5-on-3-yl)-2-thienylmethanamide hydrochloride

20 4.6 g (7.4 mmol) of the amide oxime obtained in a) were dissolved in 30 ml of pyridine and, after addition of 1.3 g (8.0 mmol) of carbonyldiimidazole, refluxed for three hours. The pyridine was distilled off in vacuo, and the residue was taken up in tert-butyl methyl ether and washed with 5% strength citric acid solution and saturated brine. The residue after drying over magnesium sulfate and distilling off the solvent was purified by column chromatography (dichloromethane/methanol/glacial acetic acid 95/5/1) to give 3.8 g (79%) of amorphous residue.

25

- 30 c) N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(1,2,4-oxadiazol-5-on-3-yl)-2-thienylmethanamide hydrochloride

35 The 1,2,4-oxadiazol-5-one obtained in b) (3.8 g, 5.9 mmol) was dissolved in 40 ml of glacial acetic acid and, after addition of 40 ml of 4N hydrochloric acid in 1,4-dioxane, left to stand at room temperature overnight. The solvent was distilled off as far as possible and toluene was added several times in order to be able to remove even the last residues of the solvent by distillation in a rotary evaporator. Purification by column chromatography (ethanol/25% strength aqueous ammonia

solution 50:2.5) resulted in an amorphous powder which was taken up in a dioxane/water (7:3) mixture. One equivalent of 32% strength hydrochloric acid was added, and the residue after evaporation to dryness was digested with acetonitrile to result in 1.9 g (62%) of a white powder. FAB-MS ($M+H^+$): 489

5

Example 19:

N-(Methoxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(1,2,4-oxadiazol-5-on-3-yl)-2-thienylmethanamide hydrochloride

- 10 0.8 g (1.5 mmol) of the product obtained in Example 18 c) was dissolved in 50 ml of methanol and, after addition of 5 ml of a solution of 4N hydrochloric acid in 1,4-dioxane, refluxed for eight hours. The solvent was distilled off as far as possible and toluene was added several times in order to be able to remove even the last residues of the solvent by distillation in a rotary evaporator. The residue was digested with acetonitrile and
15 filtered. 0.65 g (79%) of a white powder was obtained.
FAB-MS ($M+H^+$): 503

Example 20:

- 20 N-(Cyclohexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolylmethanamide dihydrochloride

- HO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-am)-thiaz (1.5 g, 3.24 mmol; preparation: WO 9806741, Example 21) was dissolved in 20 ml of cyclohexanol and, after addition of hydrochloric acid in ether (5N, 10 ml), stirred at 60°C for 6 h. Since the reaction was still
25 incomplete according to TLC (methylene chloride/methanol/acetic acid: 100/20/5), a further 15 ml of 5N hydrochloric acid in ether were added and the mixture was stirred at 60°C for 4 h. After concentration of the reaction mixture in vacuo it was codistilled several times with methylene chloride and ether to remove adherent hydrochloric acid. The product was then dissolved in a little methylene chloride and precipitated with ether,
30 and the residue was filtered off with suction and dried in vacuo. 1.85 g of the title compound were obtained as a white hygroscopic solid.
FAB-MS ($M+H^+$): 545

Example 21:

N-(Hexadecyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolylmethylamide dihydrochloride

- 5 Preparation took place in analogy to Example 20 by esterification of $\text{HO}_2\text{C}-\text{CH}_2-(\text{Boc})-(\text{D})-\text{Cha}-\text{Pyr}-\text{NH}-\text{CH}_2-2-(4\text{-am})$ -thiaz with 1-hexadecanol, the reaction taking place at 135°C for 4 h, and the subsequent purification of the reaction mixture taking place by column chromatography (silica gel/methylene chloride with increasing methanol content).
- 10 FAB-MS ($\text{M}+\text{H}^+$): 687

Example 22:

N-(Undecyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolylmethylamide diacetate

- 15 Preparation took place in analogy to Example 20 by esterification of $\text{HO}_2\text{C}-\text{CH}_2-(\text{Boc})-(\text{D})-\text{Cha}-\text{Pyr}-\text{NH}-\text{CH}_2-2-(4\text{-am})$ -thiaz with 1-undecanol [sic], the reaction mixture being purified by RP-HPLC (acetonitrile, water, acetic acid gradient).
- FAB-MS ($\text{M}+\text{H}^+$): 617

20

Example 23:

N-((O-Methyltetraethoxy)-oxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolylmethylamide diacetate

- 25 Preparation took place in analogy to Example 20 by esterification of $\text{HO}_2\text{C}-\text{CH}_2-(\text{Boc})-(\text{D})-\text{Cha}-\text{Pyr}-\text{NH}-\text{CH}_2-2-(4\text{-am})$ -thiaz with tetraethylene glycol monomethyl ether and subsequent purification of the crude product by RP-HPLC (acetonitrile, water, acetic acid gradient).
- FAB-MS ($\text{M}+\text{H}^+$): 653

30

Example 24:

N-(Cyclohexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

a) Boc-2-aminomethyl-thiazole-4-carboxamide

Ethyl bromopyruvate (386 g, 1.98 mol) was added dropwise to a solution of Boc-glycinethioamide (370 g, 1.94 mol) in 3.9 liters of ethanol at 10°C, and the mixture was then stirred at 20°-25°C for 5 h. 299 ml of a 25% strength aqueous ammonia solution were then added. 940 ml of this mixture (corresponds to 19.9% of the total volume) were distilled to remove 380 ml of ethanol and, after addition of a further 908 ml of a 25% strength aqueous ammonia solution, stirred at 20 to 25°C for 110 h. After cooling to 0°C, the solid was filtered off, washed twice with water and dried. 60.1 g of the Boc-protected thiazolecarboxamide were obtained with an HPLC purity of 97.9% area, corresponding to a yield over these two stages of 60.5%.

¹H-NMR (DMSO-d₆, in ppm): 8.16 (s, 1H, Ar-H), 7.86 (t, broad, 1H, NH), 7.71 and 7.59 (2x s, broad, 1H each, NH₂ [sic]), 4.42 (d, 2H, CH₂ [sic]), 1.41 (s, 9H, tert butyl)

b) 2-Aminomethyl-4-cyanothiazole hydrochloride

Boc-2-aminomethylthiazole-4-carboxamide (75.0 g, 0.29 mol) was suspended in 524 ml of methylene chloride and, at -5 to 0°C, triethylamine (78.9 g, 0.78 mol) and 79.5 g (0.38 mol) of trifluoroacetic anhydride were added. The mixture was stirred for 1 h and then allowed to warm to 20 to 25°C, 1190 ml of water were added and the phases were separated. 160 ml of 5 - 6N isopropanolic hydrochloric acid were added to the organic phase, which was boiled for 3 h, left to stir at 20°- 25°C overnight, cooled at -5 to 0°C for 2.5 h and filtered to remove solid. This was washed with methylene chloride and dried. 48.1 g of 2-aminomethyl-4-cyanothiazole were obtained with an HPLC purity of 99.4% area, corresponding to a yield over these two stages of 94.3%.

¹H-NMR (DMSO-d₆, in ppm): 8.98 (s, broad, 2H, NH₂), 8.95 (s, 1H, Ar-H), 4.50 (s, 2H, CH₂)

c) 3,4-Dehydroproline 4-cyano-2-thiazolylmethylamide hydrochloride

Preparation took place in analogy to Example 1a) by coupling Boc-3,4-dehydroproline to 2-aminomethyl-4-cyanothiazole hydrochloride and then eliminating the protective group.

- d) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-cyano-2-thiazolylmethylamide

Preparation took place in analogy to Example 1b) by coupling t-BuO₂C-CH₂-(Boc)-(D)-Cha-OH (WO 9806741) to H-Pyr-NH-CH₂-2-(4-CN)-thiaz hydrochloride.

- e) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (22.2 g, 36.7 mmol) was dissolved in ethanol (250 ml), and hydroxylamine hydrochloride (6.41 g, 92.2 mmol) was added and, while this suspension was cooled (waterbath), diisopropylethylamine (23.8 g, 31.6 ml, 184.5 mmol) was slowly added dropwise.

The reaction solution was stirred at room temperature for 3 h and then concentrated in vacuo and taken up in methylene chloride/water, and the aqueous phase was adjusted to pH 3 with 2N hydrochloric acid and extracted. The organic phase was washed several times with water, dried over magnesium sulfate and concentrated in vacuo. The residue was extracted by stirring with n-hexane, resulting in 22.5 g of t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz as an almost pure white solid.

- f) N-(Cyclohexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz (2.0 g, 3.15 mmol) was dissolved in cyclohexanol (25 ml) and, after addition of 10 ml of 5N hydrochloric acid in ether, stirred at 60°C for 6 h. Since TLC (methylene chloride/methanol/acetic acid: 100/20/5) showed that the reaction was not yet complete, a further 10 ml of 5N hydrochloric acid in ether were added, and the mixture was stirred at 60°C for 4 h. Evaporation of the reaction mixture in vacuo was followed by codistillation several times with methylene chloride and ether to remove adherent hydrochloric acid. The product was then dissolved in a little methylene chloride and precipitated with ether, and the residue was filtered off with suction and dried in vacuo. 1.81 g of the title compound were obtained as a white hygroscopic solid.

FAB-MS (M+H⁺): 561

Example 25:

N-(Hexadecyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 5 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in hexadecanol/dioxane with 5M hydrochloric acid at 135°C, and the subsequent purification of the reaction mixture by column chromatography (silica gel/methylene chloride with increasing methanol content (0-10%)).
- 10 FAB-MS ($M+H^+$): 703

Example 26:

N-(Undecyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 15 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in undecanol/dioxane with 5M hydrochloric acid at 65°C, and the subsequent purification of the reaction mixture by column chromatography (silica gel/methylene chloride with increasing methanol content (0-10%)).
- 20 FAB-MS ($M+H^+$): 633

Example 27:

N-(Methoxyethoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 25 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in ethylene glycol monomethyl ether/dioxane with 5M hydrochloric acid at 65°C, and the subsequent purification of the reaction mixture by column chromatography (silica gel/methylene chloride with increasing methanol content (0-10%)).
- 30 FAB-MS ($M+H^+$): 537

Example 28:

N-((O-Methyldiethoxy)oxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 5 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in diethylene glycol monomethyl ether/dioxane with 5M hydrochloric acid at 65°C, and the subsequent purification of the reaction mixture by column chromatography (silica gel/methylene chloride with increasing methanol content (0-10%)).
- 10 FAB-MS ($M+H^+$): 581

Example 29:

N-(Hexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 15 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in hexanol/dioxane with 5M hydrochloric acid at 60°C, and precipitating the product from ether after concentration in vacuo.
- 20 FAB-MS ($M+H^+$): 563

Example 30:

N-(Ethoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 25 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in ethanol/dioxane with 5M hydrochloric acid at 60°C, and precipitating the product from ether after concentration in vacuo.
- 30 FAB-MS ($M+H^+$): 507

Example 31:

N-(3-Fluoropropylloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in 3-fluoropropanol/dioxane with 5M hydrochloric acid at 60°C, and precipitating the product from ether after concentration in vacuo.

5 FAB-MS (M+H⁺): 539

Example 32:

N-(Isopropoxyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

10

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in isopropanol/dioxane with 5M hydrochloric acid at 60°C, and precipitating the product from ether after concentration in vacuo.

15 FAB-MS (M+H⁺): 521

Example 33:

N-(2,2-Dimethylpropyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

20

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in 3,3-dimethylpropyl alcohol/dioxane with 5M hydrochloric acid at 60°C, and precipitating the product from ether after concentration in vacuo.

25 FAB-MS (M+H⁺): 549

Example 34:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

30

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups with 1M hydrochloric acid at 60°C and precipitating the product from ether after concentration in vacuo.

FAB-MS (M+H⁺): 479

Example 35:

N-(Hydroxycarbonylmethyl)-N-(cyclohexyloxycarbonyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolymethylamide hydrochloride

- 5 HO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-am)-thiaz (0.5 g, 1.08 mmol; preparation: WO 9806741, Example 21) was suspended in a mixture of 2.5 ml of acetone and 2.5 ml of water, and cyclohexyl chloroformate (0.18 g, 1.08 mmol) and then, dropwise, diisopropylethylamine (0.14 g, 0.19 ml, 1.08 mmol) were added (pH 6-7), whereupon the precursor dissolved. After stirring at room temperature overnight, acetone was removed
10 by distillation in vacuo, the residue was mixed with water, adjusted to pH 3 with dilute hydrochloric acid and extracted with methylene chloride, and the organic phase was dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in a little methylene chloride and precipitated with ether. 0.6 g of the title compound was obtained as a white solid.
- 15 FAB-MS (M+H⁺): 589

Example 36:

N-(Propyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxycarbonyl)amidino-2-thiazolymethylamide

20

- a) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolymethylamide

- 25 t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (2.0 g, 3.3 mmol, Example 24d)) was dissolved in methanol [sic] (20 ml) and, after addition of N-acetyl-L-cysteine (0.6 g, 3.66 mmol), refluxed while passing in ammonia until the precursor had completely reacted (about 12 h, TLC check: methylene chloride/methanol:95/5 and methylene chloride/methanol/acetic acid: 100/20/5). The reaction solution was concentrated in vacuo, the residue was taken up in dilute
30 hydrochloric acid (pH 3) and extracted with ether, the aqueous phase was made alkaline with dilute sodium hydroxide solution (pH 9) and extracted with methylene chloride, and this organic phase was dried over magnesium sulfate and concentrated in vacuo. This resulted in 1.8 g of the title compound as a white solid.

- 35 b) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxycarbonyl)amidino-2-thiazolymethylamide:

The crude product obtained in a), $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-CH}_2\text{-2-(4-C=NH(NH}_2\text{))-thiaz}$ (2.0 g, 3.32 mmol) was dissolved in 50 ml of methylene chloride, and diisopropylamine (4.2 g, 32.32 mmol) was added and then, while cooling with a waterbath, methyl chloroformate (0.34 g, 3.56 mmol) in 5 ml of methylene chloride was added dropwise, and the mixture was stirred at room temperature for 1 h. The residue after concentration in vacuo was mixed with n-hexane, water and dilute hydrochloric acid (pH 3), and extracted, the aqueous phase was then extracted with ethyl acetate, and the ethyl acetate phase was dried over magnesium sulfate and concentrated in vacuo. 2.0 g of crude title compound were obtained as a colorless foam, which was reacted further without further purification.

- c) N-(Propyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxycarbonyl)amidino-2-thiazolylmethylamide:

The crude product obtained in b), $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-CH}_2\text{-2-(4-C=NH(NH-COOCH}_3\text{))-thiaz}$ (2.0 g, 2.95 mmol), was dissolved in a mixture of 35 ml of n-propanol and 20 ml of 4.5N hydrochloric acid in ether and stirred with exclusion of moisture overnight. The reaction solution was concentrated in vacuo, the residue was taken up in water and rapidly extracted with ethyl acetate, the aqueous phase was treated with alkali to pH 7 and extracted several times with ethyl acetate, and these ethyl acetate phases were dried over magnesium sulfate and concentrated in vacuo. Purification of the product by column chromatography on silica gel (short column, diluent: methylene chloride with increasing methanol content) resulted in 1.4 g of the title compound as a white solid.

FAB-MS ($M+H^+$): 563

Example 37:

N-(Cyclohexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxycarbonyl)amidino-2-thiazolylmethylamide

Preparation took place in analogy to Example 36c) from $t\text{-BuO}_2\text{C-CH}_2\text{-(Boc)-(D)-Cha-Pyr-NH-CH}_2\text{-2-(4-C=NH(NH-COOCH}_3\text{))-thiaz}$ by elimination of protective groups and subsequent transesterification/esterification of the carboxyl function in cyclohexanol with 4.5M hydrochloric acid in ether.

FAB-MS ($M+H^+$): 603

Example 38:

N-(Methoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxycarbonyl)amidino-2-thiazolylmethylamide

- 5 Preparation took place in analogy to Example 36c) from t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-C=NH(NH-COOCH₃))-thiaz by elimination of protective groups and subsequent transesterification/esterification of the carboxyl function in methanol with 4.5 M hydrochloric acid in ether.

FAB-MS (M+H⁺): 535

10

Example 39:

N-(Methoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-cyclohexyloxycarbonyl)amidino-2-thiazolylmethylamide

- 15 Preparation took place in analogy to Example 36b) and c) from t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-C=NH(NH₂))-thiaz by reaction with cyclohexyl chloroformate and subsequent elimination of protective groups and transesterification/esterification of the carboxyl function in methanol.

FAB-MS (M+H⁺): 603

20

Example 40:

N-(tert-Butyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

- 25 a) (D)-cyclohexylalanyl-3,4-dehydroproline 4-cyano-2-thiazolylmethylamide

H-Pyr-NH-CH₂-2-(4-CN)-thiaz-hydrochloride (Example 24c) and Boc-(D)-Cha-OH were reacted in analogy to Example 1b) to give Boc-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz, and the Boc protective group was then eliminated with hydrochloric acid in isopropanol, resulting in H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz hydrochloride as a white solid. The product was converted into the base H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz in analogy to Example 17b) with ammonia in methylene chloride.

30

- b) N-(tert-Butyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-cyano-2-thiazolylmethylamide

35

The product obtained in a), H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz, was converted in analogy to Example 17b) by alkylation with tert-butyl bromoacetate into t-BuO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz.

- 5 c) N-(tert-Butyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

10 The product obtained in b), t-BuO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz, and hydroxylamine were reacted in analogy to Example 24e) to give t-BuO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz.
FAB-MS (M+H⁺): 535

Example 41:

- 15 N-(Adamantyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

- a) Adamantyl bromoacetate

20 1-Adamantol (3.0 g, 20.0 mmol) was dissolved in 30 ml of methylene chloride and, after addition of pyridine (9.5 g, 9.6 ml, 120 mmol) and cooling to -10°C, bromoacetyl bromide (4.4 g, 22.0 mmol) in 15 ml of methylene chloride was added dropwise to this solution with stirring. Warming to room temperature (2 h) was followed by addition of aqueous citric acid solution (pH 2) and extraction, and the organic phase was washed with water, dried over magnesium sulfate and
25 concentrated in vacuo. The resulting crude product Ada-O₂C-CH₂-Br was employed without further purification in the subsequent alkylation.

- b) N-(Adamantyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-cyano-2-thiazolylmethylamide

30 Ada-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz was prepared in analogy to Example 40 starting from H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz and Ada-O₂C-CH₂-Br.

- 35 c) N-(Adamantyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

Ada-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz was prepared in analogy to Example 24e) starting from Ada-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz and [sic] hydroxylamine.

FAB-MS (M+H⁺): 613

5

Example 42:

N-(Adamantyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolymethylamide diacetate

- 10 Ada-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (Example 41b) was converted in analogy to Example 36a) with ammonia and acetylcysteine into Ada-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-am)-thiaz and the resulting crude product was purified by RP-HPLC.

FAB-MS (M+H⁺): 597

15

Example 43:

N-(Hydroxyethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

- 20 a) N-(Hydroxyethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-cyano-2-thiazolymethylamide

H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (4.0 g, 10.3 mmol, Example 40a)) was stirred together with iodoethanol (1.5 ml) in an oil bath at 100°C for 5 h. Since TLC (methylene chloride/methanol/acetic acid: 100/20/5) showed precursor still present,
25 the mixture was cooled and the base was liberated with ammoniacal methylene chloride solution, and the reaction mixture was again heated at 100°C with iodoethanol (1.5 ml) for 2 h. Volatiles were then removed in vacuo, and the residue was extracted by stirring with ether three times. 5.3 g of the title compound were
30 obtained as a pale yellow solid which was employed without further purification in the following reaction.

- b) N-(Hydroxyethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

35

The crude product obtained in a), HO-CH₂-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz, was converted in analogy to Example 24e) with hydroxylamine hydrochloride

into the corresponding hydroxyamidino compound, which was then converted with hydrochloric acid in ether into the hydrochloride HO-CH₂-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz hydrochloride.

FAB-MS (M+H⁺): 465

5

Example 44:

N-(Hydroxyethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolylmethylamide diacetate

- 10 HO-CH₂-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (Example 43a) was reacted in analogy to Example 36a) with ammonia and N-acetyl-L-cysteine to give HO-CH₂-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-am)-thiaz, and the resulting crude product was then purified by column chromatography (silica gel; methylene chloride/methanol/acetic acid: 80/20/1), resulting in the title compound as a colorless solid.

15 FAB-MS (M+H⁺): 449

Example 45:

N-(n-Hexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thiazolylmethylamide hydrochloride

20

- a) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-aminothiocarbonyl-2-thiazolylmethylamide

25 t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (Example 24d)) was reacted in analogy to Example 1c) with hydrogen sulfide in pyridine/triethylamine to give the corresponding thioamide t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-CSNH₂)-thiaz.

- 30 b) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-methylthioiminomethyl-2-thiazolylmethylamide hydroiodide

The product obtained from a), t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-CSNH₂)-thiaz, was reacted in analogy to Example 1d) with methyl iodide to give t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-C=NH(SCH₃))-thiaz HI.

35

- c) N-(tert-Butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thiazolylmethylamide

The product obtained from b), t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-C=NH(SCH₃))-thiaz was reacted in analogy to Example 8a) with methoxylamine to give t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-methoxyamidino)-thiaz.

5

- d) N-(Hexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thiazolylmethylamide hydrochloride

10

The elimination of protective groups and the transesterification/esterification of the carboxyl function in t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-C=NH(NHOCH₃))-thiaz was carried out in analogy to Example 24f) in hexanol with 5M hydrochloric acid in ether at 60°C, and the resulting crude product was purified by extraction (methylene chloride/water) and subsequent precipitation from ether, resulting in the title compound as a white solid.

15

FAB-MS (M+H⁺): 577

Example 46:

N-(Ethoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thiazolylmethylamide hydrochloride

20

The elimination of protective groups and the transesterification/esterification of the carboxyl function in t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-C=NH(NHOCH₃))-thiaz was carried out in analogy to Example 24f) in ethanol with 5M hydrochloric acid in ether at 60°C, and the resulting crude product was purified by extraction (methylene chloride/a little water) and subsequent precipitation from ether, resulting in the title compound as a white solid.

25

FAB-MS (M+H⁺): 521

Example 47:

30

N-(Cyclohexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(N-methoxyamidino)-2-thiazolylmethylamide hydrochloride

The elimination of protective groups and the transesterification/esterification of the carboxyl function in t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-C=NH(NHOCH₃))-thiaz was carried out in analogy to Example 24f) in cyclohexanol with 5M hydrochloric acid in ether at 60°C, and the resulting crude product was purified by extraction

(methylene chloride/a little water) and subsequent precipitation from ether, resulting in the title compound as a white solid.

FAB-MS ($M+H^+$): 575

5 Example 48:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(1,2,4-oxadiazol-5-on-3-yl)-2-thiazolymethylamide hydrochloride

Preparation took place starting from t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-

10 ham)-thiaz (Example 24d) in analogy to Example 18), resulting in the title compound as a white amorphous powder.

FAB-MS ($M+H^+$): 505

Example 49:

15 N-(Methoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-(1,2,4-oxadiazol-5-on-3-yl)-2-thiazolymethylamide hydrochloride

Preparation took place starting from t-BuO₂C-CH₂-(Boc)-(D)-Cha-Pyr-NH-CH₂-2-(4-

20 ham)-thiaz (Example 24d) in analogy to Example 19), resulting in the title compound as a white amorphous powder.

FAB-MS ($M+H^+$): 519

Example 50:

25 N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-(N-hydroxycarbonylmethoxyamidino)-2-thienylmethylamide hydrochloride:

This compound was prepared by dissolving 2.47 g (3.24 mmol) of the product obtained in 13c), N-(tert-butoxycarbonylmethyl)-(Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-methylthioiminomethyl-2-thienylmethylamide hydroiodide, in 40 ml of methanol and, at
30 room temperature, adding 2.86 g (19.43 mmol) of tert-butyl aminoxyacetate, and heating at 40°C for 20 min. The residue after concentration was taken up in ethyl acetate and washed twice with 10% strength sodium thiosulfate solution and once each with 20% strength sodium bisulfate solution and saturated sodium chloride solution. The residue (2.5 g) after drying over magnesium sulfate and concentrating the solution was purified
35 by column chromatography (eluent: hexane/ethyl acetate 1:1). 2.3 g of a yellowish oil were obtained. The protective groups were eliminated with dioxane/HCl at room temperature within three hours.

FAB-MS ($M+H^+$): 522

Example 51:

5 N-(n-Hexyloxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydro-proline 4-hydroxyamidino-2-thienylmethylamide

10 ml (40 mmol) of a 4 molar solution of hydrogen chloride in 1,4-dioxane were added to a solution of 2.5 g (4 mmol) of the product obtained in Example 18a, N-(tert-butoxycarbonylmethyl)-(N-Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-
10 hydroxyamidino)-2-thienylmethylamide in 25 ml 1-hexanol, and the reaction mixture was heated to 40°C. It was stirred at this temperature for eight hours and at room temperature overnight. Although conversion was incomplete, the reaction mixture was evaporated to dryness in a rotary evaporator and stirred with diethyl ether. The precipitate was filtered off, washed with ether, dissolved in methanol and converted into
15 the salt of acetic acid using an ion exchanger. The residue was purified by column chromatography (normal phase MPLC, eluent: dichloromethane/methanol = 95:5). 1.8 g (73%) of the title compound were obtained as a white solid.

ESI-MS ($M+H^+$): 548

20 Example 52:

N-(Ethoxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-hydroxyamidino-2-thienylmethylamide

10 ml (40 mmol) of a 4 molar solution of hydrogen chloride in 1,4-dioxane were added to
25 a solution of 2.5 g (4 mmol) of the product obtained in Example 18a, N-(tert-butoxycarbonylmethyl)-(N-Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-hydroxyamidino)-2-thienylmethylamide in 25 ml ethanol, and the reaction mixture was heated to 40°C. It was stirred at this temperature for eight hours and at room temperature overnight. Although conversion was incomplete, the reaction mixture was
30 evaporated to dryness in a rotary evaporator and stirred with diethyl ether. The precipitate was filtered off, washed with ether, dissolved in methanol and converted into the salt of acetic acid using an ion exchanger. The residue was purified by column chromatography (normal phase MPLC, eluent: dichloromethane/methanol = 95:5). 0.59 g (27%) of the title compound was obtained as a white solid.

35 ESI-MS ($M+H^+$): 492

Example 53:

N-(Cyclopentyloxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-hydroxyamidino-2-thienylmethylamide

- 5 10 ml (40 mmol) of a 4 molar solution of hydrogen chloride in 1,4-dioxane were added to a solution of 2.5 g (4 mmol) of the product obtained in Example 18a, N-(tert-butoxycarbonylmethyl)-(N-Boc)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-hydroxyamidino-2-thienylmethylamide in 25 ml cyclopentanol, and the reaction mixture was heated to 40°C. It was stirred at this temperature for two days. Although conversion
10 was incomplete, the reaction mixture was evaporated to dryness in a rotary evaporator and stirred with diethyl ether. The precipitate was filtered off, washed with ether, dissolved in methanol and converted into the salt of acetic acid using an ion exchanger. The residue was purified by column chromatography (normal phase MPLC, eluent: ethyl acetate/n-hexane = 8:2). 1.38 g (58%) of the title compound were obtained as a white
15 solid.

ESI-MS ($M+H^+$): 532

Example 54:

- N-(Cyclohexyloxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydroproline 4-
20 hydroxyamidino-2-thienylmethylamide

Preparation took place starting from t-BuO₂C-CH₂-(Boc)-(D)-Chg-Pyr-NH-CH₂-5-(3-ham)-thioph (Example 18a) and cyclohexanol in analogy to Example 53, resulting in the title compound as a white amorphous powder.

- 25 ESI-MS ($M+H^+$): 546

Example 55:

N-(Cyclopropylmethyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 30 Preparation took place starting from N-(hydroxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydro-proline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride (Example 34) and cyclopropylmethanol in analogy to Example 53, resulting in the title compound as a white amorphous powder.

- 35 ESI-MS ($M+H^+$): 533

Example 56:

N-(Cyclopentylloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 5 Preparation took place starting from N-(hydroxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride (Example 34) and cyclopentanol in analogy to Example 53, resulting in the title compound as a white amorphous powder.

ESI-MS ($M+H^+$): 547

10

Example 57:

N-[(5-Methyl-2-oxo-1,3-dioxol-4-enyl)methyloxycarbonyl-methyl]-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

- 15 a) 4-Bromomethyl-5-methyl-2-oxo-1,3-dioxolene

4-Bromomethyl-5-methyl-2-oxo-1,3-dioxolene was prepared by the method of Sakamoto, Ikeda and Tsukamoto (Chem. Pharm. Bull. 1984, 32, 6, 2241-2248) by free-radical bromination from 11.4 g of 4,5-dimethyl-2-oxo-1,3-dioxolene and 17.6 g of bromine.

20

- b) 4-Hydroxymethyl-5-methyl-2-oxo-1,3-dioxolene

The 4-bromomethyl-5-methyl-2-oxo-1,3-dioxolene obtained a) was converted in analogy to Alexander et al. (J. Med. Chem. 1996, 39, 480-86) via the formyl ester intermediate into the title compound.

25

- c) (5-Methyl-2-oxo-1,3-dioxol-4-enyl)methyl bromoacetate

4-Hydroxymethyl-5-methyl-2-oxo-1,3-dioxolene (0.44 g, 3.4 mmol) was dissolved in 5 ml of dichloromethane and, after addition of pyridine (0.27 g, 0.3 ml, 3.4 mmol), cooled to 0°C and then bromoacetyl bromide (0.68 g, 3.4 mmol) dissolved in 3 ml of dichloromethane was added dropwise with stirring. After warming to room temperature (1.5 h), the reaction mixture was diluted with ethyl acetate and extracted several times with a small amount of water in order to remove the pyridine. The combined organic extracts were dried over magnesium sulfate and, after removal of the desiccant by filtration, concentrated in vacuo. The resulting crude product 1,3-dioxol-2-on-4-enyl-O₂C-CH₂-Br was employed without further purification in the subsequent alkylation.

30

35

- d) N-[(5-Methyl-2-oxo-1,3-dioxol-4-enyl)methyloxycarbonyl-methyl]-(D)-cyclohexylalanyl-3,4-dehydroproline 4-cyano-2-thiazolymethylamide

1,3-Dioxol-2-on-4-enyl-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz was prepared in analogy to Example 40 starting from H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz and 1,3-dioxol-2-on-4-enyl-O₂C-CH₂-Br.

- e) N-[(5-Methyl-2-oxo-1,3-dioxol-4-enyl)methyloxycarbonyl-methyl]-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide

1,3-Dioxol-2-on-4-enyl-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz was prepared in analogy to Example 24e) starting from 1,3-dioxol-2-on-4-enyl-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz and and [sic] hydroxylamine.
ESI-MS (M+H⁺): 591

Example 58:

N-(Hydroxycarbonylmethyl)-N-(methyloxycarbonyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolymethylamide hydrochloride

Preparation took place in analogy to Example 35 starting from HO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-am)-thiaz and methyl chloroformate, resulting in the title compound as a white amorphous powder.

FAB-MS (M+H⁺): 521

Example 59:

N-(Hydroxycarbonylmethyl)-N-(hexyloxycarbonyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolymethylamide hydrochloride

Preparation took place in analogy to Example 35 starting from HO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-am)-thiaz and hexyl chloroformate, resulting in the title compound as a white amorphous powder.

FAB-MS (M+H⁺): 591

Example 60: N-(Methoxyethoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolymethylamide dihydrochloride

Preparation took place in analogy to Example 20 by esterification of $\text{HO}_2\text{C}-\text{CH}_2-(\text{Boc})-(\text{D})-\text{Cha}-\text{Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{am})-\text{thiaz}$ with ethylene glycol monomethyl ether, the reaction being carried out at about $60-65^\circ\text{C}$ and the subsequent purification of the reaction mixture being carried out by column chromatography (silica gel/methylene chloride with increasing methanol content).

FAB-MS ($\text{M}+\text{H}^+$): 521

Example 61:

N-((O-Methyldiethoxy)oxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolylmethanamide dihydrochloride

Preparation took place in analogy to Example 20 by esterification of $\text{HO}_2\text{C}-\text{CH}_2-(\text{Boc})-(\text{D})-\text{Cha}-\text{Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{am})-\text{thiaz}$ with diethylene glycol monomethyl ether, the reaction being carried out at $60-65^\circ\text{C}$. After exchange of the chloride ions for acetate ions using an ion exchanger, the reaction mixture was purified by HPLC (RP phase, lyophilization of the aqueous solution with addition of hydrochloric acid), and the product was obtained as white solid.

FAB-MS ($\text{M}+\text{H}^+$): 565

Example 62:

N-(6-Aminohex-1-yloxyoxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-amidino-2-thiazolylmethanamide x acetic acid

BOC-NH-(CH_2)₆-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz [sic] was prepared initially in analogy to Example 41a by reacting BOC-NH-(CH_2)₆-OH [sic] with bromoacetyl bromide to give BOC-NH-(CH_2)₆-OCO-CH₂-Br [sic] which was then employed in analogy to Example 17b or 40b in the alkylation with H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz. After reaction of the resulting intermediate BOC-NH-(CH_2)₆-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz [sic] with (BOC)₂O [sic] to give BOC-NH-(CH_2)₆-O₂C-CH₂-(BOC)-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz [sic], the nitrile function was converted into the amidine function in analogy to WO 9806741 [sic]. After elimination of protective groups with hydrochloric acid in dioxane, exchange of the chloride ions for acetate ions using an ion exchanger and subsequent purification by chromatography (HPLC; RP phase, lyophilization of the aqueous solution), the title compound H₂N-(CH_2)₆-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-am)-thiaz x CH₃COOH was obtained as a white powder.

FAB-MS ($\text{M}+\text{H}^+$): 562

Example 63:

N-(Decahydro-2-naphthyloxycarbonylmethyl)-(D)-cyclohexylalanyl-
3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

- 5 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in decahydro-2-naphthol/dioxane with 5M hydrochloric acid at 60°C. After concentration in a rotary evaporator, the residue was stirred with ether to remove excess hydrochloric acid and alcohol, the residue was dissolved in aqueous potassium carbonate solution
10 (pH 8) and extracted several times with methylene chloride, and the organic phases were dried over magnesium sulfate, mixed with ethereal hydrochloric acid and concentrated in a rotary evaporator. The residue was codistilled several times with ether and then stirred with ether, resulting in $C_{10}H_{17}-O_2C-CH_2(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.
15 FAB-MS ($M+H^+$): 615

Example 64:

N-(Cyclohexylmethyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

- 20 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in cyclohexylmethyl alcohol/dioxane with 5M hydrochloric acid at 60°C. The workup took place as described in Example 63, resulting in
25 $C_6H_{11}-CH_2-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.
FAB-MS ($M+H^+$): 575

Example 65:

- 30 N-(4-tert-Butylcyclohexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

- Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in 4-tert-butylcyclohexanol/dioxane with 5M hydrochloric acid at 60°C. The workup took
35 place as described in Example 63, resulting in $4-(CH_3)_3C-C_6H_{10}-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid, which, according to HPLC and NMR, is a mixture of 75% trans and 25% cis ester.

FAB-MS ($M+H^+$): 617

Example 66:

5 N-(Adamant-1-ylmethyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

10 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in adamant-1-ylmethyl alcohol/dioxane with 5M hydrochloric acid at 60°C. The workup took place as described in Example 63, resulting in $C_{10}H_{15}-CH_2-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.

FAB-MS ($M+H^+$): 627

Example 67:

15 N-(4-tert-Butylcyclohexylmethyloxycarbonylmethyl)-(D)-cyclohexyl-alanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolyl-methylamide hydrochloride

20 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in 4-tert-butylcyclo-hexylmethyl alcohol/dioxane with 5M hydrochloric acid at 60°C. The workup took place as described in Example 63, resulting in $4-(CH_3)_3C-C_6H_{10}-CH_2-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.

FAB-MS ($M+H^+$): 631

25

Example 68:

N-(4-Methoxycyclohexyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

30 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in 4-methoxycyclo-hexanol/dioxane with 5M hydrochloric acid at 60°C. The workup took place as described in Example 63, resulting in $4-CH_3O-C_6H_{10}-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.

35 FAB-MS ($M+H^+$): 591

Example 69:

N-(Cycloheptyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

- 5 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in cycloheptanol/dioxane with 5M hydrochloric acid at 60°C. The workup took place as described in Example 63, resulting in $C_7H_{13}-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.
- 10 FAB-MS ($M+H^+$): 575

Example 70:

N-(3,3,5,5-Tetramethylcyclohexyloxycarbonylmethyl)-(D)-cyclo-hexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolyl-methylamide hydrochloride

- 15 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in 3,3,5,5-tetramethylcyclohexanol/dioxane with 5M hydrochloric acid at 60°C. The workup took place as described in Example 63, resulting in $3,3,5,5-(CH_3)_4-C_6H_{10}-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.
- 20 FAB-MS ($M+H^+$): 617

Example 71:

N-(4-Pyranyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydro-proline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

- 25 Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in 4-pyranyl alcohol/dioxane with 5M hydrochloric acid at 60°C. The workup took place as described in Example 63, resulting in $4-pyranyl-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz \times HCl$ as a white solid.
- 30 FAB-MS ($M+H^+$): 563

Example 72:

- 35 N-(Methyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydro-proline 4-hydroxyamidino-2-thiazolymethylamide hydrochloride

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in methanol/dioxane with 5M hydrochloric acid at 60°C. Stirring with ether resulted in CH₃-O₂C-CH₂(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz x HCl as white solid.

5 FAB-MS (M+H⁺): 493

Example 73:

N-(n-Propyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydro-proline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

10

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in propanol/dioxane with 5M hydrochloric acid at 60°C. Stirring with ether resulted in CH₃-CH₂-CH₂-O₂C-CH₂(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz x HCl as white solid.

15

FAB-MS (M+H⁺): 521

Example 74:

N-(n-Butyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydro-proline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

20

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in n-butanol/dioxane with 5M hydrochloric acid at 60°C. Stirring with ether resulted in CH₃-CH₂-CH₂-CH₂-O₂C-CH₂(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz x HCl as white solid.

25

FAB-MS (M+H⁺): 535

Example 75:

N-(i-Butyloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydro-proline 4-hydroxyamidino-2-thiazolylmethylamide hydrochloride

30

Preparation took place in analogy to Example 24, carrying out the elimination of the protective groups and the transesterification/esterification of the carboxyl function in isobutanol/dioxane with 5M hydrochloric acid at 60°C. Stirring with ether resulted in CH₃-CH(CH₃)-CH₂-O₂C-CH₂(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz x HCl as white solid.

35

FAB-MS (M+H⁺): 535

Example 76:

N-(2,4-Dimethylpent-3-yloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

- 5 a) (2,4-dimethylpent-3-yl) bromoacetate
 2,4-Dimethylpentan-3-ol (4.0 g, 4.8 ml, 34.4 mmol), n-pentane (40 ml) and pyridine (16.3 g, 16.6 ml, 206.5 mmol) were placed in a flask and cooled to -10°C, and bromoacetyl bromide (9.0 g, 3.9 ml, 44.75 mmol) was slowly added dropwise to this solution. After stirring at room temperature for 5 hours, further pentane was
 10 added, and the organic solution was washed successively with water, 10% strength citric acid and water and then dried over magnesium sulfate and cautiously concentrated in a rotary evaporator. 7.2 g of $[(CH_3)_2CH]_2CH-O_2C-CH_2-Br$ were obtained as a colorless liquid.
- 15 b) $[(CH_3)_2CH]_2CH-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz$
 H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (Example 40a) was alkylated with $[(CH_3)_2CH]_2CH-O_2C-CH_2-Br$ in analogy to Example 40b to give $[(CH_3)_2CH]_2CH-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-CN)-thiaz$ and then reacted with
 20 hydroxylamine in analogy to Example 24e to give $[(CH_3)_2CH]_2CH-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz$. The residue after concentration of the reaction mixture in a rotary evaporator was taken up in methylene chloride and extracted with hydrochloric acid solution (pH 1-2), and the aqueous phase which contained the required product was then adjusted to pH 5 and again extracted with methylene chloride. Drying over magnesium sulfate and concentration of the solution in a
 25 rotary evaporator resulted in $[(CH_3)_2CH]_2CH-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz$ as a white solid.
 FAB-MS (M+H⁺): 577

Example 77:

- 30 N-(1-Methylcyclopentylloxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

The 1-methylcyclopentyl bromoacetate prepared in analogy to 76a was reacted with H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (Example 40a) to give $(1-CH_3)C_5H_8-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-CN)-thiaz$, which was then converted in analogy to Example 24e
 35 into $(1-CH_3)C_5H_8-O_2C-CH_2-(D)-Cha-Pyr-NH-CH_2-2-(4-ham)-thiaz$. The product was isolated in analogy to Example 76b.

FAB-MS ($M+H^+$): 561

Example 78:

5 N-(α,α -Dicyclohexylmethyloxycarbonylmethyl)-(D)-cyclohexylalanyl-
3,4-dehydroproline [sic] 4-hydroxyamidino-2-thiazolylmethylamide

10 The 1-dicyclohexylmethyl bromoacetate prepared in analogy to 76a was reacted with H-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz (Example 40a) to give (C₆H₁₁)₂CH-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz, which was then converted in analogy to Example 24e
into (C₆H₁₁)₂CH-O₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-ham)-thiaz. The product was isolated in analogy to Example 76b.

FAB-MS ($M+H^+$): 657

Example 79:

15 N-(tert-Butylaminocarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

a) N-(Hydroxycarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-cyano-2-thiazolylmethylamide(CH₃)₃C-O₂C-CH₂-(BOC)-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz
20 [sic] (7.0 g, 11.6 mmol; Example 24d) were [sic] dissolved in methylene chloride (70 ml) and, after addition of dioxane/hydrochloric acid (14.4 ml, 4M), stirred at room temperature overnight. The intermediate which had separated out as an oil was detached from the wall of the flask and the mixture was stirred for a further 4 h. The solution was then concentrated in a rotary evaporator and codistilled
25 several times with ether. The product was purified by column chromatography (silica gel; eluent: methylene chloride with increasing methanol content).

b) N-(Hydroxycarbonylmethyl)-(BOC)-(D)-cyclohexylalanyl-3,4-dehydroproline [sic] 4-cyano-2-thiazolylmethylamide HO₂C-CH₂-(D)-Cha-Pyr-NH-CH₂-2-(4-CN)-thiaz
30 (4.2 g, 8.7 mmol; see a)) was suspended in methylene chloride (40 ml) and mixed with diisopropylethylamine (11.3 g, 14.9 ml, 87.2 mmol) and, at room temperature, (BOC)₂O [sic] (3.8 g, 54.5 mmol) in methylene chloride (5 ml) was added dropwise to this solution. Reaction was complete (TLC check) after stirring at room temperature for 5 hours. The reaction solution was concentrated in a rotary
35 evaporator, the residue was mixed with aqueous hydrochloric acid (ph [sic] 3) and extracted several times with ether, and the organic phases were dried over

magnesium sulfate and concentrated in a rotary evaporator, resulting in the title compound as a white solid.

c) N-(tert-Butylaminocarbonylmethyl)-(BOC)-(D)-cyclohexyl-alanyl-3,4-dehydroproline [sic] 4-cyano-2-thiazolylmethylamide. $\text{HO}_2\text{C}-\text{CH}_2-(\text{BOC})-(\text{D})-\text{Cha-Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{CN})-\text{thiaz}$ [sic] (1.0 g, 1.8 mmol; see b)) was dissolved in methylene chloride (47 ml) together with tert-butylamine (5 ml, 47 mmol) and cooled to 5°C, and propanephosphonic anhydride solution in ethyl acetate (50% strength solution, 1.7 ml, 2.16 mmol) was slowly added at 5°C. After stirring at 10°C for 1 h, a TLC check showed that conversion was complete. The residue after concentration in a rotary evaporator was taken up in ether, washed successively with water, 0.3N hydrochloric acid solution and water, dried over magnesium sulfate and concentrated in a rotary evaporator, resulting in the title compound as a white foam.

d) N-(tert-Butylaminocarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide $(\text{CH}_3)_3\text{C}-\text{NH}-\text{CO}-\text{CH}_2-(\text{BOC})-(\text{D})-\text{Cha-Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{CN})-\text{thiaz}$ [sic] was reacted in analogy to Example 24e with hydroxylamine to give $(\text{CH}_3)_3\text{C}-\text{NH}-\text{CO}-\text{CH}_2-(\text{BOC})-(\text{D})-\text{Cha-Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{ham})-\text{thiaz}$ [sic], from which the title compound was obtained as a white solid by eliminating the protective group with hydrochloric acid in dioxane/methylene chloride.

FAB-MS ($\text{M}+\text{H}^+$): 534

Example 80:

N-(n-Hexylaminocarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide

Preparation took place by coupling

$\text{HO}_2\text{C}-\text{CH}_2-(\text{Boc})-(\text{D})-\text{Cha-Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{CN})-\text{thiaz}$ (Example 79b) with n-hexylamine, subsequent reaction with hydroxylamine to give $\text{CH}_3-(\text{CH}_2)_5-\text{NH}-\text{CO}-\text{CH}_2-(\text{Boc})-(\text{D})-\text{Cha-Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{ham})-\text{thiaz}$, which was converted into $\text{CH}_3-(\text{CH}_2)_5-\text{NH}-\text{CO}-\text{CH}_2-(\text{D})-\text{Cha-Pyr}-\text{NH}-\text{CH}_2-2-(4-\text{ham})-\text{thiaz}$ by elimination of protective groups.

FAB-MS ($\text{M}+\text{H}^+$): 562

Example 81:

N-(Hydroxyaminocarbonylmethyl)-(D)-cyclohexylalanyl-3,4-dehydroproline 4-hydroxyamidino-2-thiazolylmethylamide $\text{CH}_3\text{-O}_2\text{C-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-2-(4-ham)-thiaz x HCl}$ (1.8 g, 3.4 mmol, Example 72), methanol (20 ml), hydroxylamine hydrochloride (3.6 g, 54 mmol) and diisopropylethylamine (10.5 g, 13.9 ml, 81 mmol) were stirred at room temperature overnight. The reaction mixture was filtered and concentrated in a rotary evaporator under high vacuum (removal of as much diisopropylethylamine as possible), the residue was dissolved in water and then the reaction mixture was converted into the acetate on an ion exchanger column. The later fractions contained the desired product with only a small diisopropylethylammonium acetate content, which was removed by lyophilization of the solution. $\text{HONH-OC-CH}_2\text{-(D)-Cha-Pyr-NH-CH}_2\text{-2-(4-ham)-thiaz}$ (1.0 g) was obtained as a white solid. FAB-MS ($\text{M}+\text{H}^+$): 494

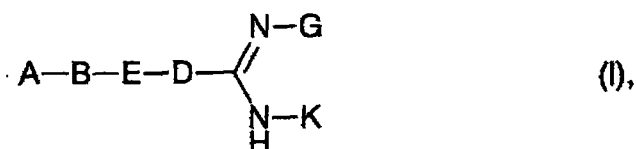
Example 82:

N-(Hydroxycarbonylmethyl)-(D)-cyclohexylglycyl-3,4-dehydro-proline 4-hydroxyamidino-2-thienylmethylamide hydrochloride

Preparation took place starting from $(\text{CH}_3)_3\text{C-O}_2\text{C-CH}_2\text{-(D)-Chg-Pyr-NH-CH}_2\text{-5-(3-ham)-thioph}$ by eliminating the protective group with 1M hydrochloric acid at 60°C , the product being precipitated from ether after concentration in a rotary evaporator. FAB-MS ($\text{M}+\text{H}^+$): 464

We claim:

1. A compound of the formula I



5

in which A, B, D, E, g and K have the following meanings:

- 10 A: $\text{R}^1\text{OOC}-\text{CH}_2-$, $\text{R}^1\text{OOC}-\text{CH}_2-\text{CH}_2-$, $\text{R}^1\text{OOC}-\text{CH}(\text{CH}_3)-$, $\text{R}^1\text{OOC}-\text{C}(\text{CH}_3)_2-$, $\text{R}^1\text{OOC}-\text{CH}(\text{C}_2\text{H}_5)-$, $\text{C}_{1-4}\text{-alkyl}-\text{SO}_2-(\text{CH}_2)_{2-6}-$, $\text{HO}_3\text{S}-(\text{CH}_2)_{2-6}-$, 5-tetrazolyl- $(\text{CH}_2)_{1-6}-$, $\text{C}_{1-4}\text{-alkyl}-\text{O}-(\text{CH}_2)_{2-6}-$, $\text{R}^2\text{R}^3\text{N}-(\text{CH}_2)_{2-6}-$, $\text{R}^2\text{S}-(\text{CH}_2)_{2-6}-$, $\text{R}^2\text{R}^3\text{NSO}_2-(\text{CH}_2)_{2-6}-$, $\text{HO}-(\text{CH}_2)_{2-6}-$, $\text{R}^{1a}\text{S}(\text{O})\text{C}-\text{CH}_2-$, $\text{R}^{1a}\text{O}(\text{S})\text{C}-\text{CH}_2-$, $\text{R}^2\text{R}^3\text{N}(\text{O})\text{C}-\text{CH}_2-$, $\text{R}^2\text{R}^3\text{N}-\text{O}-\text{CO}-\text{CH}_2-$, $\text{R}^2\text{N}(\text{OH})-\text{CO}-\text{CH}_2-$, where R^2 and R^3 are, independently of one another, h, $\text{C}_1-\text{C}_6\text{-alkyl}$, $\text{C}_{3-8}\text{-cycloalkyl}$ or $\text{C}_{3-8}\text{-cycloalkyl}-\text{C}_{1-3}\text{-alkyl}$ or R^2 and R^3 together form a $\text{C}_{4-6}\text{-alkylene}$ chain,
- 15

in which

- 20 R^1 : is H-, $\text{C}_1-\text{C}_{16}\text{-alkyl}$, $\text{H}_3\text{C}-[\text{O}-\text{CH}_2-\text{CH}_2]_q$ ($q = 1-4$), $\text{C}_7-\text{C}_{12}\text{-bicycloalkyl}$, $\text{C}_{10}\text{-tricycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}-\text{C}_1-\text{C}_3\text{-alkyl}$, pyranyl, piperidiny, aryl or phenyl- $\text{C}_1-\text{C}_4\text{-alkyl}$, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical or different radicals selected from $\text{C}_1-\text{C}_4\text{-alkyl}$, CF_3 , F, Cl, NO_2 , HO or $\text{C}_1-\text{C}_4\text{-alkoxy}$ radicals,

- 25 or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by $\text{C}_1-\text{C}_{16}\text{-alkyl}$ or aryl,

- 30 R^{1a} : is H-, $\text{C}_1-\text{C}_{16}\text{-alkyl}$, $\text{H}_3\text{C}-[\text{O}-\text{CH}_2-\text{CH}_2]_q$ ($q = 1-4$), $\text{C}_7-\text{C}_{12}\text{-bicycloalkyl}$, $\text{C}_{10}\text{-tricycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}$, $\text{C}_3-\text{C}_8\text{-cycloalkyl}-\text{C}_1-\text{C}_3\text{-alkyl}$, aryl or phenyl- $\text{C}_1-\text{C}_3\text{-alkyl}$, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from $\text{C}_1-\text{C}_4\text{-alkyl}$, CF_3 , F, Cl, NO_2 , HO or $\text{C}_1-\text{C}_4\text{-alkoxy}$ radicals,

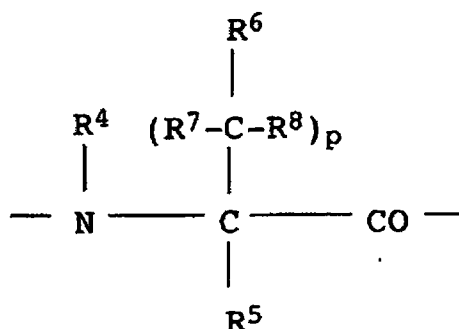
or



R¹: is R^{1b}-C(O)O-C(R^{1c})₂-, R^{1b}-(CO)NR²-C(R^{1c})₂-, where R^{1b} can be C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, C₃-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₃-C₈-cycloalkyl-C₁-C₃-alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are, independently of one another, h, CH₃ or C₂H₅, and R² has the meaning stated above,

or R²OOC-C₁-C₆-alkyl, R²R³N(O)C-C₁-C₆-alkyl, R²R³N-C₂-C₆-alkyl, and in which R² and R³ have the same meanings as above or, if R¹ is R²R³N(O)C-C₁-C₆-alkyl, R² and R³ together form a C₄-C₆-alkylene chain,

B



in which



p is 0, 1,

R⁴ is H-, R⁹OOC- with R⁹= C₁₋₁₆-alkyl, C₃₋₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, R¹⁰C(O)-O-CH₂-, R¹⁰C(O)-O-CH(CH₃)-, where R¹⁰ can be C₁-C₄-alkyl, phenyl, benzyl, C₃-C₈-cycloalkyl or cyclohexyl-CH₂-,

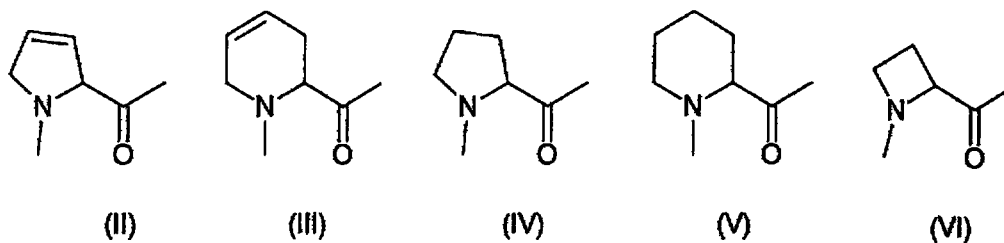
R⁵ is H-,

R⁶ is H-, C₁₋₈-alkyl, C₇-C₁₂-bicycloalkyl or C₁₀-tricycloalkyl, phenyl which may carry up to three identical or different radicals from the group of C₁₋₄-alkyl, CF₃-, C₁₋₄-alkoxy, F- or Cl-, or C₃₋₈-cycloalkyl which may carry up to four identical or different C₁₋₄-alkyl radicals, or where one or two C-C single bonds in the ring can be replaced by a C=C double bond, or a phenyl ring can be fused on,

R⁷ is H-, C₁₋₈-alkyl, phenyl which may carry up to three identical or different radicals from the group of C₁₋₄-alkyl, CF₃-, C₁₋₄-alkoxy, F- or Cl-, or C₃₋₈-cycloalkyl which may carry up to four identical or different C₁₋₄-alkyl radicals,

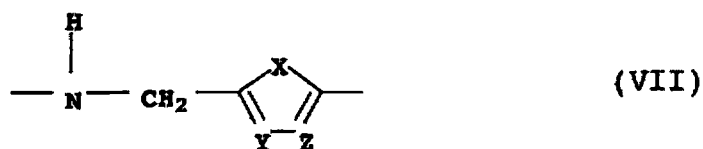
R^8 is H-, CH_3 -,

E



5

D



10

with

$X = S, O$

$Y = CH, C-CH_3, C-Cl, C-CF_3$ and

$Z = CH, C-CH_3, C-Cl, C-CF_3$

15

or $X = S, O$

$Y = N$

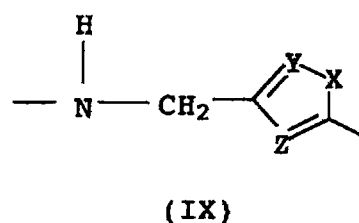
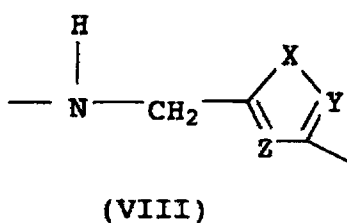
$Z = CH, C-CH_3, C-CF_3$

or $X = S, O$

$Y = CH, C-CH_3, C-CF_3$

$Z = N,$

or D is equal to



20

with

X = S, O

Y = CH, C-CH₃ and C-CF₃

Z = CH, C-CH₃, C-Cl and C-CF₃

5

or	X = O	Y = N	Z = CH, C-CH ₃ , C-CF ₃
or	X = O, S	Y = CH, C-CH ₃ , C-CF ₃	Z = N

G: -H, -OH, -OR¹⁸, -OC(O)R¹⁹, -C(O)OR²⁰, -SR¹⁸, -C(S)SR²⁰,

in which

10 R¹⁸: is -C₁₋₈-alkyl, -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -aryl or -C₁-C₆-alkylphenyl, each of which may carry optionally up to three C₁-C₄-alkyl, CF₃, F, Cl, NO₂ or C₁-C₄-alkoxy radicals

R¹⁹: is -C₁₋₃-alkyl, -phenyl,

15 R²⁰: is -C₁₋₈-alkyl, -CH₂CCl₃, -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -C₃-C₈-cycloalkyl, -phenyl or -C₁-C₃-alkylphenyl, each of which may carry optionally up to three identical or different radicals selected from the group of C₁-C₄-alkyl, CF₃, F, Cl, NO₂ or C₁-C₄-alkoxy radicals, or CH₂O-C(O)R^{10a}, -CH(CH₃)O-C(O)R^{10a}, where R^{10a} can be C₁-C₁₀-alkyl, -phenyl, benzyl, -C₃-C₈-cycloalkyl or -CH₂-cyclohexyl, or -C(R^{10b})₂-CH₂-O-(O)C-R^{10c}, where the two R^{10b} radicals can be, independently of one another, H, CH₃ or ethyl, and R^{10c} is -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -C₃-C₈-cycloalkyl or -C₁-C₄-alkyl,

20

K: H,

or g and K together form a -C(O)O-, -C(O)S-, -C(S)S- or -C(S)O- group,



25

the configurational isomers thereof, tautomers and the salts thereof with physiologically tolerated acids,

where the following applies, with retention of the meanings of D:

30

(i)

when E is II or III, and g and K are h, then A and B have the following meanings:

A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^1OOC-CH(C_2H_5)-$, $R^1OOC-C(CH_3)_2-$, $R^{1a}S(O)C-CH_2-$, $R^{1a}O(S)C-CH_2-$, $R^2R^3N(O)C-CH_2-$, $R^2R^3N-O-CO-CH_2-$, $R^2N(OH)-CO-CH_2-$, C_{1-4} -alkyl- $SO_2-(CH_2)_{2-6}-$, $HO_3S-(CH_2)_{2-6}-$, 5-tetrazolyl- $(CH_2)_{1-6}-$, C_{1-4} -alkyl- $O-(CH_2)_{2-6}-$, $R^2R^3N-(CH_2)_{2-6}-$, $R^2S-(CH_2)_{2-6}-$, $R^2R^3NSO_2-(CH_2)_{2-6}-$, where R^2 and R^3 are, independently of one another, h, C_1-C_6 -alkyl or C_3-8 -cycloalkyl or R^2 and R^3 together form a C_{4-6} -alkylene chain,

in which

10 R^1 : is C_7-C_{16} -alkyl, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_7-C_{12} -bicycloalkyl, C_{10} -tricycloalkyl, C_3-C_8 -cycloalkyl, C_3-C_8 -cycloalkyl- C_1-C_3 -alkyl, pyranyl, piperidinyl, it being possible for all the radicals mentioned to carry optionally up to four C_1-C_4 -alkyl, CF_3 , F, Cl, NO_2 , HO or C_1-C_4 -alkoxy radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C_1-C_{16} -alkyl or aryl,

15

R^{1a} : is H-, C_1-C_{16} -alkyl, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_7-C_{12} -bicycloalkyl, C_{10} -tricycloalkyl, C_3-C_8 -cycloalkyl, C_3-C_8 -cycloalkyl- C_1-C_3 -alkyl, aryl or phenyl- C_1-C_3 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three C_1-C_4 -alkyl, CF_3 , F, Cl, NO_2 , HO or C_1-C_4 -alkoxy radicals, or

20

R^1 : is $R^{1b}-C(O)O-C(R^{1c})_2-$, $R^{1b}-C(O)NR_2-C(R^{1c})_2-$, where R^{1b} can be C_1-C_4 -alkyl, C_3-C_8 -cycloalkyl- C_1-C_3 -alkyl, C_3-C_8 -cycloalkyl, C_1-C_4 -alkyloxy, C_3-C_8 -cycloalkyl- C_1-C_3 -alkyloxy, C_3-C_8 -cycloalkoxy,

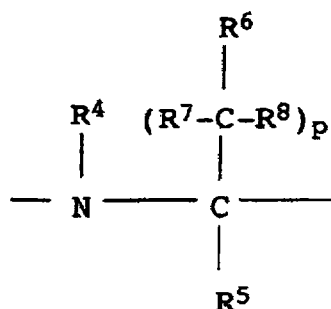
aryl or phenyl- C_1-C_6 -alkyl, the two R^{1c} radicals are, independently of one another, h, CH_3

25

or C_2H_5 , and R^2 has the meaning stated above

or $R^2OOC-C_1-C_6$ -alkyl, $R^2R^3N(O)C-C_1-C_6$ -alkyl, $R^2R^3N-C_2-C_6$ -alkyl, where R^2 and R^3 have the same meanings as above or, if R^1 is $R^2R^3N(O)C-C_1-C_6$ -alkyl, R^2 and R^3 together form a C_4-C_6 -alkylene chain,

30 B



in which

p is 0, 1,

5 R^4 is H-, R^9OOC - with $R^9 = C_{1-16}$ -alkyl, C_{3-8} -cycloalkyl, phenyl- C_1 - C_4 -alkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1 - C_4 -alkyl, phenyl, benzyl, C_3 - C_8 -cycloalkyl or cyclohexyl- CH_2 -, and R^5 , R^6 , R^7 and R^8 have the same meanings as above;

(ii)

10

when E is II or III, and g and K are h, then A and B have the following meanings

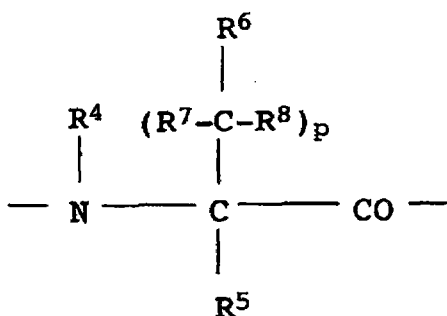
A: $R^1OOC-CH_2$ -, $R^1OOC-CH_2-CH_2$ -, $R^1OOC-CH(CH_3)$ -, $R^1OOC-C(CH_3)_2$ -, $R^1OOC-CH(C_2H_5)$ -, $HO-(CH_2)_{2-6}$ -,

15

in which

20 R^1 : is H-, C_1 - C_6 -alkyl, aryl or phenyl- C_1 - C_4 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C_1 - C_4 -alkyl, CF_3 , F, Cl, NO_2 , HO or C_1 - C_4 -alkoxy radicals,

B



25 in which

p is 0, 1,

30 R^4 is R^9OOC - with $R^9 = C_{7-16}$ -alkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1 - C_4 -alkyl, phenyl, benzyl, C_3 - C_8 -cycloalkyl or cyclohexyl- CH_2 -, and R^5 , R^6 , R^7 and R^8 have the same meanings as above;

(iii)

when E is II or III, and g is -OH, -OR¹⁸, -OC(O)R¹⁹, C(O)OR²⁰, -SR¹⁸, -C(S)SR²⁰, where R¹⁸, R¹⁹ and R²⁰ have the same meanings as above, and K is h, or g and K together form a -C(O)O-, -C(O)S-, -C(S)S- or -C(S)O- group, then A and B have the following meanings:

A: R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)-, R¹OOC-C(CH₃)₂-, R¹OOC-CH(C₂H₅)-, C₁₋₄-alkyl-SO₂-(CH₂)₂₋₆-, HO₃S-(CH₂)₂₋₆-, 5-tetrazolyl-(CH₂)₁₋₆-, C₁₋₄-alkyl-O-(CH₂)₂₋₆-, R²R³N-(CH₂)₂₋₆-, R²S-(CH₂)₂₋₆-, R²R³NSO₂-(CH₂)₂₋₆-, HO-(CH₂)₂₋₆-, R^{1a}S(O)C-CH₂-, R^{1a}O(S)C-CH₂-, R²R³N(O)C-CH₂-, R²R³N-O-CO-CH₂-, R²N(OH)-CO-CH₂-, where R² and R³ are, independently of one another, h, C₁-C₆-alkyl or C₃₋₈-cycloalkyl or R² and R³ together form a C₄₋₆-alkylene chain,

in which

R¹: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, pyranyl, piperidiny, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals, or R¹ is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C₁-C₁₆-alkyl or aryl,

R^{1a}: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals,

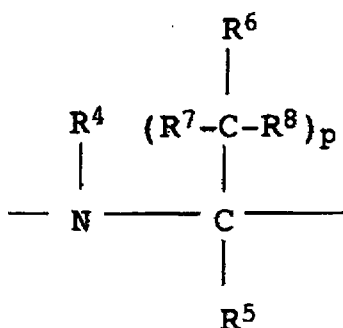
or



R¹: is R^{1b}-C(O)O-C(R^{1c})₂-, R^{1b}-C(O)NR₂-C(R^{1c})₂-, where R^{1b} can be C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, C₃-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₃-C₈-cycloalkyl-C₁-C₃-alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are, independently of one another, h, CH₃ or C₂H₅, and R² has the meaning stated above,

or $R^2OOC-C_1-C_6$ -alkyl, $R^2R^3N(O)C-C_1-C_6$ -alkyl, $R^2R^3N-C_2-C_6$ -alkyl, and in which R^2 and R^3 have the same meanings as above or, if R^1 is $R^2R^3N(O)C-C_1-C_6$ -alkyl, R^2 and R^3 together form a C_4-C_6 -alkylene chain,

B



5

in which

p is 0, 1,

10 R^4 is H-, R^9OOC - with $R^9 = C_{1-16}$ -alkyl, C_{3-8} -cycloalkyl, phenyl, phenyl- C_1-C_4 -alkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1-C_4 -alkyl, phenyl, benzyl, cyclohexyl or cyclohexyl- CH_2 -,

and

R^5 , R^6 , R^7 and R^8 have the same meanings as above;



15 (iv)

when E is IV, V or VI, and g is h or OH and K is h, then A and B have the following meanings:

20 A: $R^1OOC-CH_2$ -, $R^1OOC-CH_2-CH_2$ -, $R^1OOC-CH(CH_3)$ -, $R^1OOC-C(CH_3)_2$ -, $R^1OOC-CH(C_2H_5)$ -, $R^{1a}S(O)C-CH_2$ -, $R^{1a}O(S)C-CH_2$ -, $R^2R^3N(O)C-CH_2$ -, $R^2R^3N-O-CO-CH_2$ -, $R^2N(OH)-CO-CH_2$ -, where R^2 and R^3 are, independently of one another, h, C_1-C_6 -alkyl, C_{3-8} -cycloalkyl or R^2 and R^3 together form a C_{4-6} -alkylene chain,

25 in which

30 R^1 : is C_7-C_{16} -alkyl, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_7-C_{12} -bicycloalkyl, C_{10} -tricycloalkyl, C_3-C_8 -cycloalkyl, C_3-C_8 -cycloalkyl- C_1-C_3 -alkyl, it being possible for all the radicals mentioned to carry optionally up to three identical or different radicals selected from C_1-C_4 -alkyl, CF_3 , F, Cl, NO_2 , HO or C_1-C_4 -alkoxy radicals, or is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C_1-C_{16} -alkyl or aryl,

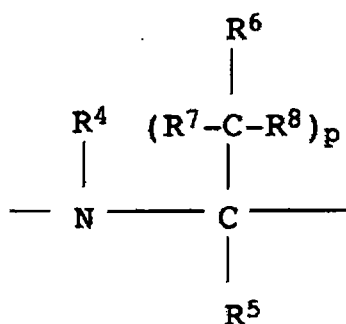
R^{1a} : is H-, C₁-C₁₆-alkyl, H₃C[-O-CH₂CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals,

or

10 R^1 : is R^{1b} -C(O)O-C(R^{1c})₂-, R^{1b} -C(O)NR²-C(R^{1c})₂-, where R^{1b} can be C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, C₃-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₃-C₈-cycloalkyl-C₁-C₃-alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are, independently of one another, h, CH₃ or C₂H₅, and R^2 has the meaning stated above,

15 or R^2 OOC-C₁-C₆-alkyl, R^2R^3 N(O)C-C₁-C₆-alkyl, R^2R^3 N-C₂-C₆-alkyl, and in which R^2 and R^3 have the same meanings as above or, if R^1 is R^2R^3 N(O)C-C₁-C₆-alkyl, R^2 and R^3 together form a C₄-C₆-alkylene chain,

B



20

in which

p is 0, 1,

R^4 is H-, R^9 OOC- with R^9 = C₁₋₁₆-alkyl, C₃₋₈-cycloalkyl, phenyl, phenyl-C₁-C₄-alkyl, R^{10} C(O)-O-CH₂-, R^{10} C(O)-O-CH(CH₃)-, where R^{10} can be C₁-C₄-alkyl, phenyl, benzyl, C₃-C₈-cycloalkyl or cyclohexyl-CH₂-,

25

and

R^5 , R^6 , R^7 and R^8 have the same meanings as above;

(v)

30

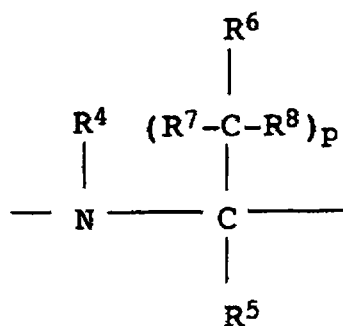
when E is IV, V or VI, and g is h or OH and K is h, then A and B have the following meanings:

- 5 A: $R^1\text{OOC-CH}_2^-$, $R^1\text{OOC-CH}_2\text{-CH}_2^-$, $R^1\text{OOC-CH(CH}_3\text{)-}$, $R^1\text{OOC-C(CH}_3\text{)}_2^-$, $R^1\text{OOC-CH(C}_2\text{H}_5\text{)-}$, $\text{HO-(CH}_2\text{)}_{2-6}^-$,

in which

- 10 R^1 : is H-, $\text{C}_1\text{-C}_6\text{-alkyl}$, aryl or phenyl- $\text{C}_1\text{-C}_4\text{-alkyl}$, it being possible for all the radicals mentioned apart from h to carry optionally up to three $\text{C}_1\text{-C}_4\text{-alkyl}$, CF_3 , F, Cl, NO_2 , HO or $\text{C}_1\text{-C}_4\text{-alkoxy}$ radicals,

B



- 15 in which

p is 0, 1,

R^4 is $R^9\text{OOC-}$ with $R^9 = \text{C}_{7-16}\text{-alkyl}$, $\text{R}^{10}\text{C(O)-O-CH}_2^-$, $\text{R}^{10}\text{C(O)-O-CH(CH}_3\text{)-}$, where R^{10} can be $\text{C}_1\text{-C}_4\text{-alkyl}$, phenyl, benzyl, $\text{C}_3\text{-C}_8\text{-cycloalkyl}$ or cyclohexyl- CH_2^- ,

and

- 20 R^5 , R^6 , R^7 and R^8 have the same meanings as above;

(vi)

- 25 when E is IV, V or VI, and g is $-\text{OR}^{18}$, $-\text{OC(O)R}^{19}$, C(O)OR^{20} , $-\text{SR}^{18}$, $-\text{C(S)SR}^{20}$, where R^{18} , R^{19} and R^{20} have the same meanings as above, and K is h, or g and K together form a $-\text{C(O)O-}$, $-\text{C(O)S-}$, $-\text{C(S)S-}$ or $-\text{C(S)O-}$ group, then A and B have the following meanings:

- 30 A: $R^1\text{OOC-CH}_2^-$, $R^1\text{OOC-CH}_2\text{-CH}_2^-$, $R^1\text{OOC-CH(CH}_3\text{)-}$, $R^1\text{OOC-C(CH}_3\text{)}_2^-$, $R^1\text{OOC-CH(C}_2\text{H}_5\text{)-}$, $\text{HO-CH}_2\text{-CH}_2^-$, $\text{R}^{1a}\text{S(O)C-CH}_2^-$, $\text{R}^{1a}\text{O(S)C-CH}_2^-$, $\text{R}^2\text{R}^3\text{N(O)C-CH}_2^-$, $\text{R}^2\text{R}^3\text{N-O-CO-CH}_2^-$, $\text{R}^2\text{N(OH)-CO-CH}_2^-$, where R^2 and R^3 are, independently of one

another, h, C₁-C₆-alkyl or C₃₋₈-cycloalkyl or R² and R³ together form a C₄₋₆-alkylene chain,

in which

5

R¹: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, pyranyl, piperidinyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals, or R¹ is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C₁-C₁₆-alkyl or aryl,

10

R^{1a}: is H-, C₁-C₁₆-alkyl, H₃C-[O-CH₂-CH₂]_q (q = 1-4), C₇-C₁₂-bicycloalkyl, C₁₀-tricycloalkyl, C₃-C₈-cycloalkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, aryl or phenyl-C₁-C₃-alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from C₁-C₄-alkyl, CF₃, F, Cl, NO₂, HO or C₁-C₄-alkoxy radicals,

15

or

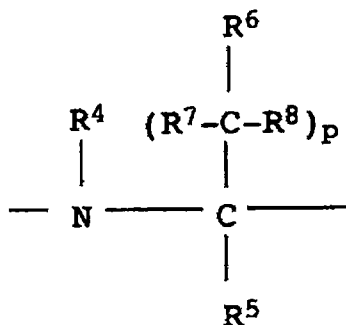
R¹: is R^{1b}-C(O)O-C(R^{1c})₂-, R^{1b}-C(O)NR²-C(R^{1c})₂-, where R^{1b} can be C₁-C₄-alkyl, C₃-C₈-cycloalkyl-C₁-C₃-alkyl, C₃-C₈-cycloalkyl, C₁-C₄-alkyloxy, C₃-C₈-cycloalkyl-C₁-C₃-alkyloxy, C₃-C₈-cycloalkoxy, aryl or phenyl-C₁-C₆-alkyl, the two R^{1c} radicals are, independently of one another, h, CH₃ or C₂H₅, and R² has the meaning stated above,

20

or R²OOC-C₁-C₆-alkyl, R²R³N(O)C-C₁-C₆-alkyl, R²R³N-C₂-C₆-alkyl, and in which R² and R³ have the same meanings as above or, if R¹ is R²R³N(O)C-C₁-C₆-alkyl, R² and R³ together form a C₄-C₆-alkylene chain,

25

B



30 in which

p is 0, 1,

R^4 is H-, R^9OOC - with $R^9 = C_{1-16}$ -alkyl, C_{3-8} -cycloalkyl, phenyl, phenyl- C_1 - C_4 -alkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1 - C_4 -alkyl, phenyl, benzyl, C_3 - C_8 -cycloalkyl or cyclohexyl- CH_2 -,

and

5 R^5 , R^6 , R^7 and R^8 have the same meanings as above;

and the physiologically tolerated salts thereof.

10 2. A compound of the formula I as claimed in claim 1, where A, B, C [sic], D, E, g, K have the following meanings

A: $R^1OOC-CH_2$ -, $R^1OOC-CH_2-CH_2$ -, $R^1OOC-CH(CH_3)$ -, $R^1OOC-C(CH_3)_2$ -, $R^{1a}S(O)C-CH_2$ -, $R^{1a}O(S)C-CH_2$ -, $R^2R^3N(O)C-CH_2$ -, $R^2R^3N-O-CO-CH_2$ -, $R^2N(OH)-CO-CH_2$ -, C_{1-4} -alkyl- $SO_2-(CH_2)_{2-6}$ -, $HO_3S-(CH_2)_{2-6}$ -, 5-tetrazolyl- $(CH_2)_{1-6}$ -, C_{1-4} -alkyl- $O-(CH_2)_{2-6}$ -,
15 , $R^2R^3N-(CH_2)_{2-6}$ -, $R^2S-(CH_2)_{2-6}$ -, $R^2R^3NSO_2-(CH_2)_{2-6}$ -, where R^2 and R^3 are, independently of one another, h, C_1 - C_6 -alkyl or C_{3-8} -cycloalkyl or R^2 and R^3 together form a butylene or pentylene chain,

in which

20

R^1 : is H-, C_1 - C_{16} -alkyl, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_7 - C_{12} -bicycloalkyl, C_{10} -tricycloalkyl, C_5 - C_8 -cycloalkyl, C_5 - C_8 -cycloalkyl- C_1 - C_3 -alkyl, pyranyl, piperidinyl, aryl or phenyl- C_1 - C_3 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical or different radicals selected from CH_3 , CF_3 ,
25 F, Cl, HO or methoxy radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C_1 - C_6 -alkyl or aryl,

R^{1a} : is H-, C_1 - C_{16} -alkyl, C_7 - C_{12} -bicycloalkyl, C_{10} -tricycloalkyl, C_5 - C_8 -cycloalkyl, C_5 - C_8 -cycloalkyl- C_1 - C_3 -alkyl, aryl or phenyl- C_1 - C_3 -alkyl, it being possible for all the
30 radicals mentioned apart from h to carry optionally up to four identical of different radicals selected from CH_3 , CF_3 , F, Cl, HO or methoxy radicals,

or

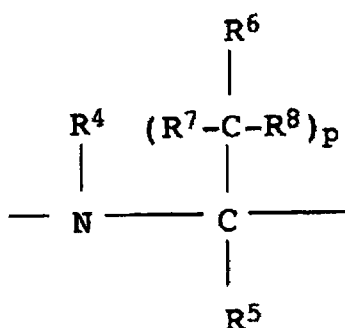


35 R^1 : is $R^{1b}-C(O)O-C(R^{1c})_2$ -, $R^{1b}-C(O)NR^2-C(R^{1c})_2$ -, where R^{1b} can be C_1 - C_4 -alkyl, C_5 - C_8 -cycloalkyl- C_1 - C_3 -alkyl, C_5 - C_8 -cycloalkyl, C_1 - C_4 -alkyloxy, C_5 - C_8 -cycloalkyl- C_1 - C_3 -alkyloxy, C_5 - C_8 -cycloalkoxy, aryl or phenyl- C_1 - C_3 -alkyl, the two R^{1c} radicals are,

independently of one another, h, CH₃ or C₂H₅, and R² has the meaning stated above,

or R²OOC-C₁-C₆-alkyl, R²R³N(O)C-C₁-C₆-alkyl, R²R³N-C₂-C₆-alkyl, and in which R² and R³ have the same meanings as above or, if R¹ is R²R³N(O)C-C₁-C₆-alkyl, R² and R³ together form a butylene or pentylene chain,

B



in which

10 p is 0, 1,

R⁴ is H-, R⁹OOC- with R⁹ = C₁₋₁₆-alkyl, C₃₋₈-cycloalkyl, R¹⁰C(O)-O-CH₂-, R¹⁰C(O)-O-CH(CH₃)-, where R¹⁰ can be C₁₋₄-alkyl, phenyl, benzyl, C₅₋₈-cycloalkyl or cyclohexyl-CH₂-,

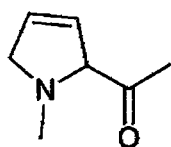
R⁵ is H-,

15 R⁶ is C₁₋₈-alkyl, C₅₋₈-cycloalkyl, which may carry up to four methyl radicals, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, norbornyl, adamantyl, indanyl, decalyl,

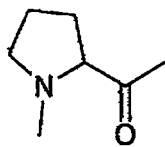
R⁷ is h,

R⁸ is h,

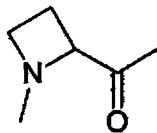
20 E



II



IV



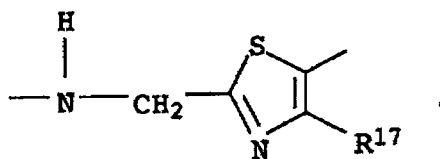
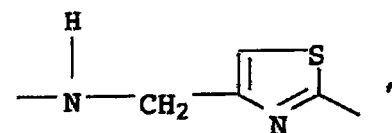
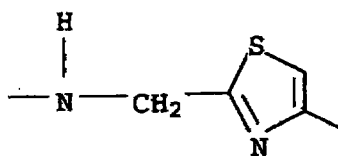
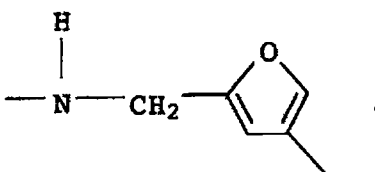
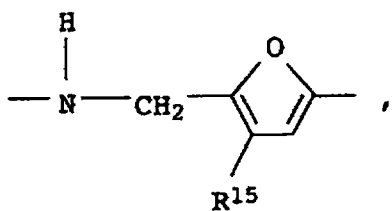
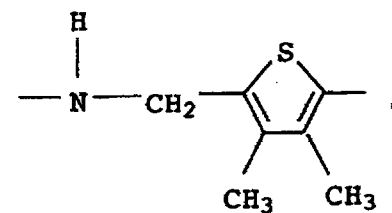
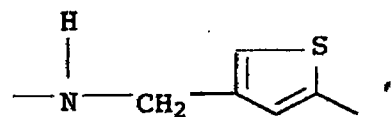
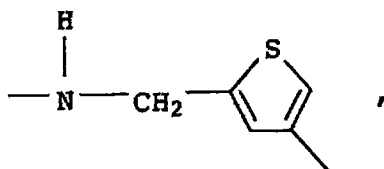
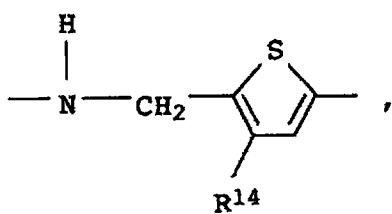
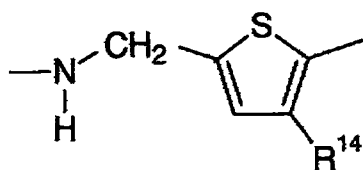
VI

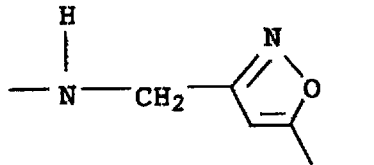
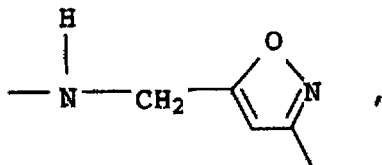
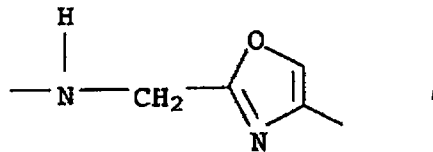
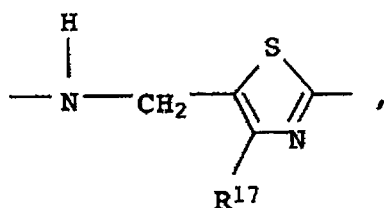


D

25

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in which

R^{14} : is h, CH_3 , Cl

5 R^{15} : is h, CF_3 ,

R^{17} : is h, CH_3 , CF_3 ,

G: H, -OH, -OR¹⁸, -OC(O)R¹⁹, -C(O)OR²⁰,

in which

10 R^{18} : is -C₁₋₈-alkyl, -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -C₁-C₃-alkylphenyl which may carry optionally up to three CH_3 , CF_3 , F, Cl or methoxy radicals,

R^{19} : is -C₁₋₃-alkyl,

R^{20} : is -C₁₋₈-alkyl, -CH₂CCl₃, -C₁-C₃-alkyl-C₅-C₈-cycloalkyl, -C₅-C₈-cycloalkyl, -phenyl or -C₁-C₃-alkylphenyl, each of which may carry optionally up to three CH_3 , CF_3 , F, Cl or methoxy radicals, -CH₂O-C(O)R^{10a}, -CH(CH₃)O-C(O)R^{10a}, where R^{10a} can be -C₁-C₈-alkyl, -phenyl, -benzyl, -C₅-C₈-cycloalkyl or -CH₂-cyclohexyl, or -C(R^{10b})₂-CH₂-O-(O)CR^{10c}, where the R^{10b} radicals can be, independently of one another, h or CH_3 , and R^{10c} is -C₁-C₃-alkyl-C₅-C₈-cycloalkyl, -C₅-C₈-cycloalkyl or -C₁-C₄-alkyl,

20 or

K is h or g and K together form a -C(O)O- or -C(O)S- group.



3. A compound of the formula I as claimed in either of claims 1 or 2, where A, B, C, [sic] D, E, g and K have the following meanings

25

A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^1OOC-C(CH_3)_2-$, $R^2R^3N(O)C-CH_2-$, C₁₋₄-alkyl-SO₂-(CH₂)₂₋₆-, 5-tetrazolyl-(CH₂)₁₋₆-, C₁₋₄-alkyl-O-(CH₂)₂₋₆-, $R^2R^3N-(CH_2)_{2-6}-$, $R^2S-(CH_2)_{2-6}-$, $R^2R^3NSO_2-(CH_2)_{2-6}-$, where R² and R³ are, independently of one another, h or C₁-C₄-alkyl,

in which

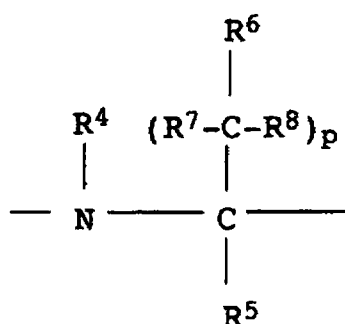
5 R^1 : is H-, C_1 - C_{16} -alkyl, $H_3C-[O-CH_2-CH_2]_q$ ($q = 1-4$), C_{10} -tricycloalkyl, C_5 - C_8 -cycloalkyl, C_5 - C_8 -cycloalkyl- C_1 - C_3 -alkyl, phenyl- C_1 - C_3 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to three identical or different radicals selected from CH_3 , CF_3 , F, Cl, HO or methoxy radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C_1 - C_3 -alkyl or aryl,

10 or

R^1 : is $R^{1b}-C(O)O-C(R^{1c})_2$, where R^{1b} can be C_1 - C_4 -alkyl, C_5 - C_8 -cycloalkyl, C_1 - C_4 -alkyloxy, C_5 - C_8 -cycloalkyloxy or phenyl- C_1 - C_3 -alkyl, the two R^{1c} radicals are, independently of one another, h or CH_3 ,

15 or $R^2OOC-C_1-C_6$ -alkyl, $R^2R^3N(O)C-C_1-C_6$ -alkyl, $R^2R^3N-C_2-C_6$ -alkyl, and in which R^2 and R^3 have the same meanings as above or, if R^1 is $R^2R^3N(O)C-C_1-C_6$ -alkyl, R^2 and R^3 together form a butylene or pentylene chain,

B



20

in which

p is 0, 1,

R^4 is H-, R^9OOC - with $R^9 = C_{1-16}$ -alkyl, C_5 - C_8 -cycloalkyl, $R^{10}C(O)-O-CH_2$ -, $R^{10}C(O)-O-CH(CH_3)$ -, where R^{10} can be C_1 - C_4 -alkyl,

25 R^5 is H-,

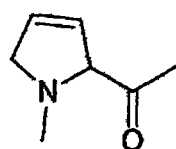
R^6 is C_{1-8} -alkyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, norbornyl, adamantyl, indanyl, decalynyl,

R^7 is h,

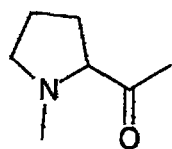
R^8 is h,

30

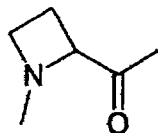
E



II



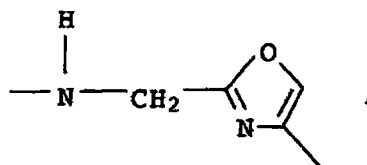
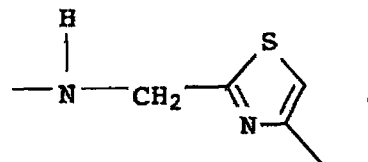
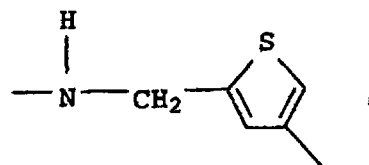
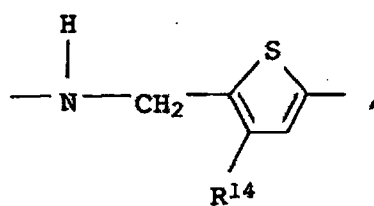
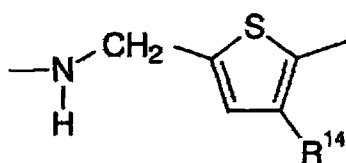
IV



VI

D

5



in which

 R^{14} : is H, CH_3 , Cl,

10

G: H, -OH, -OR¹⁸, -C(O)OR²⁰,

in which

R^{18} : is -C₁₋₈-alkyl, -C₁-C₃-alkyl-C₃-C₈-cycloalkyl, -C₁-C₃-alkylphenyl which may carry optionally up to three CH_3 , CF_3 , F, Cl, or methoxy radicals,

R^{20} : is $-C_{1-8}$ -alkyl, $-C_1-C_3$ -alkyl- C_5-C_8 -cycloalkyl, $-C_5-C_8$ -cycloalkyl or $-C_1-C_3$ -alkylphenyl which may carry optionally up to three CH_3 , CF_3 , F , Cl or methoxy radicals, or $-CH_2O-C(O)R^{10a}$, $-CH(CH_3)O-C(O)R^{10a}$, where R^{10a} can be $-C_1-C_4$ -alkyl, $-benzyl$, $-C_5-C_8$ -cycloalkyl or $-CH_2$ -cyclohexyl,

5

K is h,

or g and K together form a $-C(O)O-$ or $-C(O)S-$ group.

10

4. A compound of the formula I as claimed in claim 1, where A, B, C, D, E, g and K have the following meanings

A: $R^1OOC-CH_2-$, $R^1OOC-CH_2-CH_2-$, $R^1OOC-CH(CH_3)-$, $R^1OOC-C(CH_3)_2-$, C_{1-4} -alkyl- $SO_2-(CH_2)_{2-4}-$, 5-tetrazolyl- $(CH_2)_{1-3}-$, C_{1-4} -alkyl- $O-(CH_2)_{2-4}-$, $H_2N-(CH_2)_{2-3}-$, $CH_3-NH-(CH_2)_{2-3}-$, $(CH_3)_2N-(CH_2)_{2-3}-$, $H_2NSO_2-(CH_2)_{2-4}-$, $CH_3-NHSO_2-(CH_2)_{2-4}-$,

15

in which

20

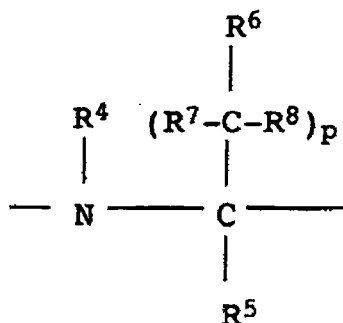
R^1 : is $H-$, C_1-C_8 -alkyl, C_5-C_8 -cycloalkyl, C_5-C_8 -cycloalkyl- C_1-C_3 -alkyl, it being possible for all the radicals mentioned apart from h to carry optionally up to four identical or different radicals selected from CH_3- , CF_3- , $F-$, $Cl-$ or methoxy radicals, or R^1 is 2-oxo-1,3-dioxolen-4-ylmethyl which may be substituted in position 5 by C_1-C_3 -alkyl or aryl,

or

25

R^1 : is $R^{1b}-C(O)O-CH_2-$, $R^{1b}-C(O)O-CH(CH_3)-$, where R^{1b} can be C_1-C_4 -alkyl, C_5-C_8 -cycloalkyl, C_1-C_4 -alkyloxy or C_5-C_8 -cycloalkyloxy

B



30



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- 135 -

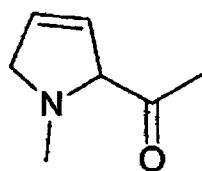
in which

p is 0,1,

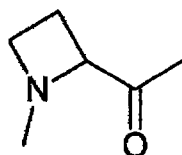
 R^4 is H-, R^5 is H-,5 R^6 is cyclopentyl, cyclohexyl, cycloheptyl, R^7 is h, R^8 is h,

E

10

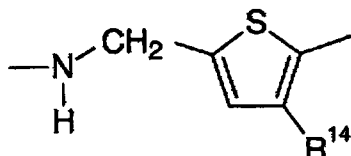


II

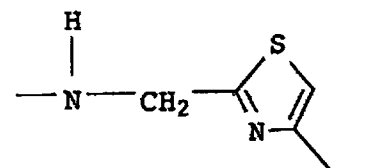
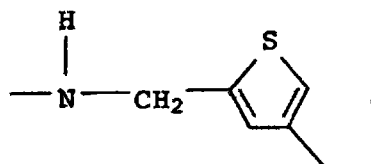
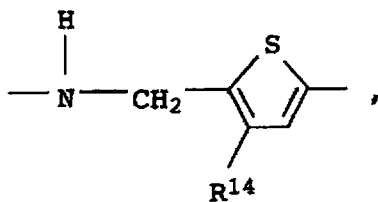


VI

D



* C L M S *



15

in which

 R^{14} is h, CH_3 , Cl,

G: -OH, -C(O)OR²⁰,

in which

R²⁰: is -C₁₋₈-alkyl, -C₁₋₃-alkyl-C₅₋₈-cycloalkyl, -C₅₋₈-cycloalkyl,

K = is h.

5

5. A compound of the formula I as claimed in claim 4, where A, B, C, D, E, g and K have the following meanings

A: R¹OOC-CH₂-, R¹OOC-CH₂-CH₂-, R¹OOC-CH(CH₃)-, R¹OOC-C(CH₃)₂-,

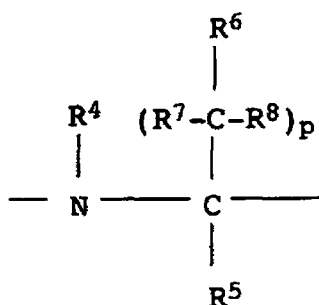
10

in which

R¹: is C₁₋₈-alkyl, C₅₋₈-cycloalkyl, C₅₋₈-cycloalkyl-CH₂-alkyl, it being possible for all the radicals mentioned to carry optionally up to four identical or different radicals selected from CH₃ or methoxy radicals,

15

B



This Sheet Has Been Replaced



20 in which

p is 0,1,

R⁴ is H-,

R⁵ is H-,

R⁶ is cyclohexyl,

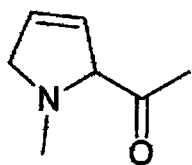
25 R⁷ is h,

R⁸ is h,

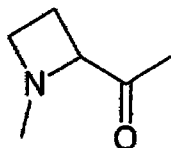


* C L N S *

E

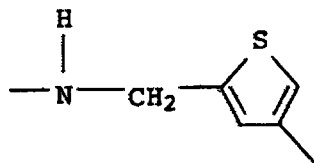
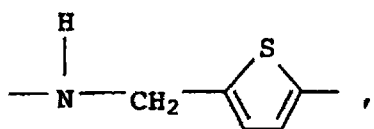


II

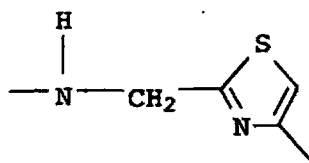


VI

D



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* C L M S *

G: -OH,

K = is h.

- 5
- 10 6. A drug comprising one or more compounds of the formula I as claimed in any of claims 1 to 5 in addition to conventional carriers and excipients.
- 15 7. The use of compounds of the formula I as claimed in any of claims 1 to 5 for producing drugs for the therapy and prophylaxis of thrombin-dependent thromboembolic events.
- 20 8. The use of compounds of the formula I as claimed in any of claims 1 to 5 for producing drugs for the therapy and prophylaxis of
- disorders whose pathomechanism is based directly or indirectly on the proteolytic effect of thrombin,
- disorders whose pathomechanism is based on the thrombin-dependent activation of receptors and signal transductions,

- disorders associated with stimulation or inhibition of the expression of genes in body cells,
- 5 - disorders based on the mitogenic effect of thrombin,
- disorders based on a thrombin-dependent change in the contractility and permeability of epithelial cells,
- 10 - thrombin-dependent thromboembolic events,
- disseminated intravascular coagulation (DIC),
- reocclusion and for reducing the reperfusion time on comedication with
- 15 thrombolytics,
- the occurrence of early reocclusion and late restenosis after PTCA,
- thrombin-dependent proliferation of smooth muscle cells,
- 20 - accumulation of active thrombin in the CNS,
- tumor growth, and to counter the adhesion and metastasis of tumor cells.
- 25 9. The use of compounds of the formula I as claimed in any of claims 1 to 5 as prodrugs for producing a drug for oral or parenteral administration.
- 10. The use of compounds of the formula I as claimed in any of claims 1 to 5 for
- 30 producing drugs with an improvement in the absorption in the gastrointestinal tract or a reduction in the amplitude of the plasma concentration-time profile over the dosage interval or an increase in the duration of action of the active substance, comparing in each case with the pharmacologically active substance.

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