633128

FORM 1

Regulation 9

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

APPLICATION FOR A STANDARD PATENT OF ADDITION

We, MERRELL DOW PHARMACEUTICALS INC of 2110 East Galbraith Road, Cincinnati, Ohio, UNITED STATES OF AMERICA, hereby apply for the grant of a patent of addition for an invention entitled "Anticoagulant Peptides" which is described in the accompanying complete specification.

I request that the patent may be granted as a patent of addition to the patent applied for on Application No 10729/88, in the name of MERRELL DOW PHARMACEUTICALS INC.

I request that the term of the patent of addition be the same as that for the main invention or so much of the term of the patent for the main invention as is unexpired.

My address for service is:

PHILLIPS ORMONDE & FITZPATRICK
367 Collins Street
MELBOURNE VIC 3000

DATED: 10 August 1990

PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys for:
IMPERIAL CHEMICAL INDUSTRIES PLC

David B Fitzpatrick

M

ADDITIONAL
(10729/88
No. 6018

AUSTRALIA

Patents Act

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS
(a) Insert "Convention" if applicable
(b) Insert FULL name(s) of applicant(s)

In support of the (a) application made by (b)

MERRELL DOW PHARMACEUTICALS INC

(c) Insert "of addition" if applicable
(d) Insert TITLE of invention

(hereinafter called "applicant(s) for a patent (c) of addition for an invention entitled (d)

ANTICOAGULANT PEPTIDES

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote*)

I/We (e) Gary D Street of General Patent Counsel, Merrell Dow Pharmaceuticals Inc, Cincinnati, Ohio, United States of America.

do solemnly and sincerely declare as follows:

1. I am/We are the applicant(s).
   (or, in the case of an application by a body corporate)
1. I am/We are authorized to make this declaration on behalf of the applicant(s).
2. I am/We are the actual inventor(s) of the invention.
   (or, where the applicant(s) is/are not the actual inventor(s))

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

2. (f) John L Krstenansky
   3749 Ault Park
   Cincinnati, Ohio 45208
   UNITED STATES OF AMERICA

   Simon J T Mao
   9373 Kentonsrun Court
   Loveland, Ohio 45140
   UNITED STATES OF AMERICA

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote**)

is/are the actual inventor(s) of the invention and the facts upon which the applicant(s) is/are entitled to make the application are as follows:

(g) Applicant is the assignee of the invention by virtue of Deeds of Assignment from the actual inventors dated January 23, 1987 and May 21, 1987.

*(**Note:** Paragraphs 3 and 4 apply **only** to Convention applications)*

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

3. The basic application(s) for patent or similar protection on which the application is based is/are identified by **country, filing date, and basic applicant(s)** as follows:

(h)

4. The basic application(s) referred to in paragraph 3 hereof was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

(k) Insert PLACE of signing

(l) Insert DATE of signing

(m) Signature(s) of declarant(s)

Note: No legalization or other witness required

Declared at (k) Cincinnati, Ohio, United STates of America

Dated (l) September 4, 1990

(m) MERRELL DOW PHARMACEUTICALS INC.

By Gary D Street

Gary D. Street
General Patent Counsel

To: The Commissioner of Patents

P18/7/78 M01256A AU-A

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-60959/90
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 633128

(54) Title
ANTICOAGULANT PEPTIDES

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(61) Related to Addition(s) : **10729/88**

(71) Applicant(s)
MERRELL DOW PHARMACEUTICALS INC

(72) Inventor(s)
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(56) Prior Art Documents
AU 63688/90 C07K 7/06
AU 34517/89 C07K 7/06

(57) Claim

1. A peptide derivative which is Ac-Thr-Pro-Lys-Pro-Gln-Ser-His-Asn-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH.

2. A peptide derivative which is Ac-Thr-Pro-Asn-Pro-Glu-Ser-His-Asn-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH.

3. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Ala-Cha-Asn-OH.

4. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Tyr-Cha-Gln-OH.

5. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH.

6. A peptide derivative which is Suc-Tha-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH.

7. A peptide derivative which is Suc-Npa-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

8. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

9. A peptide derivative which is Mal-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

10. A peptide derivative which is Glt-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

.../2

11. A peptide derivative which is Fum-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

12. A method of reducing blood coagulation in a patient in need thereof which comprises administering an anticoagulant effective amount of a peptide derivative of one of claims 1-11 and a pharmaceutically acceptable carrier.

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COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:

Lodged:

Complete Specification Lodged:

Accepted:

Published:

Priority

Related Art:

APPLICANT'S REF.: Patent of Addition of 10729/88

Name(s) of Applicant(s):

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Address(es) of Applicant(s):

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Actual Inventor(s):

John L KRSTENANSKY - and - Simon J T MAO

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Melbourne, Australia, 3000

Complete Specification for the invention entitled:

ANTICOAGULANT PEPTIDES

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

ANTICOAGULANT PEPTIDES

FIELD OF THE INVENTION

The present application is a Patent of Addition to Australian Patent Application No 10729/88, the entire disclosure of which is incorporated herein by reference.

This invention relates to novel peptides which are useful anticoagulant agents.

BACKGROUND OF INVENTION

Anticoagulants are useful therapeutic agents in the pharmacological treatment of, for example, acute deep venous thrombosis, pulmonary embolism, acute arterial embolization of the extremities, myocardial infarction, and disseminated intravascular coagulation. Proplylactic administration of anticoagulants is believed to prevent a recurrance of embolism in patients with rheumatic or arteriosclerotic heart disease and to prevent certain thromboembolic complications of surgery. Administration of anticoagulants has also been indicated in the treatment of coronary artery and cerebrovascular disease. Artrial thrombosis, particularly in arteries supplying the heart muscle and brain, is a leading cause of death.

Hirudin is a 65 residue polypeptide isolated from the salivary glands of leeches. It is an anticoagulant agent, which is a thrombin specific inhibitor. Although quite potent, clinical use of hirudin isolated from leech extracts seems unlikely because of its limited quantity, expense and allergic reactions which commonly follow administration of any foreign protein of this size.

In Australian Patent Application No 10729/88, applicants described their discovery of a specific region of hirudin that is responsible, at least in part, for its anticoagulant activity. This region was chemically synthesized and certain of its analogs appeared to bind to the recognition site of thrombin but not the enzymatic cleavage site which is spatially separate. Binding of the synthetic peptides competitively prevents binding of the

fibrinogen to the recognition site of thrombin, a prerequisite to fibrin production and clot formation. The peptides of Australian Patent Application No 10729/88 possessed significant anticoagulant activity and their unusual ability to bind only to the recognition site without binding to the cleavage site of thrombin may allow for a scientifically interesting and therapeutically significant adjunct to anticoagulant therapy.

Australian Patent Application No 10729/88 describes peptide derivatives of the formula

$$X\text{-}A_1\text{-}A_2\text{-}A_3\text{-}A_4\text{-}A_5\text{-}A_6\text{-}A_7\text{-}A_8\text{-}A_9\text{-}A_{10}\text{-}Y$$

wherein X is an amino terminal residue selected from hydrogen, one or two alkyl groups of from 1 to 6 carbon atoms, one or two acyl groups of from 2 to 10 carbon atoms, carbobenzyloxy or t-butyloxy carbonyl;

wherein A_1 is a bond or is a peptide containing from 1 to 11 residues of any amino acid;

wherein A_2 is Phe, SubPhe, ß-(2- and 3-thienyl)alanine, ß-(2-and 3-furanyl)alanine, ß-(2-, 3-, and 4-pyridyl)alanine, ß-(benzothienyl-2- and 3-yl)alanine, ß-(1- and 2-naphthyl)alanine, Tyr or Trp;

wherein A_3 is Glu or Asp;

wherein A_4 is any amino acid;

wherein A_5 is Ile, Val, Leu, Nle or Phe

wherein A_6 is Pro, Hyp, 3,4-dehydroPro, thiazolidine- 4-carboxylate, Sar, NMePgl or D-Ala;

wherein A_7 is any amino acid;

wherein A_8 is any amino acid;

wherein A_9 is a lipophilic amino acid selected from Tyr, Tyr(SO_3H), Trp, Phe, Leu, Nle, Ile, Val, Cha and Pro or is a dipeptide containing at least one of these lipophilic amino acids;

wherein A_{10} is a bond or is a peptide fragment containing from one to five residues of any amino acid; and

wherein Y is a carboxy terminal residue selected from OH, C_1-C_6 alkoxy, amino, mono- or di-(C_1-C_4) alkyl substituted amino, or benzylamino;

are useful anticoagulant agents.

Further peptides which possess significant anticoagulant activity have now been synthesised. A number

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of these peptides contain fragments very different from those described as preferred in Australian Patent Application No 10729/88.

According to the present invention there is provided a peptide selected from any one of the following:

Ac-Thr-Pro-Lys-Pro-Gln-Ser-His-Asn-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH

Ac-Thr-Pro-Asn-Pro-Glu-Ser-His-Asn-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Ala-Cha-Asn-OH

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Tyr-Cha-Gln-OH

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH

Suc-Tha-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH

Suc-Npa-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

Mal-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

Glt-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

Fum-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

DETAILED DESCRIPTION OF THE INVENTION

The following common abbreviations of the amino acids are used throughout this specification and the claims:

Gly - glycine
Ala - alanine
Val - valine
Leu - Leucine
Ile - isoleucine
Pro - proline
Phe - phenylalanine
Trp - tryptophan
Met - methionine
Ser - serine
Thr - threonine
Cys - cysteine
Tyr - tyrosine
Asn - asparagine
Gln - glutamine
Asp - aspartic acid

Glu - glutamic acid
Lys - lysine
Arg - arginine
His - histidine
Nle - norleucine
Hyp - hydroxyproline
3,4-dehydroPro - 3,4-dehydroproline
Tyr(SO_3H) - tyrosine sulfate
Pgl - phenylglycine
NMePgl - N-methyl-phenylglycine
Sar - sarcocine (N-methylglycine)
pSubPhe - para substituted phenylalanine
SubPhe - ortho, meta, or para, mono- or di-substituted phenylalanine
DAla - D-alanine
Ac - acetyl
Suc - succinyl
pClePhe - para-chloro-phenylalanine
pNO_2Phe - para-nitro-phenylalanine
Cha - cyclohexylalanine
Orn - ornithine
Glt - glutaryl
Mal - maleyl
Npa - ß- (2-naphthyl) alanine
Thg - ß - (2-thienyl) alanine

An alkyl group and the alkyl portion of an alkoxy group is taken to include straight, branched, or cyclic alkyl groups, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, sec-pentyl, cyclopentyl, hexyl, isohexyl, cyclohexyl and cyclopentylmethyl. An acyl group of from 2 to 10 carbon atoms is taken to include straight, branched, cyclic, saturated and unsaturated acyl groups having 1 or 2 carbonyl moities per group, for example, acetyl, benzoyl, maleyl, glutaryl and succinyl. A halogen group is a fluoro, chloro, bromo or iodo group.

The term "any amino acid" as used herein includes the naturally occurring amino acids as well as other "non-protein" α-amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogs of naturally occurring peptides. The naturally occurring

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amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, ornithine, and lysine. Examples of "non-protein" α-amino acids are norleucine, norvaline, alloisoleucine, homoarginine, thiaproline, dehydroproline, hydroxyproline (Hyp), homoserine, cyclohexylglycine (Chg), α-amino-n-butyric acid (Aba), cyclohexylalanine (Cha), aminophenylbutyric acid (Pba), phenylalanines substituted at the ortho, meta, or paraposition of the phenyl moiety with one or two of the following, a (C_1-C_4)alkyl, (C_1-C_4) alkoxy, halogen, or nitro groups or substituted with a methylenedioxy group, ß-2- and 3-thienylal- anine, ß-2- and 3-furanylalanine, ß-2-, 3-, and 4-pyridylalanine, ß-(benzothienyl-2- and 3-yl)alanine, ß-(1- and 2-naphthyl)alanine, O-alkylated derivatives of serine, threonine, or tyrosine, S-alkylated cysteine, the O-sulfate ester of tyrosine, 3,5- diiodotyrosine and the D-isomers of the naturally occurring amino acids.

The term "lipophilic amino acid" includes Tyr, Phe, Leu, Nle, Ile, Val, His and Pro.

The natural amino acids with the exception of glycine, contain a chiral carbon atom. Unless otherwise specifically indicated, the optically active amino acids, referred to herein, are of the L-configuration. For example, any of the amino acids of the A_1 or A_{10} group can be of the D- or L-configuration. As is customary, the structure of peptides written out herein is such that the amino terminal end is on the left side of the chain and the carboxy terminal end is on the right side of the chain.

The polypeptides of formula I can form pharmaceutically acceptable salts with any non-toxic, organic or inorganic acid. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono, di and tricarboxylic acids. Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic,

malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Salts of the carboxy terminal amino acid moiety include the non-toxic carboxylic acid salts formed with any suitable inorganic or organic bases. Illustratively, these salts include those of alkali metals, as for example, sodium and potassium; alkaline earth metals, such as calcium and magnesium; light metals of Group IIIA including aluminum; and organic primary, secondary and tertiary amines, as for example, trialkylamines, including triethylamine, procaine, dibenzylamine, 1-ethenamine, N,N'-dibenzylethylenediamine, dihydroabietylamine, N-(lower) alkylpiperidine, and any other suitable amine.

EXAMPLES

This invention is illustrated by the following examples. The peptides of the following examples 1-12 were prepared in the same manner as described in Australian Patent Application No 10729/88.

EXAMPLE 1

Ac-Thr-Pro-Lys-Pro-Gln-Ser-His-Asn-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH

EXAMPLE 2

Ac-Thr-Pro-Asn-Pro-Glu-Ser-His-Asn-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH

EXAMPLE 3

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Ala-Cha-Asn-OH

EXAMPLE 4

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Tyr-Cha-Gln-OH

EXAMPLE 5

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH

EXAMPLE 6

Suc-Tha-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH

EXAMPLE 7

Suc-Npa-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

EXAMPLE 8

Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

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EXAMPLE 9

Mal-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

EXAMPLE 10

Glt-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

EXAMPLE 11

Fum-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH

The peptides of examples 1-6 have the following properties:

Example No.	Amino Acids Analysis (6N HCl Hydrolysis: 24 Hrs at 106°C)											
	His	Asx	Ser	Glx	Pro	Ala	Gly	Ile	Leu	Tyr	Phe	Lys
1 +	1.01(1)	2.99(3)	0.81(1)	5.93(6)	3.02(3)		1.04(1)	0.98(1)	1.05(1)	0.96(1)		
2 ++	1.02(1)	4.05(4)	0.92(1)	6.01(6)	3.14(3)		1.05(1)	0.98(1)	1.03(1)	0.84(1)		
3		0.98(1)		2.06(2)	2.03(2)	0.98(1)		0.95(1)		0.85(1)		
4				4.09(4)	2.00(2)			0.93(1)		1.98(2)		
5	***			4.06(4)	2.97(3)			0.96(1)		1.00(1)		
6	***			4.07(4)	2.98(3)			0.96(1)				

*(Me)Tyr coelutes but not quantitated. **(Orn standard used to quantitate)

***Cha present, not calculated ****Tha present, not calculated

+Thr0.99(1) ++Thr0.95(1)

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Physical Characteristics						
Example No.	HPLC t_r(min) (14-40%)gradient)	TLCI (Rf)	TLCII (Rf)	TLC III (Rf)	FAB-MS (M + H)	ε_{280}
1	13.70				2513.9	1297
2	14.03				2501	
3	15.83				1185	
4	18.02				1420	
5	16.85				1345.6	
6	19.08				1377*	

*(M + Na)

EXAMPLE 12

This example illustrates the effectiveness of the peptides of Examples 1-11 in reducing blood coagulation.

Human plasma was collected in EDTA (final concentration = 0.1%) from a healthy female volunteer who had fasted for 12 hours. The plasma was immediately sterilized by passing it through a 0.2 μ filter membrane (Gelman) then aliquoted into 1 ml portions and stored at - 20°C. In all assays, unsulfated Nα-acetylhirudin$_{45-65}$ was included as a control. A bovine thrombin solution (50 μl; 0.2 pmol; Sigma) was added to the wells of a 96 well micotiter plate (Falcon) containing 50 μl of a solution of the peptide to be tested. After a minute of agitation and a 10 minute incubation at 24°C, 100 μl of 1:10 diluted human plasma in 0.12 M sodium chloride, 0.01 M sodium phosphate, 0.01% sodium azide, 0.1% bovine serum albumin (pH 7.4) was added. The mixture was agitated for 10 seconds and the turbidity (A_{405}) of the solution was measured at 5 minute intervals by an autoreader (Bio-Tek Model EL 309).

Reported is the ability of a 5μM concentration of peptide to delay two-fold the amount of fibrin-clot present

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at 15 minutes in the control well. (+ = Delayed clot formation but less than twofold. ++ = Delayed clot formation but more than twofold).

Fibrin-clot inhibition by the examples in the present application:

+: Examples 3, 5, 6.

++: Examples 1, 2, 4, 7-11.

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The claims defining the invention are as follows:

1. A peptide derivative which is Ac-Thr-Pro-Lys-Pro-Gln-Ser-His-Asn-Asp-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH.

2. A peptide derivative which is Ac-Thr-Pro-Asn-Pro-Glu-Ser-His-Asn-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-Gln-OH.

3. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Ala-Cha-Asn-OH.

4. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Tyr-Cha-Gln-OH.

5. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH.

6. A peptide derivative which is Suc-Tha-Glu-Pro-Ile-Pro-Glu-Glu-Pro-Cha-D-Glu-OH.

7. A peptide derivative which is Suc-Npa-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

8. A peptide derivative which is Suc-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

9. A peptide derivative which is Mal-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

10. A peptide derivative which is Glt-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

11. A peptide derivative which is Fum-Tyr-Glu-Pro-Ile-Pro-Glu-Glu-Ala-Cha-D-Glu-OH.

12. A method of reducing blood coagulation in a patient in need thereof which comprises administering an anticoagulant effective amount of a peptide derivative of one of claims 1-11 and a pharmaceutically acceptable carrier.

DATED: 8 August 1990

PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys for:
MERRELL DOW PHARMACEUTICALS INC. David B Fitzpatrick

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