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<td>(54) Title:</td>
<td>KININOGEN INHIBITORS</td>
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<tr>
<td>(57) Abstract:</td>
<td>Kininogenase inhibiting peptides or peptide analogues with C-terminal residues related to agmatine or noragmatine.</td>
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KININOGEN INHIBITORS

FIELD OF INVENTION

The invention relates to enzyme inhibition and to treatment of disease.

BACKGROUND - KININS

Kinis are natural vasoactive peptides liberated in the body from high molecular weight precursors (kininogens) by the action of selective proteases known as kininogenases.

There is evidence for the involvement of kinins in the following pathological states:

(a) Conditions associated with vasodilatation and hypotension, e.g. septic, anaphylactic and hypovolaemic shock; carcinoid syndrome and dumping syndrome

(b) Conditions involving inflammation, e.g. acute arthritis, pancreatitis, local thermal injury, crush injury and brain oedema

(c) Conditions involving bronchoconstriction, especially for example the initial, acute allergic reaction in asthma

(d) Allergic inflammation, particularly allergic rhinitis and conjunctivitis, together generally known as hay fever, and the bronchial inflammation and consequent occlusion found in the non-acute but serious and even fatal inflammatory phase of asthma.

The kinins (bradykinin, kallidin and Met-Lys-bradykinin) are potent mediators of inflammation. Their main actions are as follows:
(a) They increase capillary permeability which leads to exudate formation and oedema

(b) They are potent vasodilators in arterioles and therefore reduce blood pressure and increase blood flow

(c) They induce pain

(d) They contract bronchial smooth muscle

(e) They activate phospholipase A2 and thus stimulate the biosynthesis of prostaglandins (PG’s) which mediate some of their actions.

In regard to prostaglandins, it may be noted that certain actions of kinins, particularly pain and vascular permeability above, are potentiated by PG’s, although PG’s themselves do not cause pain nor do they induce vascular permeability at the concentrations found in inflamed tissue. PG’s therefore act as either mediators or potentiatators of kinins.

In spite of the above knowledge of kinins and their actions, relatively little attention has been paid to reduction of their action. In asthma treatment for example clinical attention is primarily directed to the acute bronchoconstrictive reaction, for which there are effective drugs. Deaths continue to occur from the gradually developing bronchial occlusion. At present there are no selective inhibitors of kinin release in clinical use, and their potential use in allergic inflammation appears to have been unpublished prior to our PCT application WO 9204371 of 19th March 1992.
BACKGROUND - KININOGENASES

The kininogenases are serine proteinases, that is to say proteinases in which the hydroxy group of a serine residue is the nucleophile involved in forming the substrate transition state. They liberate the kinins (bradykinin, kallidin) from the kininogens by limited proteolysis. There are several kinds of kininogenase:-

(a) Tissue kallikrein (TK, also called glandular kallikrein GT or urinary kallikrein UK) which is found in the pancreas, brain, salivary and sweat glands, intestines, kidney and urine. It has MW = 30,000 and acts preferentially on low molecular weight kininogen (LMWK) to release the kinin kallidin (KD). Tissue kallikrein has no potent and fast acting endogenous inhibitor present in plasma. Recently it has been established that at least three homologous genes code for TK’s. The hPK gene is expressed in the tissues mentioned above. Additionally, the PSA gene encodes a prostate specific TK and the hGK-1 gene expresses a TK in neutrophils.

(b) Plasma kallikrein (PK) occurs in plasma as an inactive zymogen which is activated by Factor XIIa, and is part of the intrinsic coagulation cascade. It has MW = 100,000 and its preferred substrate is high molecular weight kininogen (HMWK) from which it releases bradykinin (BK). Plasma kallikrein is rapidly and effectively inhibited in plasma, by endogenous inhibitors known as cl-inactivator and α₂-macroglobulin.

(c) Mast cell tryptase (MT) has been found in large amounts in the pulmonary mast cells of asthmatics. MT has been shown to release bradykinin from both LMWK and HMWK and may therefore be of aetiological significance in asthma (as indeed TK appears to be).
BACKGROUND - KININOGENS

The kininogens which are the natural substrates for the kininogenases (they act also as potent inhibitors, Ki approx. \(10^{-11}\)M, of cysteine proteinases such as cathepsins B, H and L, calpain and papain) occur in two types:

(a) Low molecular weight kininogen (LMWK) with molecular weight in the range 50,000 - 70,000 depending on species of origin and degree of glycosylation.

(b) High molecular weight kininogen (HMWK) with molecular weight in the range 88,000 - 114,000 which, in addition to serving as an alternative precursor of kinins and a cysteine proteinase inhibitor, also plays an obligatory role with plasma kallikrein in the initiation of the intrinisic coagulation cascade.

The two kininogens, whose mRNA's are transcribed from the same gene, have identical primary sequences throughout the N-terminal or heavy chain (H-chain) region, the kinin region and the first twelve amino acids of the C-terminal or light chain (L-chain). At this point their structures diverge, HMWK having a longer L-chain (MW approximately 45K) than LMWK (4.8K).

The cleavage of human HMWK by plasma kallikrein is for example shown schematically in Fig. 1, with details of the sequence at the cleavage sites in Fig. 2 and a more detailed sequence in Fig. 3 where the conventional numbering of residues adjacent to a cleavage site is shown for cleavage site I. After excision of one or other kinin sequence, the H- and L-Chains are held together by a single disulphide bridge:-
Figure 1. Cleavage of HMWK by PK: Overall scheme

Figure 2. Cleavage of human kininogens by PK and TK: Details of sequence

Figure 3. Sequences flanking cleavage site I in human HMWK
As shown, PK, TK and MT act at a single site to free the kinin C-terminal site, cleaving between residues 389 and 390, but at sites one residue apart, either side of residue 380, to free the N-terminal of bradykinin (by PK and MT) or kallidin (by TK).

The role of PK and HMWK as clotting factors in the intrinsic cascade does not involve enzymic cleavage. However many of the effects of PK and probably all those of TK and MT do involve proteolytic cleavages either of kininogens to liberate kinins or of other substrates, e.g. precursors of growth factors.

INDICATIONS

The main clinical indications for kininogenase inhibitors are inflammatory conditions, particularly allergic inflammation (e.g. asthma and hay fever). A fuller list of indications is given below:

(1) Allergic inflammation (e.g. asthma, rhino-conjunctivitis [hay fever], rhinorrhea, urticaria), excess lung mucus, ascites build-up.

(2) Inflammation (e.g. arthritis, pancreatitis, gastritis, inflammatory bowel disease, thermal injury, crush injury, conjunctivitis), periodontal disease, chronic prostate inflammation, chronic recurrent parotitis, inflammatory skin disorders (e.g. psoriasis, eczema), hepatic cirrhosis, spinal cord trauma and SIRS (systemic inflammatory response syndrome).

(3) Smooth muscle spasm (e.g. asthma, angina), RDS (respiratory distress syndrome).

(4) Hypotension (e.g. shock due to haemorrhage, septicaemia or anaphylaxis, carcinoid syndrome, dumping syndrome)
(5) Oedema (e.g. burns, brain trauma, angioneurotic oedema whether or not as a result of treatment with inhibitors of angiotensin converting enzyme)

(6) Pain and irritation (e.g. burns, wounds, cuts, rashes, stings, insect bites), migraine.

(7) Male contraceptive agents by virtue of inhibition of prostate kallikrein.

(8) Prevention of excessive blood loss during surgical procedures.

(9) Growth factor regulation: TK is implicated in processing of precursors of various growth factors e.g. EGF, NGF.

STATEMENT OF INVENTION

In one aspect the invention provides a method of treatment (including prophylactic treatment) of an inflammatory or other condition set out in the indications above, particularly an allergic inflammatory condition, wherein an effective amount of a peptide or peptide-analogue kininogenase inhibitor as described herein is administered topically or systemically to a patient suffering from or at risk of the condition. It is believed that for optimum activity administrability and stability in the body the compounds should not exceed the size of a hexapeptide, that is to say should not comprise more than six amino acid or amino acid analogue residues; the presence of further residues, particularly in a pro-drug from which residues are cleaved in the body to give the compound primarily exerting the desired effect, is however not excluded.

Particularly, the invention provides a method of treatment of the allergic inflammatory phase of asthma,
wherein an effective amount of a kininogenase inhibitor, as described herein, is administered topically or systemically to a patient suffering from or at risk of the condition.

The invention extends further to a method of preparation of a medicament for the topical or systemic treatment (including prophylactic treatment) of conditions as above particularly for allergic inflammatory conditions and especially for asthma as above, wherein a kininogenase inhibitor as described herein is associated with a pharmaceutically acceptable diluent or carrier to constitute said medicament.

In the above, the kininogenase inhibitor is of the novel kind now described whereby in another aspect, without limitation to any particular clinical indication, the invention provides synthetic, low molecular weight compounds that selectively inhibit kininogenases and thus block the release of kinins from kininogens and also block the processing of various growth factors or any other action of these enzymes. The inhibitors are peptides or peptide analogues, desirably (as above) not exceeding the size of a hexapeptide in terms of amino acid or analogue residues.

The inhibitors are essentially of the structure A-B-C, in which A represents the P3 residue, B the P2 residue, C the P1 residue and where A, B are amino acyl or amino acyl analogue groups linked by peptide bonds or conformational analogues thereof giving a peptide mimic, and C is as defined below. Other residues in addition to these essential ones may of course be present, including amino acyl or amino acyl analogue residues.
In particular:-

i) $\text{C is:}$

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\text{---E---} \\
\text{R}^3 \quad \text{R}^4 \\
\text{Z} \quad \text{NH} \\
\text{R}^5 \\
\end{array}
\]

wherein:

$Y$ is $-\text{H}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CONH}_2$, $-\text{OH}$ or $-\text{NH}_2$; $Z$ is $-\text{CH}_2-$, $-\text{NH}-$, $-\text{S}-$ or $-\text{O}-$;

$R^1$, $R^2$, $R^3$, $R^4$, are $-\text{H}$, alkyl (C1 to C6), $-\text{OH}$, alkoxy, halide, $-\text{SH}$, or $-\text{S}-$alkyl (C1 to C6), or one or both of $R^1R^2$, $R^3R^4$, constitute a carbonyl group or a cycloalkyl (C3 to C6) group;

$D$ is $-\text{NR}^{11}$ where $R^{11} = \text{H}$, lower alkyl C1 to C6 or OH; or $\text{SO}_2$, $\text{CO}$, $\text{CH}_2$, $\text{O}$ or $\text{S}$; or $= \text{CH}-$ (when the amide bond between $B$ and $C$ is replaced by $-\text{CH}=$);

$E$ is $-\text{CR}^5R^6-$ (defined as $R^1R^2$, $R^3R^4$ above); $-\text{NR}^{11}$- ($R^{11}$ as above); $O$; or $S$;

$F$ is absent or $-\text{CR}^9R^{10}$- where $R^9$ and $R^{10}$ are $\text{H}$ or alkyl (C1 to C6) or if $E$ is $-\text{CR}^5R^6$- then $R^9$ and $R^{10}$ are as defined for $R^1$, $R^2$, $R^3$, $R^4$ above;

and further, the carbonyl of amino-acyl group $B$ together with $D$, $E$ and $F$ may be replaced by a heterocyclic ring e.g. oxazolidine, oxazole, azole, tetrazole, isooxazoline, oxazoline, thiazoline;

ii) $A$ and $B$, one of which may be absent, are amino acyl or amino acyl analogue residues the same or different and in particular:-

$A$ is

a) a residue of an amino or imino acid or analogue of L- or preferably D- configuration and preferably
selected from Aib; Aic; Ala; Aha; Apa; Arg; Atc; Aze; Bta; Cdi; Cha; Cin; Cit; Cpg; α-Dhn; β-Dhn; Dpn; Glu; 4-Gph; 3-Gph; Har; Hch; Hci; His; Hph; Hyp; Ile; Leu; Lys; Nip; α-Nal; β-Nal; 2-Pal, 3-Pal; 4-Pal; Phe; 4-CF₃-Phe; 4-Cl-Phe; 4-CN-Phe; 4-F-Phe; 3-F-Phe; 2-Me-Phe; 4-NO₂-Phe; 4-NH₂-Phe; 2,4-Cl₂-Phe; 3,4-Cl₂-Phe or other substituted Phe; Phg; Pic; Pro; β-Pro; 3-Ph-Pro; α-homo-Pro; Pse; Pse(OR) where R = Cl to C10 alkyl; Pyr; Ser; Ser (O⁻Bu); Tal; Tic; α-Tna; Trp; Tyr; Tyr(Et); Val; optionally with an N-terminal group which may in particular be selected from -HCO, lower alkyl- (Cl to C6) – acyl or aromatic acyl; lower alkyl (Cl to C6) – sulphonyl; alkyl (Cl to C10); HO₂C(CH₂)ₙ⁻, where n = 1 to 3, or esters or amides thereof; amino-acyl; alkyloxycarbonyl; aryloxycarbonyl; R-alkylacyl where alkyl is Cl to C10 and end-group R is selected from guanidino, amidino, benzamidino, guanidinophenyl and amidinophenyl; aryl sulphonyl; or in general a Boc, Z, Fmoc or other protecting group;

b) an N,N-dialkyl - (Cl to C20) substituted, or N,N-[HO₂C(CH₂)ₙ⁻]₂⁻ (n = 1 to 3) substituted amino acid preferably of D- configuration and preferably as above;

c) a group as follows (B = absent)

\[
\begin{align*}
\text{R}^7 & \quad \text{O} \\
\text{CH} & \quad \text{R}^8 \\
\text{(CH}_2\text{)}_n & \quad \text{-R}^8
\end{align*}
\]
where n = 1 to 5; R^7 = a lipophilic group such as aryl, heteroaryl or alkyl (C1 to C20) and preferably Nap, substituted Nap, cyclooctyl, or decahydroanaphthyl; and R^8 = R^7 preferably phenyl (including substituted phenyl) or heteroaryl, and in particular phenylalkyl acyl-, D- or L- aryl- or heteroaryl- alaninyl, or aryl- or heteroaryl- aminoalkyl generally (where 'alkyl' is C1 to C6 and aryl may be substituted);

B is a residue of a lipophilic amino acid or analogue of D- or preferably L-configuration optionally alkyl (C1 to C6) substituted at the 8-nitrogen but which is not proline or a proline analogue when R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10} are all H and may in particular be selected from Ada; Aha; Cha; α-Dhn; β-Dhn; homo-α-Dhn; Hch; Leu; α-Nal; β-Nal; homo-α-Nal; Nse; Phe; 4-F-Phe; 5-F-Phe; Ser(O^3Bu); Ser(Obn); homo-α-Tra and where aromatic amino acids may be further substituted in their rings;

iii) further:-
the amide function -CONH- between A and B, or B and C (when D = NH), or both may be replaced by a mimetic including -CH=CH-; -CF=CH-; -CH_2NR^{12} where R^{12} = H; alkyl; OH; -COCH_2-; -CH(OH)CH_2-; -CH_2O-; -CH_2S-; -CH_2SO_x- where x = 1, 2; -NH CO-; -CH_2CH_2-; or heterocyclic rings as under definition of C (when D, E, F may also be encompassed). Such mimetics are well known in the scientific literature especially in the area of peptidomimetic research;

"alkyl" unless otherwise specified encompasses straight-chain, branched and cyclo.

The invention further relates to compounds as represented by C above and their use, both as new compounds and as new elements in pharmaceutically active compounds generally, as
more particularly set out in claims 6 to 8 herein.

In the following, two hundred and sixty six examples of compounds according to the invention are given numbered 101 - 366 in Table 1, accompanied by a Table of abbreviations. Table 1 is preceded by four detailed examples, concerning in Example 1 the syntheses of compound 101; in Example 2 the synthesis of compound 102, illustrating also the route of synthesis of compounds 103 - 265 and 358 - 366; in Example 3 the synthesis of compound 266; and in Example 4 the synthesis of compound 267, illustrating also the route of synthesis of compounds 268 - 325.

The examples refer further to and are supplemented by eighteen synthesis schemes following them:-

Scheme I - Compound 101 (Example 1)
Scheme II - Compound 102 (Example 2, referring therefore also to compounds 103 - 265 and 358 - 366)
Scheme III - Compound 266 (Example 3)
Scheme IV - Compound 267 (Example 4, referring therefore also to compounds 268-325)
Scheme V - Compound 326, also illustrating the synthesis of compounds 327, 328
Scheme VI; VII - Compound 329, also illustrating the synthesis of compound 330; compound 331, also illustrating the synthesis of compound 332
Scheme VIII - Compound 333, also illustrating the synthesis of compounds 334 - 337
Scheme IX - Compound 338
Scheme X - Compound 339, also illustrating the synthesis of compound 340
Scheme XI - Compound 341, also illustrating the synthesis of compounds 342 - 344
Schemes XII; XIII - Compound 345; compound 346
Scheme XIV - Compound 347
Scheme XV - Compound 348, also illustrating the
   synthesis of compounds 349, 350
Scheme XVI - Compound 351
Scheme XVII - Compound 352, also illustrating the
   synthesis of compound 353
Scheme XVIII - Compound 354, also illustrating the
   synthesis of compounds 355 - 357

In Table 1 the compounds are given with reference number,
structure and molecular ion as determined by FAB (fast atom
bombardment) spectrometry. All structure of intermediates
were verified by NMR, and where applicable all final products
gave satisfactory amino acid analysis.

Kinogenase inhibition assay gave in vitro values in the
range 10^{-3} to 10^{-9} M for the compounds listed in Table I.
Activity was further shown in vivo in the well established
ovalbumin-sensitised guinea pig model of allergic
inflammation.

When the compounds of the present invention are used as a
medicine, there are no critical limitations to the
administration methods. The present enzyme inhibitor can be
formulated by any conventional method in pharmaceutics. For
example, the present enzyme inhibitor may be applied in any
conventional manner including intravenous injection,
intramuscular injection, instillation, oral administration,
respiratory inhalation, rhinenchysis, and external skin
treatment. Although there are no critical limitations to the
administration dosage, the suitable dosage is 1 to 1000
mg/day-person.
EXAMPLE I

101 H-DPro-Phe-Nag

The synthesis of 101 was carried out according to Scheme I. Arabic numerals underlined e.g. 1 refer to structures in these schemes. Roman numerals in parentheses e.g. (i) refer to reaction steps.

(i) Triethylamine (62 mmol) and diphenylphosphoryl azide (62 mmol) were added to a solution of Boc-4-aminobutyric acid (31.3 mmol) in toluene (200 cm³). After 3 hours at 100°C benzyl alcohol (94 mmol) was added. After a further 18 hours at 100°C the reaction mixture was washed with 2M NaOH, H₂O and brine. The crude product was purified by flash chromatography on silica EtOAc - petrol (1:3). The pure 1 was isolated as a colourless oil (46%).

(ii) The Boc group of 1 (4.3 mmol) was removed with sat. HCl/Dioxan and the product acylated with Boc-Phe-ONSu (6.45 mmol) in CH₂Cl₂ (30 cm³) at 0°C in the presence of N-methylmorpholine. After 3 hours the reaction mixture was worked up using standard procedures and the crude product purified by flash chromatography on silica with EtOAc - petrol (4:6). The pure 2 was isolated as a white solid (99%).

(iii) The Boc group of 2 (4.2 mmol) was removed with sat. HCl/Dioxan and the product acylated with Boc-DPro-ONSu (6.3 mmol) in CH₂Cl₂ (30 cm³) at 0°C in the presence of N-methyl morpholine. After 3 hours the reaction mixture was worked up using standard procedures and the crude product purified by flash chromatography on silica with EtOAc - petrol (13:7). The pure 2 was isolated as a white solid (86%).

(iv) The Z protected amine 2 (3.63 mmol) was hydrogenated over 5% Pd/C in AcOH/H₂O (9:1, 40 cm³) at atmospheric pressure and room temperature. After 30 mins the catalyst was filtered off, washed with AcOH/H₂O (9:1, 20 cm) and the combined filtrates evaporated in vacuo. The residue was dissolved in dry DMF (10 cm³), the pH adjusted to pH 9 with triethylamine and 3,5-dimethyl pyrazole-1-carboxamidine nitrate (4.0 mmol) was added. After 3 days at room temperature the solvent was removed in vacuo to give the crude guanidine 4 (100%).
The crude guanidine 4 (3.63 mmol) was treated with 2M HCl (30 cm²). After 2 hours at room temperature the solvent was removed in vacuo. The crude material was purified by mpic on *Vydac C_{18} (15 - 25 μ) using MeCN/H₂O/TFA to give pure 101 as a white solid (134 mg). Hplc, *Novapak C_{18}, 4 μ (8 x 100 mm), linear gradient 10 → 50% 0.1% TFA/MeCN into 0.1% TFA/H₂O over 25 min at 1.5 ml min⁻¹ indicated a single product (T_R = 8.8 min). After hydrolysis at 110ºC/22 hr with 6N HCl, amino acid analysis Phe 1.03, Pro, 0.97. FAB mass spec [M+H]^+ = 361 (calc. m/z = 360.23).

* Trade Name

EXAMPLE II

102 H-DPro-1Nal-Nag (see Scheme II)

(i) 1,3-Diaminopropane (0.3 mol) was converted to the mono-Z diamine hydrochloride 5 by a method outlined in G.J. Atwell and W.A. Denny, Synthesis, 1984, 1032-33.

(ii) Mercuric oxide (63.3 mmol) was added to a solution of 5 (63 mmol) and N,N' bis Boc-S-methoxysulphoxide (63.3 mmol, R.J. Bergeron and J.S. McManus, J. Org. Chem. 1987, 52, 1700-1703) in ethanol (200 cm³). After 3½ hours at 40ºC the inorganic solid was filtered off and the crude product purified by flash chromatography on silica with EtOAc - petrol (1:9). The pure protected guanidine 6 was isolated as a white solid (94%).

(iii) A solution of 6 (59.5 mmol) and 1M HCl (1 equiv.) in methanol (100 cm³) was hydrogenated over 10% Pd/C at atmospheric pressure and room temperature. After 3 hours the catalyst was filtered off. The filtrate was evaporated and the white solid recrystallised (MeOH/Et₂O) to give pure 7 (92%).

(iv) H-1Nal-OMe. HCl (60 mmol) was acylated with Boc-DPro-ONSu (84 mmol) in CH₂Cl₂ (40 cm³) at 0ºC in the presence of N-methylmorpholine. After 18 hours the reaction mixture was worked up using standard procedures and the crude product purified by flash chromatography on silica with EtOAc - petrol (1:4). Pure 8 was isolated as a white solid (64%).
(v) 8 (38 mmols) was dissolved in THF/H₂O (9:1, 200 cm³). Lithium hydroxide (114 mmols) was added. After 4 hours at room temperature the reaction mixture was worked up to give pure 9 (100%) which was isolated as a white solid.

(vi) The dipeptide 9 (43.5 mmol) and 7 (43.5 mmols) were dissolved in CH₂Cl₂/DMF (20:1, 40 cm³). HOBt (52 mmol) and water soluble carbodiimide (52 mmol) were added to this solution at 0°C. After 15 mins the pH was adjusted to pH 8 with N-methylmorpholine. After 18 hours at room temperature the reaction mixture was worked up using standard procedures and the crude product purified by flash chromatography on silica with EtOAc - petrol (4:6). Pure 10 was isolated as a white solid (69%).

(vii) 10 (30 mmol) was treated with TFA/H₂O (95:5, 50 cm³). After 1.5 hours the solvent was removed in vacuo. The crude material was purified as described in Example I (v). Pure 102 (1.796 g) was isolated as a white solid. Hplc, linear gradient 15 → 50% 0.1% TFA/MeCN into 0.1% TFA/H₂O over 25 mins at 1.5 ml min⁻¹ indicated a single product (T_R = 10.6 min). FAB mass spec [M+H]⁺ = 411.2 (calc. m/z = 410.24).

Compounds 103 - 265 were also synthesised by this route. Unusual amino acids were synthesised by standard methods. Agmatine based compounds 358 - 366 were also synthesised by this route.

EXAMPLE III

266 H-Dlle-1-Nal-Nag (see Scheme III)

(i) 3-Amino-1-propanol (0.33 mol) and di-tert-butyl dicarbonate (0.33 mol) were dissolved in CH₂Cl₂ (150 cm³) and the pH was adjusted to pH 9 with diisopropylethylamine. After four hours at room temperature the reaction mixture was worked up by standard procedure to give pure alcohol (11) as a colourless oil (100%).

(ii) Methanesulphonyl chloride (0.36 mol) was added to a solution of 11 (0.33 mol) and triethylamine (0.36 mol) in CH₂Cl₂ (200 cm³) at 0°C. After 4 hours the reaction mixture was worked using standard procedures to give the mesylate 12 (100%).
(iii) Sodium azide (1 mol) was added to a solution of 12 (0.33 mol) in dry DMF (100 cm$^3$). After 18 hours at 60°C the reaction mixture was worked up using standard procedures. The crude product was purified by flash chromatography on silica with EtOAc - petrol (1:9). The pure azide 13 was isolated as a colourless oil (80%).

(iv) The azide 13 (20 mmol) was treated with 4 M HCl/Dioxan (100 cm$^3$). After 30 mins at room temperature the solvent was removed in vacuo and the residue dissolved in EtOH (100 cm$^3$) N,N'-bis-Boc-S-methoxyisothioure (22 mmol) and mercuric oxide (22 mmol) were added. After 2 hours at 40°C the reaction mixture was worked up using standard procedures. The crude product was purified by flash chromatography on silica with EtOAc - petrol (1:9). The pure azide 14 was isolated as a white solid (68%).

(v) A solution of the azide 14 (1 mmol) in methanol (40 cm$^3$) and 1M HCl (1 mmol) was hydrogenated over 5% Pd/C at atmospheric pressure and room temperature. After one hour the catalyst was filtered off and the filtrate evaporated in vacuo. The residue was recrystallised from MeOH/Et$_2$O to give the amine 15 as a white solid (92%).

(vi) Water soluble carbodiimide (0.89 mmol) and HOBT (0.89 mmol) were added to a solution of 15 (0.74 mmol) and Fmoc-1Na-OH (0.74 mmol) in CH$_2$Cl$_2$/DMF (9:1, 20 cm$^3$) at 0°C. After 15 mins the pH was adjusted to pH 8 with N-methylmorpholine. After 18 hours at room temperature the reaction mixture was worked up using standard procedures. The crude product was purified by flash chromatography on silica with EtOAc - petrol (3:7). Pure 16 was isolated as a white solid (94%).

(vii) Diethylamine (5 cm$^3$) was added to a solution of 16 (0.69 mmol) in CH$_2$Cl$_2$ (15 cm$^3$). After 4 hours at room temperature the solvent was removed in vacuo. The residue was acylated with Boc-DIle-ONSu (1.0 mmol) in CH$_2$Cl$_2$ (30 cm$^3$) at 0°C in the presence of N-methylmorpholine. After 18 hours the reaction mixture was worked up using standard procedures and the product purified by flash chromatography on silica with EtOAc - petrol (4:6). Pure 17 was isolated as a white solid (54%).
(viii) The protected guanidine 17 (0.35 mmol) was treated with TFA/H₂O (9:1, 10 cm³) for one hour at room temperature. The crude product was purified as described in Example I (v). Pure 266 (50 mg) was isolated as a white solid. Hplc, linear gradient 20 → 80% 0.1% TFA/MeCN into 0.1% TFA/H₂O over 25 mins at 1.5 ml min⁻¹ indicated a single product (Tᵣ = 8.4 min). FAB mass spec [M+H]⁺ = 427.4 (calc. m/z = 426.27).

EXAMPLE IV

267 (2-MeO)Ph-CH = CHCO-Nag (see Scheme IV)

(i) H-Nag. (Boc)₂. HCl 7 (0.17 mmol) was acylated with (2-MeO)Ph-CH = CHCO. ONSu (0.22 mmol) in CH₂Cl₂ (10 cm³) at 0°C in the presence of N-methylmorpholine. After 18 hours the reaction mixture was worked up using standard procedures and the crude product purified by flash chromatography on silica using EtOAc/petrol (1:1). Pure 18 was isolated as a colourless oil (80%).

(ii) 18 (0.136 mmol) was treated with TFA/H₂O (9:1, 10 cm³) for one hour at room temperature. Pure 267 (71 mg) was isolated as a white solid. Hplc, linear gradient 10 → 45% 0.1% TFA/MeCN into 0.1% TFA/H₂O over 30 mins at 1.5 ml min⁻¹ indicated a single product (Tᵣ = 19 min). FAB mass spec [M+H]⁺ = 277.2 (calc. m/z = 276.16).

Compounds 268 - 325 were also synthesised by this methodology. The required cinnamic acid derivatives were either commercially available or synthesised by standard synthetic methods. See also Scheme XVII.
Scheme I
(Synthesis of compound 101)

Boc-NH(CH$_2$)$_2$CO$_2$H $\xrightarrow{(i) \text{ DPPA/Et$_3$N/Toluene/100°C}}$ Boc-NH(CH$_2$)$_3$NHZ

Boc-DPro-Phe-NH(CH$_2$)$_3$NHZ $\xrightarrow{(iii) \text{ HCl/Dioxan}}$ Boc-DPro-ONSu
NMM/CH$_2$Cl$_2$

Boc-DPro-Phe-NH(CH$_2$)$_3$NHZ $\xrightarrow{(ii) \text{ HCl/Dioxan}}$ Boc-Phe-ONSu
NMM/CH$_2$Cl$_2$

(v) 2M HCl

H-DPro-Phe-NH(CH$_2$)$_3$NH NH
NH$_2$

3,5-Dimethyl pyrazole-1-carboxamidine nitrate
Et$_3$N/DMF

101
Scheme II

(Synthesis of compound 102)

H₂N(CH₂)₃NH₂

(i) ZCl/Dioxan/EtOH
CH₃SO₃H
KOAc/H₂O

ZNH(CH₂)₃NH₂·HCl

(ii) MeS

N

N

NH

NH

HBoc

/NH

HBoc

/HgO

EtOH/40°C

H₂N(CH₂)₃-NH

N

N

HBoc

HCl

MeOH/1M HCl

(iii) H₂ Pd/C

ZNH(CH₂)₃-NH

N

N

HBoc

HBoc

Z

(iv) H-1Nal-OMe·HCl

NMM/CH₂Cl₂

Boc-DPro-1Nal-OMe

(v) LiOH/H₂O/THF

(vi) HOSe/WSC

DMF/CH₂Cl₂

NMM

Boc-DPro-1Nal-OH

(vii) TFA/H₂O

H-DPro-1Nal-NH(CH₂)₃NH

NH

NH₂

102
Scheme III
(Synthesis of compound 266)

\[ \text{HO(CH}_2\text{NH}_2 \xrightarrow{\text{i. Boc-O/DIEA/CH}_2\text{Cl}_2} \text{HO(CH}_2\text{NH)}_{\text{Boc}} \]

\[ \text{(ii. MeCl/Et}_3\text{N/CH}_2\text{Cl}_2 \]

\[ \text{N}_2\text{(CH}_2\text{NH)}_{\text{Boc}} \xrightarrow{\text{iii. NaN}_3/\text{DMF/60°C}} \text{MsO(CH}_2\text{NH)}_{\text{Boc}} \]

\[ \text{(iv. HCl/Dioxan} \]

\[ \text{MeS}\xrightarrow{\text{HgO/EtOH/40°C}} \text{HNHBoc} \]

\[ \text{N}_2\text{(CH}_2\text{NH)}_{\text{Boc}} \xrightarrow{\text{v. H}_2\text{Pd/C/MeOH/1M HCl}} \text{H}_2\text{(CH}_2\text{NH)}_{\text{Boc}} \]

\[ \text{(vi. Fmoc-1-Nal-OH/ HOBr/wsc/DMF/CH}_2\text{Cl}_2/\text{NMM} \]

\[ \text{Boc-Dlle-1-Nal-NH(CH}_2\text{NH)}_{\text{Boc}} \xrightarrow{\text{vii. Et}_3\text{NH/CH}_2\text{Cl}_2} \text{Boc-Dlle-ONSu} \]

\[ \text{NMM/CH}_2\text{Cl}_2 \]

\[ \text{Fmoc-1-Nal-NH(CH}_2\text{NH)}_{\text{Boc}} \]

\[ \text{(viii. TFA/H}_2\text{O} \]

\[ \text{H-Dlle-1-Nal-NH(CH}_2\text{NH)}_{\text{NH}_2} \]

266
Scheme IV
(Synthesis of compound 267)

\[
\text{H}_2\text{N}(\text{CH}_2)_3\text{NH} \overset{\text{NBoc}}{\longrightarrow} \overset{\text{NHBoC}}{\longrightarrow} \text{HCl}
\]

1

(i) \[
\begin{array}{c}
\text{O}\text{Me} \\
\text{CH}_2\text{Cl}_2/\text{NMM}
\end{array}
\]

\[
\begin{array}{c}
\text{OMe} \\
\text{NH}(\text{CH}_2)_3\text{NH} \overset{\text{NBoc}}{\longrightarrow} \overset{\text{NHBoC}}{\longrightarrow}
\end{array}
\]

18

(ii) \[
\begin{array}{c}
\text{TFA/}H_2O
\end{array}
\]

\[
\begin{array}{c}
\text{OMe} \\
\text{NH}(\text{CH}_2)_3\text{NH} \overset{\text{NH}}{\longrightarrow} \overset{\text{NH}_2}{\longrightarrow}
\end{array}
\]

267
Scheme V
(Synthesis of compound 326)

\[
\begin{align*}
\text{CN(CH}_2\text{)}_2\text{NH}_2 & \xrightarrow{(i) \text{MeS}\text{NBOC} / \text{HgO/ExOH/40°C/2h}} \text{CN(CH}_2\text{)}_2\text{NH} \text{NBOC} \\
& \xrightarrow{(ii) \text{H}_2 / \text{Pd/C} \text{MeOH/1M HCl}} \text{H}_2\text{N(CH}_3\text{)}_2\text{NH} \text{NBOC} \text{NBOC} \text{HCl} \\
& \xrightarrow{(iii) \text{H-1Nal-OMe, HCl}} \text{Boc-(4-DPhe-1Nal-OMe}} \\
& \xrightarrow{(iv) \text{HCl/Dioxan}} \text{BuO}_{2}\text{CCH}_2(4-DPhe-1Nal-OH} \\
& \xrightarrow{(v) \text{LiOH/H}_2\text{O/THF}} \text{BuO}_{2}\text{CCH}_2(4-DPhe-1Nal-OMe} \\
& \xrightarrow{(vi) \text{HOBr/wscd} \text{DMF/CH}_2\text{Cl}_2 \text{NMM/18 h}} \text{BuO}_{2}\text{CCH}_2(4-DPhe-1Nal-NH(CH}_3\text{)}_2\text{NH} \text{NBOC} \\
& \xrightarrow{(vii) \text{TFA}} \text{HO}_2\text{CCH}_2(4-DPhe-1Nal-NH(CH}_3\text{)}_2\text{NH}_2 \\
\end{align*}
\]

Compounds 327 and 328 were also synthesised by this route.
Scheme VI
(Synthesis of compound 229)

Boc-NH(CH₂)₂NH₂ → Boc-NH(CH₂)₂NH₂, HCl

MeOH/1 M HCl

(i) H₂ Pd/C

(ii) MeS →
NHZ
HgO/EtOH/40°C
3 h

(vi) MsCl/ Et₂N/CH₂Cl₂

(v) HCl/Dioxan

(iv) Boc-DIle-1NaI-OH → Boc-NH(CH₂)₂NH₂
HOBt/wsc/DMF/CH₂Cl₂
NMM/18 h

(vi) MsCl/ Et₂N/CH₂Cl₂

(vii) HBr/CH₂Cl₂

Ms-DIle-1NaI-NH(CH₂)₂NH₂ → Ms-DIle-1NaI-NH(CH₂)₂NH₂

25

26

27

28

29

Compound 229 was also synthesised by this route

Scheme VII
(Synthesis of compound 331)

Boc-DIle-1NaI-NH(CH₂)₂NH₂, HCl → Ac-DIle-1NaI-NH(CH₂)₂NH₂
HCl

DIEA/CH₂Cl₂

(v) HCl/Dioxan

(i) Acetyl imidazole

(ii) Ac-DIle-1NaI-NH(CH₂)₂NH₂ → Ac-DIle-1NaI-NH(CH₂)₂NH₂

30

31

(viii) HBr/CH₂Cl₂

Ac-DIle-1NaI-NH(CH₂)₂NH₂ → Ac-DIle-1NaI-NH(CH₂)₂NH₂

NH₂

331

Compound 331 was also synthesised by this route
Scheme VIII
(Synthesis of compound 333)

1. \( \text{ZONSu/KHCO}_3 \) in Dioxan/H$_2$O

2. \( \text{PPTS/CH}_2\text{Cl}_2 \)

3. Boc$_2$O/DMAP in MeCN

4. Cs$_2$CO$_3$/MeOH

5. HCl in Dioxan/MeOH

6. H$_2$/Pd/C in MeOH/1M HCl

7. Boc-Depro-1Nal-OH
   HOBt/wsc/DMF/CH$_2$Cl$_2$
   NMM

8. TFA/H$_2$O

Compounds 334 - 337 were also synthesised by this route.
Scheme IX

(Synthesis of compound 338)

\[
\begin{align*}
\text{Boc-DPro-1Nal-NH} & \xrightarrow{(i) \text{ Dess-Martin Periodinane}} \text{Boc-DPro-1Nal-NH} \\
\text{OH} & \xrightarrow{(ii) \text{ TFA/H}_2\text{O}} \text{H-DPro-1Nal-NH}
\end{align*}
\]
Compound 340 was also synthesised by this route.
Scheme XI
(Synthesis of compound 341)

(i) iBuOCCl/NMM/THF/-20°C
(ii) CH₃N₂/Et₃O

(iii) Silver benzylate
     Et₃N/MeOH

(v) PPh₃/DEAD/THF
     HN₃/4 h

(vi) NaBH₄/THF
     MeOH

(vii) MeS
     NHBOC
     HgO/EtOH/40°C
     3 h

(viii) H₂ Pd/C MeOH/1M HCl

(ix) Boc-D-Pro-1-Nal-OH
     HOBt/wsc/DMF/CH₂Cl₂
     NMM/18 h

(x) TFA/H₂O/1 h

Compounds 342 - 344 were also synthesised by this route.
**Scheme XII**
(Synthesis of compound 345)

1. Boc-NH(CH₂)₂NH₂ → Boc-NH(CH₂)₂NH₂
   - (i) H₂, Pd/C, EtOH/1M HCl
   - (ii) NH₃, H₂O/EtOH

2. Boc-DPro-1Nal-NH(CH₂)₂NH₂
   - (iii) HCl, Dioxan
   - (iv) Boc-DPro-1Nal-OH
     - HOBu/wesser/DMF/CH₂Cl₂
     - NMM/18 h

3. H-DPro-1Nal-NH(CH₂)₂NH₂

**Scheme XIII**
(Synthesis of compound 346)

1. H-DPro-1Nal-NH(CH₂)₂NH₂
   - (i) TFA/MeCN/H₂O

2. H-DPro-1Nal-NH(CH₂)₂NH₂
**Scheme XIV**
(Synthesis of compound 347)

1. \( \text{ZNH(CH}_2\text{)}_2\text{OH} \) reacted with \( \text{THF/PPH}_3, \text{DEAD/3 h} \) to form \( \text{ZNH(CH}_2\text{)}_2\text{O-NH} \).

2. \( \text{ZNH(CH}_2\text{)}_2\text{O-NH} \) reacted with \( \text{N}_2\text{H}_4, \text{H}_2\text{O/EtOH, Reflux/1.5 h} \) and \( \text{HCl} \) to form \( \text{ZNH(CH}_2\text{)}_2\text{O-NH}_2\text{HCl} \).

3. \( \text{ZNH(CH}_2\text{)}_2\text{ONH} \) reacted with \( \text{MeS/MeOH/40\% DMSO/DMF/CH}_2\text{Cl}_2, \text{NMM/18 h} \) to form \( \text{HNH(CH}_2\text{)}_2\text{ONH} \).

4. \( \text{HNH(CH}_2\text{)}_2\text{ONH} \) reacted with \( \text{TFA/1 h} \) to form \( \text{H-DPro-1Nal-NH(CH}_2\text{)}_2\text{ONH} \).

**Reagents and Conditions:**
- THF/PPH₃, DEAD/3 h
- \( \text{N}_2\text{H}_4, \text{H}_2\text{O/EtOH, Reflux/1.5 h} \)
- \( \text{HCl} \)
- \( \text{MeS/MeOH/40\% DMSO/DMF/CH}_2\text{Cl}_2, \text{NMM/18 h} \)
- TFA/1 h
Scheme XV
(Synthesis of compound 348)

Boc-DPro-1Nal-OH $\xrightarrow{(i) \text{BuOCCl/NMM/THF/-20°C}}$ Boc-DPro-1Nal$_2$OH
$\xrightarrow{(ii) \text{NaBH}_4/\text{H}_2\text{O}}$ $\xrightarrow{(iii) \text{MsCl/} \text{Et}_2\text{N/CH}_2\text{Cl}_2}$ Boc-DPro-1Nal$_2$OMs

Boc-DPro-1Nal$_2$N$_3$ $\xrightarrow{(iv) \text{NaN_3/DMF/60°C/18 h}}$ Boc-DPro-1Nal$_2$OMs

(v) NaBH$_4$/THF MSOH

Boc-DPro-1Nal$_2$NH$_3$ $\xrightarrow{(vi) \text{HO}_2\text{C(CH}_3)_2\text{NH/NH}_2/\text{NBoc}}$ Boc-DPro-1Nal$_2$NHCO(CH$_3$)$_2$NH/CH$_2$Cl$_2$/NMM/18 h

(vii) TFA/H$_2$O

1 h

H-DPro-1Nal$_2$NHCO(CH$_3$)$_2$NH$_2$/NH$_2$

Compounds 349 and 350 were also synthesised by this route.
Scheme XVI
(Synthesis of compound 351)

\[
\text{HO(CH}_2\text{)}_3\text{NH}_2 \xrightarrow{\text{(i)} \text{MeS}} \text{HO(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{HgO/EtOH/40°C/2h}} \text{HO(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{66}} \text{HO(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{(ii) Boc-DPro-1Nal-OH}} \text{Boc-DPro-1Nal-O(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{wscd/DMAP/CH}_2\text{Cl}_2} \text{Boc-DPro-1Nal-O(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{67}} \text{Boc-DPro-1Nal-O(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{(iii) HCl/Dioxan}} \text{Boc-DPro-1Nal-O(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{(iv) Pd/C, AcOH/H}_2\text{O}} \text{H-DPro-1Nal-O(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{351}} \text{H-DPro-1Nal-O(CH}_2\text{)}_3\text{NH} \xrightarrow{\text{NH}_2} \text{NH}_2\]
Scheme XVII
(Synthesis of compound 352)

(1) NaH/DMF/-5°C/Ph(CH₂)₄I/4 h

(2) NaH/THF/-20°C

1-Nap-CHO

(iii) LiOH/H₂O/THF

70

(iv) H₂N(CH₂)₃NH-NBoc

HOBt/wscd/DMF/CH₂Cl₂

NMM/18 h

71

(v) TFA/H₂O/1 h

352

Compound 353 was also synthesised by this route.
Scheme XVIII
(Synthesis of compound 354)

Boc-Phe-OH

(i) 1BuOCCl/NMM/THF/-20°C → Boc-Phe-CHN₂

(ii) CH₂N₂ →

Boc-Phe-CH₂Br

(vi) NaH/DMF/-5°C → (EtO)₂CHCO₂Me

(EtO)₂P CH₂CO₂Me

(v) NaH/THF/-20°C

1-Nap-CHO

1-Nap

1-Nap

PhCH₂-(S)CH(NHBoc)COCH₂

(vii) H₂N(CH₂)₂NH→NHBoc . HCl

HOBr/wscd/DMF/CH₂Cl₂

NMM/18 h

1-Nap

PhCH₂-(S)CH(NHBoc)COCH₂

(viii) TFA/H₂O/1 h

1-Nap

PhCH₂-(S)CH(NH₂)COCH₂

Compounds 355 - 357 were also synthesized by this route
### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Formula</th>
<th>Mass (M+H)^+</th>
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<tbody>
<tr>
<td>101</td>
<td>H-DPro-Phe-Nag</td>
<td>361</td>
</tr>
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<td>102</td>
<td>H-DPro-1Nal-Nag</td>
<td>411.2</td>
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* No [M+H]$^+$ observed
ABBREVIATIONS

Ac    Acetyl
AcOH  Acetic acid
Ada   Adamantylalanine
Aib   2-Amino-isobutyric acid
Aic   2-Aminoindan-2-carboxylic acid
Agm   Agmatine
Amp   2-Amino-3-(7-methoxy-4-coumaryl) propionic acid
Ant   Anthracene
Atc   2-Aminotetralin-2-carboxylic acid
Aze   Azetidine-2-carboxylic acid
Boc   tert-Butyloxy carbonyl
Bta   Benzo thienyl alanine
Bu    Butyl
Bzl   Benzyl
Cd    Carboxydecahydroisoquinoline
Cdd   Cyclododecyl
Cha   Cyclohexylalanine
Ch    Cyclohexyl
Chg   Cyclohexyglycine
Cin   Carboxyindoline
Cit   Citrulline
Coc   Cyclooctyl
Cp    Cyclopentyl
Cpc   Cyclopentane carboxylic acid
Cpr   Cyclopropyl
Cti   Carboxy-1,2,3,4-tetrahydroisoquinoline
Cud   Cycoundecyl
DEAD  Diethyl azodicarboxylate
Dhn   Decahydonaphthyl alanine
DIBAL Diisobutylaluminium hydride
DIEA  N,N-Diisopropylethylamine
DMAP  4-Dimethylaminopyridine
DMF   Dimethylformamide
Dna   Decahydonaphthyl
Dnma  Di-(1-naphthylmethyl) acetic acid
DPPA  Diphenylphosphoryl azide
Dpn  α,β-Dehydrophenylalanine
e  erythro
Et  Ethyl
EtOAc  Ethyl acetate
EtOH  Ethanol
FAB  Fast atom bombardment
Fen  Fluorenyl
Fmoc  9-Fluorenylmethoxycarbonyl
Gha  6-Guanidino hexanoic acid
Gpa  5-Guanidino pentanoic acid
Gph  Guanidinophenylalanine
Har  Homoarginine
Hci  Homocitrulline
Hch  Homocyclohexylalanine
HoBT  1-Hydroxybenzotriazole
Hph  Homophenylalanine
Hplc  High performance liquid chromatography
Hx  n-Hexyl
Hyp  Hydroxyproline
Inc  Indoline carboxylic acid
Iqc  Isoquinoline carboxylic acid
Me  Methyl
MeCN  Acetonitrile
MeOH  Methanol
mplc  Medium pressure liquid chromatography
Ms  Mesyl
Nag  Noragmatine
Nal  Naphthylalanine
Nap  Naphthyl
Nip  Nipecotic acid
NMM  N-Methylmorpholine
Nse  Naphthylserine
ONSu  Hydroxysuccinimide
Pal  Pyridylalanine
Petrol  Petroleum ether 60-80°C
Phg  Phenylglycine
Pic  Pипеcolinic acid
Piz    Piperazinyl
PPTS  Pyridinium p-toluenesulphonate
Pr    Propyl
Pse   Phenylserine
Py    Pyridyl
Pyr   Pyroglutamic acid
Pyz   Pyrazinyl
Qui   Quinoline
[R] or R Reduced isostere -CH₂- replacing -CO-; eg. BocNHCH₂CH₂OH = BocGlyBzOH
Tal   3(2-Thienyl)alanine
TFA   Trifluoroacetic acid
th    threeo
THF   Tetrahydrofuran
Thi   1,2,3,4-Tetrahydroisoquinoline
Thp   Thiophene
tlc   Thin layer chromatography
Tna   1,2,3,4-Tetrahydronaphthylalanine
wscd Water soluble carbodiimide
Z     Benzyloxycarbonyl

References to test methods:

1. Kininogenase inhibiting peptides or peptide analogues of the structure A-B-C where:

i) C is:

\[
\begin{array}{c}
\text{R}^1 \text{R}^2 \\
\text{D} \text{E} \text{F} \\
\text{R}^3 \text{R}^4 \\
\text{Z} \text{NH} \\
\text{N-Y} \text{H}
\end{array}
\]

wherein:

Y is \(-\text{H} \text{-NO}_2 \text{-CN \text{-CONH}_2 \text{-OH or \text{-NH}_2}; Z is \text{-CH}_2 \text{-NH- \text{-S- or \text{-O-};}}}
\)

\(R^1, R^2, R^3, R^4\), are \(-\text{H}, \text{alkyl (C1 to C6), \text{-OH, alkoxy, halide, -SH, or -S-alkyl (C1 to C6), or one or both of R^1R^2, R^3R^4, constitute a carbonyl group or a cycloalkyl (C3 to C6) group;}}\)

D is \(-\text{NR}^{11}- \text{where R}^{11} = \text{H, lower alkyl C1 to C6 or OH; or SO}_2,\)

\(\text{CO, CH}_2, \text{O or S; or = CH- (when the amide bond between B and C is replaced by -CH=CH-)};\)

E is \(-\text{CR}^{5}\text{R}^{6}- \text{(defined as R}^1\text{R}^2, \text{R}^3\text{R}^4 \text{above); \text{-NR}^{11}- (R}^{11} \text{as above);}}\)

\(\text{F is absent or \text{-CR}^{9}\text{R}^{10}- \text{where R}^9 \text{and R}^{10} \text{are H or alkyl (C1 to C6) or if E is \text{-CR}^{5}\text{R}^{6}- then R}^9 \text{and R}^{10} \text{are as defined for R}^1,\)

\(\text{R}^2, \text{R}^3, \text{R}^4 \text{above;}}\)

and further, the carbonyl of amino-acyl group B together with D, E and F may be replaced by a heterocyclic ring e.g. \text{oxazolidine, oxazole, azole, tetrazole, isooxazoline, oxazoline, thiazoline;}}\)
ii) A and B, one of which may be absent, are amino acyl or amino acyl analogue residues the same or different and in particular:-

A is

a) a residue of an amino or imino acid or analogue of L- or preferably D- configuration and preferably selected from Aib; Aic; Ala; Aha; Apa; Arg; Atc; Aze; Bta; Cdi; Cha; Cin; Cit; Cpg; α-Dhn; β-Dhn; Dpn; Glu; 4-Gph; 3-Gph; Har; Hch; Hci; His; Hph; Hyp; Ile; Leu; Lys; Nip; α-Nal; β-Nal; 2-Pal, 3-Pal; 4-Pal; Phe; 4-CF₃-Phe; 4-Cl-Phe; 4-CN-Phe; 4-F-Phe; 3-F-Phe; 2-Me-Phe; 4-NO₂-Phe; 4-NH₂-Phe; 2,4-Cl₂-Phe; 3,4-Cl₂-Phe or other substituted Phe; Phg; Pic; Pro; β-Pro; 3-Ph-Pro; α-homo-Pro; Pse; Pse(OR) where R = Cl to C10 alkyl; Pyr; Ser; Ser (O⁻Bu); Tal; Tic; α-Tna; Trp; Tyr; Tyr(Et); Val; optionally with an N-terminal group which may in particular be selected from -HCO, lower alkyl-(Cl to C6) - acyl or aromatic acyl; lower alkyl (Cl to C6) - sulphonyl; alkyl (Cl to C10); HO₂C(CH₂)ₙ⁻, where n = 1 to 3, or esters or amides thereof; amino-acyl; alkylxycarbonyl; aryloxycarbonyl; R-alkylacyl where alkyl is Cl to C10 and end-group R is selected from guanidino, amidino, benzamidino, guanidinophenyl and amidinophenyl; aryl sulphonyl; or in general a Boc, Z, Fmoc or other protecting group;

b) an N,N-dialkyl - (Cl to C20) substituted, or N,N-[HO₂C(CH₂)ₙ⁻]₂⁻ (n = 1 to 3) substituted amino acid preferably of D- configuration and preferably as above;
c) a group as follows (B = absent)

where n = 1 to 5; \( R^7 \) = a lipophilic group such as aryl, heteroaryl or alkyl (C1 to C20) and preferably Nap, substituted Nap, cyclooctyl, or decahydronaphthyl; and \( R^8 \) = \( R^7 \) preferably phenyl (including substituted phenyl) or heteroaryl, and in particular phenylalkyl acyl-, D- or L- aryl- or heteroaryl- alaninyl, or aryl- or heteroaryl-aminoalkyl generally (where 'alkyl' is C1 to C6 and aryl may be substituted);

B is a residue of a lipophilic amino acid or analogue of D- or preferably L-configuration optionally alkyl (C1 to C6) substituted at the \( \beta \)-nitrogen but which is not proline or a proline analogue when \( R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10} \) are all \( H \) and may in particular be selected from Ada; Aha; Cha; \( \alpha \)-Dhn; \( \beta \)-Dhn; homo-\( \alpha \)-Dhn; Hch; Leu; \( \alpha \)-Nal; \( \beta \)-Nal; homo-\( \alpha \)-Nal; Nse; Phe; 4-F-Phe; 5-F-Phe; Ser(\( O^\text{Bu} \)); Ser(\( O^\text{Bn} \)); homo-\( \alpha \)-tra and where aromatic amino acids may be further substituted in their rings;

iii) further:
the amide function \(-\text{CONH}-\) between A and B, or B and C (when D = NH), or both may be replaced by a mimetic including \(-\text{CH}=\text{CH}-\); \(-\text{CF}=\text{CH}-\); \(-\text{CH}_2\text{NR}^{12}\) where \( R^{12} = \text{H, alkyl, OH; } -\text{COCH}_2-; -\text{CH(OH)CH}_2-; -\text{CH}_2\text{O}-; -\text{CH}_2\text{S}-; -\text{CH}_2\text{SO}_x-\) where \( x = 1, 2; -\text{NH CO}-; -\text{CH}_2\text{CH}_2-; \) or heterocyclic rings as under definition of C (when D, E, F may also be encompassed);

"alkyl" unless otherwise specified encompasses straight-chain, branched and cyclo.
2. A peptide or peptide analogue according to claim 1, wherein C is an agmatine or noragmatine residue.

3. A peptide or peptide analogue according to claim 1, wherein C is a substituted preferably alkyl substituted agmatine or noragmatine residue.

4. A pharmaceutical preparation containing a kininogenase-inhibiting amount of a peptide or peptide analogue according to claim 1, 2 or 3.

5. A method of treatment (including prophylactic treatment), of a condition as set out in the indications herein, or a method of preparation of a medicament for such treatment, using an effective amount of a kininogenase inhibiting peptide or peptide analogue according to claim 1 or claim 2.

6. As such, compounds

\[
\begin{array}{c}
R^1 \\
\text{H-D-E-F} \\
R^3 \\
\text{Z} \\
\text{R^2} \\
\text{R^4} \\
\text{N-Y} \\
\text{NH} \\
\text{H}
\end{array}
\]

and their protected forms wherein D = NR\(^{11}\) and E, F, R\(^1\)-R\(^4\), Z and Y are as defined above, particularly compounds where the carbon chain is substituted, preferably alkyl substituted, but excepting compounds that are simply an \(\text{N-}\text{aminoalkyl guanidine.}\)

7. The use of a compound as in claim 6 as a starting material in synthesis of a pharmaceutically active compound and particularly a kininogenase or other serine proteinase inhibitor.
8. As a structural element in a pharmaceutically active compound and particularly a kininogenase or other serine proteinase inhibitor, a residue of the formula in claim 6 but lacking the hydrogen attached to D, or having in the place of that hydrogen a carbonyl group, or (and in this case the exclusion of Ω-aminolakyl guanidines does not apply) having in place of the amide group that is formed by D and such a carbonyl group an amide-group structural mimetic.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/06 C07C279/12 A61K31/155 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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<td>EXPERIENTIA, vol.25, no.6, 15 June 1969, BASEL CH pages 573 - 574 W O JOHNSON ET AL. 'Synthesis and properties of 1-deamino, 9-decarboxy and 1-deamino-9-decarboxy-bradykinin' see scheme 1</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

A document member of the same patent family

Date of the actual completion of the international search

9 December 1994

Date of filing of the international search report

23-01-1995

Name and mailing address of the ISA

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Authorized officer

Masturzo, P

Form PCT/ISA/210 (second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>BIOLOGICAL ABSTRACTS, vol. 80, no. 12 1985, Philadelphia, PA, US; abstract no. 109946, M TAKAOKA ET AL. 'Activation of urinary inactive kallikrein by an extract from the rat kidney cortex' page 1011; see abstract &amp; LIFE SCI., vol.37, no.11, 1985 pages 1015 - 1022</td>
<td>1-4, 6-8</td>
</tr>
</tbody>
</table>
**INTERNATIONAL SEARCH REPORT**

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos: because they relate to subject matter not required to be searched by this Authority, namely:
   
   **Remark:** Although claim 5 refers to a method of treatment of the human body, the search was carried out and was based on the alleged effect of products.

2. **X** Claims Nos: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   
   See annex.

3. □ Claims Nos: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos:

**Remark on Protest**

□ The additional search fees were accompanied by the applicant's protest.

□ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
The formulas of claims 1 and 6 contain almost no fixed invariable element; moreover, they are formulated in an extremely abstruse and obscure way, which makes a complete search impossible for economical reasons.

The Search Division cannot identify a general formula which could be searched and therefore the search was limited to the examples present in the text, provided that the meaning of the unusual abbreviations was made clear, which is not always the case (e.g. the abbreviation Aha has not been explained in the list on pages 46-48).

Similarly the intermediate compounds of claims 6 and 8 were searched only insofar as they are incorporated in an example.