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(54) Titre : INHIBITEURS CYCLIQUES DE L'ADHESION
(54) Title: CYCLIC ADHESION INHIBITORS

(57) **Abrégé/Abstract:**

The invention relates to novel cyclopeptides of the formula I cyclo-(Arg-B-Asp-D-E) I in which B, D and E have the meaning given in Claim 1, and their salts. These compounds act as integrin inhibitors and can be used in particular for the prophylaxis and treatment of disorders of the circulation and in tumour therapy.



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Abstract

The invention relates to novel cyclopeptides of the formula I

cyclo-(Arg-B-Asp-D-E)

I

in which

B, D and E have the meaning given in Claim 1, and their salts.

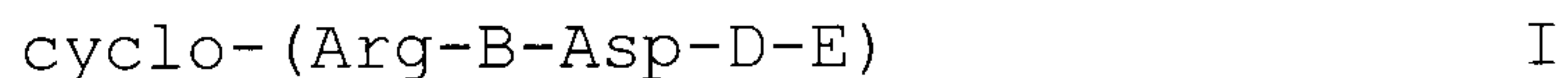
These compounds act as integrin inhibitors and can be used in particular for the prophylaxis and treatment of disorders of the circulation and in tumour therapy.

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Cyclic adhesion inhibitors

The invention relates to novel cyclopeptides of the formula I



5 in which

B is Gly, Ala, -HN-Q-CO- and

D and E in each case independently of one another are Gly, -HN-Q-CO-, Ala, Asn, Asp, Asp(OR), Arg, Cha, Cys, Gln, Glu, His, Ile, Leu, Lys, Lys(Ac), Lys(AcNH₂), Lys(AcSH),
10 Met, Nal, Nle, Orn, Phe, 4-Hal-Phe, Phg, Pro, Pya, Ser, Thr, Tia, Tic, Trp, Tyr or Val, where the said amino acid radicals can also be derivatized,

R is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I,

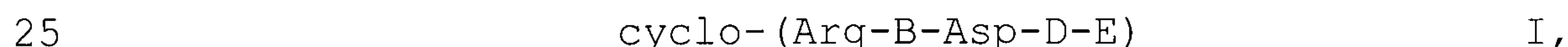
15 Q is alkylene having 1-6 C atoms and

Ac is alkanoyl having 1-10 C atoms,

where, if it is a case of radicals of optically active amino acids and amino acids derivatives, both the D and the L forms are included, and also their physiologically
20 acceptable salts.

Similar compounds are known from Pharmazie 40 (8), 532-5, (1985).

According to one aspect of the present invention, there is provided a cyclopeptide compound of formula I



wherein:

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B is Gly, Ala, or -HN-Q-CO-;

D is Phe, 4-Hal-Phe, Nal, or Phg;

E is Gly, Ala, Lys, Lys(Ac), Lys(AcNH₂), or
Lys(AcSH);

5 Hal is F, Cl, Br, or I;

Q is alkylene having 1-6 C atoms; and

Ac is alkanoyl having 1-10 C atoms,

wherein critically active amino acids or amino acid
derivatives can be in either the D or L form, or a
10 physiologically acceptable salt thereof, with the proviso
that said compound is not cyclo-(Arg-Gly-Asp-Phe-Val) or
cyclo-(Arg-Ala-Asp-Phe-Val) in which optically active amino
acids can be in either the D or L form.

According to another aspect of the present
15 invention, there is provided a cyclopeptide compound of
formula I

cyclo-(Arg-B-Asp-D-E)

wherein

B is Gly, Ala, or -NH-Q-CO-;

20 D is Nal, Phe, 4-Hal-Phe, or Phg;

E is Gly, Ala, Lys, Lys(Ac), Lys(AcNH₂), or
Lys(AcSH);

Hal is F, Cl, Br, or I;

Q is alkylene having 1-6 C atoms; and

25 Ac is alkanoyl having 1-10 C atoms,

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- 1b -

or a physiologically acceptable salt thereof, with the proviso that said compound is not cyclo-(Arg-Gly-Asp-Phe-Val) or cyclo-(Arg-Ala-Asp-Phe-Val), in which optically active amino acids can be either the D or L form for
5 prophylaxis or treatment of cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

The object of the invention was to find novel compounds having useful properties, in particular those
10 which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their salts have very useful properties. In particular, they act as integrin inhibitors, in which case they particularly inhibit the interactions of β_3 - or β_5 -
15 integrin receptors with ligands. The compounds are particularly effective in the case of the integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_{IIb}\beta_3$. This action can be demonstrated, for

example, by the method which is described by J. W. Smith
et al. in J. Biol. Chem. 265, 12267-12271 (1990). In
addition, there are anti-inflammatory effects. All these
actions can be demonstrated with the aid of methods which
5 are known from the literature.

The compounds can be employed as pharmaceutical
active compounds in human and veterinary medicine, in
particular for the prophylaxis and the treatment of
disorders of the circulation, thrombosis, cardiac
10 infarct, arteriosclerosis, inflammations, apoplexy,
angina pectoris, tumour disorders, osteolytic disorders,
in particular osteoporosis, angiogenesis and restenosis
after angioplasty. The compounds may furthermore be
employed to improve the healing of wounds.

15 The compounds are also suitable as antimicrobial agents
which avoid infections as they were caused for example
by bacteria, fungi or yeasts. The substances are useful
as accompanying antimicrobial agents in cases where
operations are effected in order to insert non-corporal
20 materials, for example such as biomaterials, implants,
catheters or heart-pacemakers. They act as antiseptics.

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The abbreviations of amino acid radicals shown above and below stand for the radicals of the following amino acids:

	Abu	4-aminobutyric acid
5	Aha	6-aminohexanoic acid
	Ala	alanine
	Asn	asparagine
	Asp	aspartic acid
	Asp(OR)	aspartic acid (β -ester)
10	Arg	arginine
	Cha	3-cyclohexylalanine
	Cit	citrulline
	Cys	cysteine
	Dab	2,4-diaminobutyric acid
15	Gln	glutamine
	Glu	glutamic acid
	Gly	glycine
	His	histidine
	Ile	isoleucine
20	Leu	leucine
	Lys	lysine
	Lys(Ac)	N ^ε -alkanoyllysine
	Lys(AcNH ₂)	N ^ε -aminoalkanoyllysine
	Lys(AcSH)	N ^ε -mercaptoalkanoyllysine
25	Met	methionine

	Nal	3-(2-naphthyl)-alanine
	Nle	norleucine
	Orn	ornithine
	Phe	phenylalanine
5	4-Hal-Phe	4-halogenophenylalanine
	Phg	phenylglycine
	Pro	proline
	Pya	3-(2-pyridyl)-alanine
	Ser	serine
10	Tia	3-(2-thienyl)-alanine
	Tic	tetrahydroisoquinoline-3-carboxylic acid
	Thr	threonine
	Trp	tryptophan
	Tyr	tyrosine
15	Val	valine.

In addition, the following have the meanings below:

	BOC	tert-butoxycarbonyl
	CBZ	benzyloxycarbonyl
	DCCI	dicyclohexylcarbodiimide
20	DMF	dimethylformamide
	EDCI	N-ethyl-N'-(3-dimethylaminopropyl)- carbodiimide hydrochloride
	Et	ethyl
	Fmoc	9-fluorenylmethoxycarbonyl
25	HOBt	1-hydroxybenzotriazole
	Me	methyl
	Mtr	4-methoxy-2,3,6-trimethylphenylsulfonyl
	OBu	tert-butyl ester
	OMe	methyl ester
30	OEt	ethyl ester
	POA	phenoxyacetyl
	TBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetra- methyluronium tetrafluoroborate
	TFA	trifluoroacetic acid.

35 If the amino acids mentioned above can occur in several enantiomeric forms, then all these forms and also their mixtures (e.g. the DL-forms) are included above and below, e.g. as constituents of the compounds of the formula I. The amino acids, e.g. as constituents of

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compounds of the formula I, may furthermore be provided with appropriate protective groups known per se.

The invention further relates to a process for the preparation of a compound of the formula I according to Claim 1 or one of its salts, characterized in that it is liberated from one of its functional derivatives by treating with a solvolysing or hydrogenolysing agent, or in that a peptide of the formula II



II

10 in which

Z is -Arg-B-Asp-D-E-
 -B-Asp-D-E-Arg-
 -Asp-D-E-Arg-B-
 -D-E-Arg-B-Asp- or
 15 -E-Arg-B-Asp-D-,

or a reactive derivative of such a peptide is treated with a cyclizing agent, and/or in that a basic or acidic compound of the formula I is converted into one of its salts by treating with an acid or base.

The radicals B, D, E and Z above and below have the meanings given in the formulae I and II, if not expressly stated otherwise.

In the above formulae, alkyl is preferably methyl, ethyl, isopropyl or tert-butyl.

The group B is preferably Gly, but also -HN(-CH₂)₂-CO-, -HN-(CH₂)₃-CO-, -HN-(CH₂)₅-CO or Ala. D is preferably Phe, in particular D-Phe, but also 4-Hal-Phe, particularly 4-I-Phe, and Pro, Tic, Lys, Nal or Phg, the D forms being particularly preferred.

Accordingly, the invention in particular relates to those compounds of the formula I in which at least one of the said radicals has one of the preferred meanings given above.

35 A preferred group of compounds can be expressed by the part formula Ia, which otherwise corresponds to the formula I, but in which

- 5 -

B is Gly, $-\text{HN}-(\text{CH}_2)_2-\text{CO}-$, $-\text{HN}-(\text{CH}_2)_3-\text{CO}-$,
 $-\text{HN}-(\text{CH}_2)_5-\text{CO}-$ or Ala

D is D-Pro, D-Tic, Phe, D-Nal, D-Phg or 4-I-Phe and

E is Val, Lys, Gly, Ala, Phe, Leu, Lys(Ac) or Nle.

5 A further preferred group of compounds can be expressed by the part formula Ib, which otherwise corresponds to the formula I, but in which

B is Gly

D is D-Phe and

10 E is Val, Lys or Gly.

The compounds of the formula I and also the starting materials for their preparation are otherwise prepared by known methods, as are described in the literature (e.g. in the standard works such as
15 Houben-Weyl, Methoden der organischen Chemie, (Methods of Organic Chemistry) Georg-Thieme-Verlag, Stuttgart), in particular under reaction conditions which are known and suitable for the said reactions. In this context, use can also be made of known variants which are not mentioned in
20 more detail here.

The starting substances can also be formed in situ, if desired, such that they are not isolated from the reaction mixture, but immediately reacted further to give the compounds of the formula I.

25 The compounds of the formula I can be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

Preferred starting materials for the solvolysis
30 or hydrogenolysis are those which contain appropriate protected amino and/or hydroxyl groups instead of one or more free amino and/or hydroxyl groups, preferably those which carry an amino protecting group instead of an H atom which is bonded to an N atom, e.g. those which correspond to the formula I, but contain an NHR' group
35 (in which R' is an amino protecting group, e.g. BOC or CBZ) instead of an NH_2 group.

In addition, starting materials are preferred which carry a hydroxyl protecting group instead of the

H atom of a hydroxyl group, e.g. those which correspond to the formula I, but contain an R''O-phenyl group (in which R'' is a hydroxyl protecting group) instead of a hydroxyphenyl group.

5 Several - identical or different - protected amino and/or hydroxyl groups can be present in the molecule of the starting material. If the protective groups present are different from one another, in many cases they can be removed selectively.

10 The expression "amino protecting group" is generally known and relates to groups which are suitable for protecting (for blocking) an amino group from chemical reactions, but which are easily removable, after the desired chemical reaction has been carried out at other
15 positions in the molecule. Typical groups of this type are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. As the amino protecting groups are removed after the desired reaction (or reaction sequence), their nature and size is
20 otherwise not critical; but those having 1-20, in particular 1-8, C atoms are preferred. The expression "acyl group" is to be taken in its widest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or
25 heterocyclic carboxylic acids or sulfonic acids and in particular alkoxycarbonyl, aryloxycarbonyl and, above all, aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl or butyryl; aralkanoyl such as phenylacetyl; aroyl such as
30 benzoyl or toluyyl; aryloxyalkanoyl such as POA; alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC, 2-iodoethoxycarbonyl; aralkyloxycarbonyl such as CBZ ("carbobenzoxo"), 4-methoxybenzyloxycarbonyl, FMOC, and arylsulfonyl such as
35 Mtr. Preferred amino protecting groups are BOC and Mtr, and in addition CBZ, FMOC, benzyl and acetyl.

The expression "hydroxy protecting group" is also generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions,

but which are easily removable, after the desired chemical reaction has been carried out at other positions in the molecule. Typical groups of this type are the above-mentioned unsubstituted or substituted aryl, aralkyl or acyl groups, and in addition also alkyl groups. The nature and size of the hydroxy protecting groups is not critical, as they are removed again after the desired chemical reaction or reaction sequence; preferred groups are those having 1-20, in particular 1-10 C atoms. Examples of hydroxyl protecting groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, benzyl and tert-butyl being particularly preferred. The COOH groups in aspartic acid and glutamic acid are preferably protected in the form of their tert-butyl esters (e.g. Asp (OBut)).

The functional derivatives of the compounds of the formula I to be used as starting materials can be prepared by customary methods of amino acid and peptide synthesis, such as are described e.g. in the standard works and patent applications mentioned, and e.g. also by the Merrifield solid phase method (B.F. Gysin and R.B. Merrifield, J. Am. Chem. Soc. 94, 3102 et seq. (1972)).

The liberation of the compounds of the formula I from their functional derivatives is carried out - depending on the protecting group used - e.g. with strong acids, preferably with TFA or perchloric acid, but also with other strong inorganic acids such as hydrochloric acid or sulfuric acid, or strong organic carboxylic acids such as trichloroacetic acid or sulfonic acids such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran or dioxane, amides such as DMF, halogenated hydrocarbons such as dichloromethane, and in addition also alcohols such as methanol, ethanol or isopropanol and also water.

In addition, mixtures of the abovementioned solvents are suitable. TFA is preferably used in an

excess without addition of a further solvent, perchloric acid in the form of a mixture of acetic acid and 70 % perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are preferably between about 0 and about 50°, preferably between 15 and 30° (room temperature).

The groups BOC, OBut and Mtr can be removed e.g. preferably using TFA in dichloromethane or with about 3 to 5 N HCl in dioxane at 15-30°, the FMOC group using an about 5- to 50 % solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

Protecting groups which can be removed by hydrogenolysis (e.g. CBZ or benzyl) can be removed, e.g. by treating with hydrogen in the presence of a catalyst (e.g. a noble metal catalyst such as palladium, preferably on a carrier such as carbon). Suitable solvents in this case are those mentioned above, in particular e.g. alcohols such as methanol or ethanol or amides such as DMF. The hydrogenolysis is carried out, as a rule, at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group is easily carried out e.g. on 5 to 10 % Pd-C in methanol or using ammonium formate (instead of H₂) on Pd-C in methanol/DMF at 20-30°.

Compounds of the formula I can also be obtained by cyclization of compounds of the formula II under the conditions of a peptide synthesis. In this case, the reaction is preferably carried out by customary methods of peptide synthesis, as are described e.g. in Houben-Weyl, loc cit. volume 15/II, pages 1 to 806 (1974).

The reaction is preferably carried out in the presence of a dehydrating agent, e.g. a carbodiimide such as DCCI or EDCI, and in addition propanephosphonic anhydride (compare Angew. Chem. 92, 129 (1980)), diphenylphosphoryl azide or 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, e.g. a halogenated hydrocarbon such as dichloromethane, an ether such as tetrahydrofuran or dioxane, an amide such as DMF or

dimethylacetamide, a nitrile such as acetonitrile, or in mixtures of these solvents, at temperatures between about -10 and 40, preferably between 0 and 30°. In order to promote intramolecular cyclization before intermolecular peptide bonding, it is preferable to work in dilute solutions (dilution principle).

Instead of II, suitable reactive derivatives of these substances can also be employed in the reaction, e.g. those in which reactive groups are intermediately blocked by protecting groups. The amino acid derivatives II can be used e.g. in the form of their activated esters which are preferably formed in situ, e.g. by addition of HOBt or N-hydroxysuccinimide.

The starting materials of the formula II are, as a rule, novel. They can be prepared by known methods, e.g. the abovementioned methods of peptide synthesis and of removal of protective groups.

As a rule, protected pentapeptide esters of the formula $R'-Z-OR''$, e.g. BOC-Z-OMe or BOC-Z-OEt, are initially synthesized, which are first hydrolyzed to give acids of the formula $R'-Z-OH$, e.g. BOC-Z-OH; the protective group R' is removed from these, by means of which the free peptides of the formula $H-Z-OH$ (II) are obtained.

A base of the formula I can be converted into the appropriate acid addition salt using an acid. Suitable acids for this reaction are in particular those which yield physiologically acceptable salts. Inorganic acids can thus be used, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid and sulfamic acid, and in addition organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2- or 3-phenylpropionic acid, citric

acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthal-
5 ene-mono- and -disulfonic acids, and laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, an acid of the formula I can
10 be converted into one of its physiologically acceptable metal or ammonium salts by reaction with a base. Suitable salts here are in particular the sodium, potassium, magnesium, calcium and ammonium salts, and also substituted ammonium salts, e.g. the dimethyl-, diethyl-
15 or diisopropylammonium salts, monoethanol-, diethanol- or triethanolammonium salts, cyclohexyl- or dicyclohexylammonium salts, dibenzylethylenediammonium salts, and furthermore e.g. salts with N-methyl-D-glucamine or with arginine or lysine.

20 The novel compounds of the formula I and their physiologically acceptable salts can be used for the production of pharmaceutical preparations by bringing them into a suitable dosage form together with at least one excipient or auxiliary and, if desired, together with
25 one or more other active compound(s). The preparations thus obtained can be employed as medicaments in human or veterinary medicine. Suitable excipient substances are organic or inorganic substances which are suitable for enteral (e.g. oral or rectal), parenteral (e.g.
30 intravenous injection) or local (e.g. topical, dermal, ophthalmic or nasal) administration or for administration in the form of an inhalant spray and which do not react with the novel compounds, for example water or aqueous isotonic saline solution, lower alcohols, vegetable oils,
35 benzyl alcohols, polyethylene glycols, glycerol triacetate and other fatty acid glycerides, gelatin, soya lecithin, carbohydrates such as lactose or starch, magnesium stearate, talc, cellulose and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices or

drops, in particular, are used for oral administration; film tablets and capsules having enteric coatings or capsule shells are especially of interest. Suppositories are used for rectal administration, and solutions, preferably oily or aqueous solutions, and in addition suspensions, emulsions or implants, are used for parenteral administration. Solutions, e.g., which can be used in the form of eye drops, and in addition, e.g. suspensions, emulsions, creams, ointments or compresses are suitable for topical application. Sprays can be used which contain the active compound either dissolved or suspended in a propellant gas or propellant gas mixture (e.g. CO₂ or chlorofluorohydrocarbons) for administration as inhalant sprays. The active compound here is preferably used in micronized form, it being possible for one or more additional physiologically tolerable solvents to be present, e.g. ethanol. Inhalant solutions can be administered with the aid of customary inhalers. The novel compounds can also be lyophilized and the lyophilizates obtained used e.g. for the production of injection preparations. The injections can be administered as a bolus or as a continuous infusion (e.g. intravenous, intramuscular, subcutaneous or intrathecal). The preparations indicated can be sterilized and/or can contain auxiliaries such as preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing osmotic pressure, buffer substances, colorants and/or flavourings. If desired, they can also contain one or more other active compounds, e.g. one or more vitamins.

The substances according to the invention can as a rule be administered in analogy to other known commercially available peptides, but in particular in analogy to the compounds described in US-A-4,472,305, preferably in dosages between about 0.05 and 500, in particular between 0.5 and 100 mg per dosage unit. The daily dose is preferably between about 0.01 and 2 mg/kg of body weight. The specific dose for each intended patient depends, however, on many different factors, for example the activity of the specific compound employed,

the age, body weight, general state of health, sex, the diet, the time and route of administration, and the rate of excretion, pharmaceutical combination and severity of the particular disorder to which the therapy applies.

5 Parenteral administration is preferred.

In addition, the novel compounds of the formula I can be used as integrin ligands for the preparation of columns for affinity chromatography for the preparation of integrins in pure form.

10 The ligand, i.e. a peptide derivative of the formula I, is in this case covalently coupled to a polymeric support via anchor functions.

Suitable polymeric support materials are the polymeric solid phases known per se in peptide chemistry, 15 having preferably hydrophilic properties, for example crosslinked polysugars, such as cellulose, Sepharose or Sephadex®, acrylamides, polymers based on polyethylene glycol or Tentakel polymers®.

Suitable anchor functions which are linked to the 20 polymeric supports are preferably linear alkylene chains having 2-12 C atoms, which are bonded directly to the polymer at one end and have a functional group, such as e.g. hydroxyl, amino, mercapto, maleimido or -COOH at the other end and are suitable to be linked to the C- or N- 25 terminal section of the respective peptide.

It is possible in this case that the peptide be bonded directly or likewise via a second anchor function to the anchor of the polymer. It is also possible that peptides which contain amino acid radicals with 30 functionalized side chains are bonded to the anchor function of the polymer via these.

Moreover, certain amino acid radicals which are a constituent of the peptides of the formula I can be modified in their side chains in such a way that they are 35 available for anchorage via e.g. SH, OH, NH₂ or COOH groups with the anchor of the polymer.

In this connection, unusual amino acids are possible, such as e.g. phenylalanine derivatives which carry a mercapto, hydroxyl, amino or carboxyalkyl chain

in position 4 of the phenyl ring, the functional group being located at the end of the chain.

Examples of amino acid radicals whose side chain can be used directly as an anchor function are e.g. Lys, Orn, Arg, Dab, Asp, Asn, Glu, Gln, Ser, Thr, Cys, Cit or Tyr.

Examples of N-terminal anchors are radicals such as e.g. $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{NH}_2$, $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{OH}$, $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{SH}$ or $-\text{CO}-\text{C}_n\text{H}_{2n}-\text{COOH}$, where $n = 2-12$, the length of the alkylene chain not being critical and it optionally also being possible to replace this e.g. by appropriate aryl or alkylaryl radicals.

C-terminal anchors can be, for example, $-\text{O}-\text{C}_n\text{H}_{2n}-\text{SH}$, $-\text{O}-\text{C}_n\text{H}_{2n}-\text{OH}$, $-\text{O}-\text{C}_n\text{H}_{2n}-\text{NH}_2$, $-\text{O}-\text{C}_n\text{H}_{2n}-\text{COOH}$, $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{SH}$, $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{OH}$, $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{NH}_2$ or $-\text{NH}-\text{C}_n\text{H}_{2n}-\text{COOH}$, what has already been said in the preceding section applying to n and also to the alkylene chain.

The N- and C-terminal anchors can also be used as anchor components for an already functionalized side chain of an amino acid radical. Suitable amino acid radicals here, for example, are those such as Lys($\text{CO}-\text{C}_5\text{H}_{10}-\text{NH}_2$), Asp($\text{NH}-\text{C}_3\text{H}_6-\text{COOH}$) or Cys($\text{C}_3\text{H}_6-\text{NH}_2$), the anchor always being bonded to the functional group of the side chain.

The preparation of the materials for affinity chromatography for purifying integrins is carried out under conditions such as are customary for the condensation of amino acids and are known per se and have already been outlined in the section for the preparation of the compounds of the formula I.

All temperatures above and below are stated in °C. In the following examples, "customary working up" means: water is added, if necessary, the mixture is neutralized and extracted with ether or dichloromethane, the organic phase is separated off, dried over sodium sulfate, filtered and evaporated and the residue is purified by chromatography on silica gel and/or crystallization. RT = retention time (minutes) for HPLC on a Lichrosorb RP select B (250-4.7 μm) column, eluent: 0.3 %

TFA in water; isopropanol gradient of 0-80 vol% in 50 min at 1 ml/min. Flow and detection at 215 nm. M^+ = molecular peak in the mass spectrum, obtained by the fast atom bombardment method.

5 Example 1

A solution of 0.2 g of H-Arg-Gly-Asp-D-Pro-Val-ONa [e.g. obtainable from Fmoc-Arg-Gly-Asp-D-Pro-Val-O-Wang, -O-Wang being the radical of a 4-oxymethylphenoxymethyl polystyrene resin used in the modified Merrifield techniques, by removal of the Fmoc group with piperidine/DMF and removal of the resin with TFA/ CH_2Cl_2 (1:1)] in 15 ml of DMF is diluted with 85 ml of dichloromethane and is treated with 50 mg of NaHCO_3 . After cooling in a dry ice/acetone mixture, 40 μl of diphenylphosphoryl azide are added. After standing at room temperature for 16 hours, the solution is concentrated. The concentrate is gel filtered (Sephadex G10 column in isopropanol/water 8:2) and then purified by means of HPLC in the customary manner. Cyclo-(Arg-Gly-Asp-D-Pro-Val) is obtained; RT = 13.4; M^+ 525.

The following are obtained analogously by cyclization of the corresponding linear peptides:

cyclo-(Arg-Gly-Asp-D-Tic-Val); RT = 18.4; M^+ 587;
 cyclo-(Arg-Gly-Asp-D-Phe-Val); M^+ 575;
 25 cyclo-(Arg-Gly-Asp-D-Lys-Val); RT = 6.8; M^+ 556;
 cyclo-(Arg-Gly-Asp-D-Phe-Lys); RT = 10.9; M^+ 604;
 cyclo-(Arg-Gly-Asp-D-Phe-Gly); RT = 13.1; M^+ 533;
 cyclo-(Arg-Gly-Asp-D-Phe-Ala); RT = 14.3; M^+ 547;
 cyclo-(Arg-Gly-Asp-D-Phe-Phe); RT = 22.0; M^+ 623;
 30 cyclo-(Arg-Gly-Asp-D-Phe-Leu); RT = 21.2; M^+ 589;
 cyclo-(Arg-Gly-Asp-D-Nal-Val); RT = 24.7; M^+ 625;
 cyclo-(Arg-Gly-Asp-D-Phg-Val); RT = 16.5; M^+ 561;
 cyclo-(Arg-Gly-Asp-Phe-Gly); RT = 13.2; M^+ 533;
 cyclo-(Arg-Gly-Asp-Phe-D-Ala); RT = 14.8; M^+ 547;
 35 cyclo-(Arg-Gly-Asp-Phe-D-Phe); RT = 20.2; M^+ 623;
 cyclo-(Arg-Gly-Asp-Phe-D-Leu); RT = 21.4; M^+ 589;
 cyclo-(Arg(Mtr)-Gly-Asp-D-Phe-Lys); RT = 23.4; M^+ 816;

- cyclo-(Arg-Gly-Asp-D-Phe-Lys(H₃C-CO)); RT = 17.0; M⁺ 646;
 cyclo-(Arg(Mtr)-β-Ala-Asp-Phe-D-Val); RT = 28.2; M⁺ 801;
 cyclo-(Arg-Gly-Asp-D-Phe-Nle); RT = 22.0; M⁺ 589;
 cyclo-(D-Arg-Gly-D-Asp-D-Phe-Val); RT = 17.5; M⁺ 575;
 5 cyclo-(Arg-Gly-D-Asp-D-Phe-D-Gly); RT = 18.7; M⁺ 575;
 cyclo-(Arg-D-Ala-Asp-D-Phe-Val); RT = 18.9; M⁺ 589;
 cyclo-(Arg-D-Ala-Asp-Phe-D-Val); RT = 19.1; M⁺ 589;
 cyclo-(Arg-Aha-Asp-D-Phe-Val); RT = 20.8; M⁺ 631;
 cyclo-(Arg-Abu-Asp-Phe-D-Val); RT = 17.2; M⁺ 603;
 10 cyclo-(Arg-Aha-Asp-Phe-D-Val); RT = 19.8; M⁺ 631;
 cyclo-(Arg-Abu-Asp-D-Phe-Val); RT = 17.8; M⁺ 603;
 cyclo-(Arg-Gly-Asp-D-(4-I-Phe)-Val); RT = 23.3; M⁺ 701;
 cyclo-(Arg-Gly-Asp-Phe-Val); RT = 21.8; M⁺ 575;
 cyclo-(Arg-Gly-D-Asp-D-Phe-Val); RT = 20.7; M⁺ 575;
 15 cyclo-(D-Arg-Gly-Asp-Phe-D-Val); RT = 20.8; M⁺ 575;
 cyclo-(D-Arg-Gly-Asp-D-Phe-Val); RT = 21.9; M⁺ 575;
 cyclo-(Arg-Gly-D-Asp-D-Phe-Val); RT = 20.7; M⁺ 575;
 cyclo-(Arg-Gly-Asp-Phe-D-Nal);
 cyclo-(Arg-Gly-Asp-Phe-D-Leu);
 20 cyclo-(Arg-Gly-Asp-Phe-D-Ser);
 cyclo-(Arg-Gly-Asp-D-Nal-Leu);
 cyclo-(Arg-Gly-Asp-Nal-D-Val);
 cyclo-(Arg-Gly-Asp-Phg-D-Val);
 cyclo-(Arg-Gly-Asp-Trp-D-Val);
 25 cyclo-(Arg-Gly-Asp-Ala(2-thienyl)-D-Val);
 cyclo-(Arg-Gly-Asp-Lys-D-Val);
 cyclo-(Arg-Gly-Asp-(4-NO₂-Phe)-D-Val);
 cyclo-(Arg-Gly-Asp-Cha-D-Val);
 cyclo-(Arg-Gly-Asp-D-Phe-β-Ala);
 30 cyclo-(Arg-Gly-Asp-D-Phe-Abu);
 cyclo-(Arg-Gly-Asp-D-Phe-Aha);
 cyclo-(Arg-Gly-Asp-D-Phe-Lys);
 cyclo-(Arg-Gly-Asp-D-Phe-Pro);
 cyclo-(Arg-Gly-Asp-D-Phe-Arg);
 35 cyclo-(Arg-Gly-Asp-D-Phe-Lys(Aha));
 cyclo-(Arg-Gly-Asp-D-Phe-Nal);
 cyclo-(Arg-Gly-Asp-D-Phe-Ser);
 cyclo-(D-Arg(Mtr)-Gly-Asp(OBut)-D-Phe-Val);
 cyclo-(Arg(Mtr)-Gly-D-Asp(OEt)-D-Phe-Val);

- cyclo-(Arg(Mtr)-Gly-Asp-Phe-D-Nal);
 cyclo-(Arg(Mtr)-Gly-Asp-Phe-D-Leu);
 cyclo-(Arg(Mtr)-Gly-Asp-Phe-D-Ser);
 cyclo-(Arg(Mtr)-Gly-Asp-D-Nal-Leu);
 5 cyclo-(Arg(Mtr)-Gly-Asp-Nal-D-Val);
 cyclo-(Arg(Mtr)-Gly-Asp-Phg-D-Val);
 cyclo-(Arg(Mtr)-Gly-Asp-Trp-D-Val);
 cyclo-(Arg-Gly-Asp-D-Phe-Lys(BOC-Aha);
 cyclo-(Arg-Gly-Asp-D-Phe-Lys(CO-CH₂SH));
 10 cyclo-(Arg-Gly-Asp-D-Phe-Lys(CO-(CH₂)₂SH));
 cyclo-(Arg-Gly-Asp-D-Phe-Lys(CO-(CH₂)₃SH));
 cyclo-(Arg-Gly-Asp-D-Phe-Lys(CO-(CH₂)₄SH));
 cyclo-(Arg-Gly-Asp-D-Phe-Lys(CO-(CH₂)₅SH));
 cyclo-(Arg-Gly-Asp-D-Tyr-Val);
 15 cyclo-(Arg-Gly-Asp-D-(4-Cl-Phe)-Val);
 cyclo-(Arg-Gly-Asp-D-Pya-Val);
 cyclo-(Arg-Gly-Asp-D-NMe-Phe-Val);
 cyclo-(Arg-Gly-Asp-D-Tyr(OEt)-Val);
 cyclo-(Arg-Gly-Asp-D-Arg-Val);
 20 cyclo-(Arg-Gly-Asp-D-Trp-Val);
 cyclo-(Arg-Gly-Asp-D-Ala(2-thienyl)-Val);
 cyclo-(Arg-Gly-Asp-D-Tyr-NMe-Val);
 cyclo-(Arg-Gly-D-Asp-D-Phe-Val);
 cyclo-(Arg-Gly-D-Asp-Phe-D-Val);
 25 cyclo-(D-Arg-Gly-Asp-Phe-D-Val);
 cyclo-(D-Arg-Gly-D-Asp-Phe-Val).

Example 2

- A solution of 0.28 g of cyclo-(Arg(Mtr)-β-Ala-Asp-Phe-D-Val) [obtainable by cyclization according to
 30 Ex. 1] in 8.4 ml of TFA, 1.7 ml of dichloromethane and 0.9 ml of thiophenol is allowed to stand at room temperature for 4 hours, then concentrated and, after diluting with water, freeze-dried. Gel filtration on Sephadex G 10 (acetic acid/water 1:1) and subsequent
 35 purification by preparative HPLC under the conditions indicated give cyclo-(Arg-β-Ala-Asp-Phe-D-Val); RT = 17.0; M⁺ 589.

The following are obtained analogously:

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from cyclo-(Arg(Mtr)-Gly-Asp-D-Phe-Lys):
cyclo-(Arg-Gly-Asp-D-Phe-Lys); RT = 10.9; M⁺ 604

from cyclo-(D-Arg(Mtr)-Gly-Asp(OBut)-D-Phe-Val):
cyclo-(D-Arg-Gly-Asp-D-Phe-Val);

5 from cyclo-(Arg(Mtr)-Gly-D-Asp(OEt)-D-Phe-Val):
cyclo-(Arg-Gly-D-Asp-D-Phe-Val);

from cyclo-(Arg(Mtr)-Gly-Asp-Phe-D-Nal);
cyclo-(Arg-Gly-Asp-Phe-D-Nal);

10 from cyclo-(Arg(Mtr)-Gly-Asp-Phe-D-Leu):
cyclo-(Arg-Gly-Asp-Phe-D-Leu);

from cyclo-(Arg(Mtr)-Gly-Asp-Phe-D-Ser):
cyclo-(Arg-Gly-Asp-Phe-D-Ser);

from cyclo-(Arg(Mtr)-Gly-Asp-D-Nal-Leu):
cyclo-(Arg-Gly-Asp-D-Nal-Leu);

15 from cyclo-(Arg(Mtr)-Gly-Asp-Nal-D-Val):
cyclo-(Arg-Gly-Asp-Nal-D-Val);

from cyclo-(Arg(Mtr)-Gly-Asp-Phg-D-Val):
cyclo-(Arg-Gly-Asp-Phg-D-Val);

20 from cyclo-(Arg(Mtr)-Gly-Asp-Trp-D-Val):
cyclo-(Arg-Gly-Asp-Trp-D-Val).

Example 3

80 mg of cyclo-(Arg-Gly-Asp-D-Phe-Leu) are dissolved in 0.01 M HCl five to six times and freeze-dried after each dissolving operation. Subsequent
25 purification by HPLC gives cyclo-(Arg-Gly-Asp-D-Phe-Leu) . HCl; RT = 20.6; M⁺ 589.

The following are obtained analogously

from cyclo-(Arg-Gly-Asp-D-Phe-Val):

cyclo-(Arg-Gly-Asp-D-Phe-Val) . HCl; RT = 18.4;
M⁺ 575;

5 from cyclo-(Arg-Gly-Asp-D-Phe-Leu):

cyclo-(Arg-Gly-Asp-D-Phe-Leu) . HCl;

from cyclo-(Arg-Gly-Asp-D-Phe-Leu) by treatment with
acetic acid:

10 cyclo-(Arg-Gly-Asp-D-Phe-Leu) . H₃C-COOH; RT = 19.2;
M⁺ 589;

from cyclo-(Arg-Gly-Asp-D-Phe-Leu) by treatment with
nitric acid:

cyclo-(Arg-Gly-Asp-D-Phe-Leu) . HNO₃; RT = 20.4;
M⁺ 589;

15 Example 4

To prepare affinity phases, 0.9 g of N-maleimido-(CH₂)₅-CO-NH-(CH₂)₅-polymer [obtainable by condensation of N-maleimido-(CH₂)₅-COOH with H₂N-(CH₂)₅-polymer] is suspended in 10 ml of 0.1 M sodium phosphate buffer at pH 7 and 1 equivalent of cyclo-(Arg-Gly-Asp-D-Phe-Lys(CO(CH₂)₅SH) is added at 4°. The reaction mixture is stirred for 4 hours with simultaneous warming to room temperature, and the solid residue is filtered off and washed twice with 10 ml each of buffer solution (pH 7) and then three times with 10 ml each of water. cyclo-(Arg-Gly-Asp-D-Phe-Lys(CO(CH₂)₅S-3-(N-maleimido-(CH₂)₅-CONH-(CH₂)₅-polymer)) is obtained.

Example 5

30 Analogously to Example 1, the following polymeric phase is obtained by condensation of polymer-O-(CH₂)₅-NH₂ [commercially available] and cyclo-(Arg-Gly-Asp-D-Pro-Lys(CO(CH₂)₅COOH) [obtainable by condensation of adipic acid with cyclo-(Arg-Gly-Asp-D-Pro-Lys) under the

conditions mentioned]:

cyclo-(Arg-Gly-Asp-D-Pro-Lys-(CO-(CH₂)₄-CO-NH-(CH₂)₃-O-polymer)

5 The following are obtained analogously by condensation of

cyclo-(Arg-Gly-Asp-D-Phe-Lys-(CO-(CH₂)₅-NH₂)) with HOOC-CH₂-O-polymer:

cyclo-(Arg-Gly-Asp-D-Phe-Lys-(CO-(CH₂)₅-NH-CO-CH₂-O-polymer)).

10 The examples below relate to pharmaceutical preparations.

Example A: Injection vials

15 A solution of 100 g of a cyclopeptide of the formula I and 5 g of disodium hydrogenphosphate in 3l of doubly distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile filtered, filled into injection vials and lyophilized under sterile conditions, and the vials are sealed in a sterile manner. Each injection vial contains 5 mg of active compound.

20 Example B: Suppositories

A mixture of 20 g of active compound of the formula I is fused with 100 g of soya lecithin and 1400 g of cocoa butter, and the mixture is poured into moulds and allowed to cool. Each suppository contains 20 mg of
25 active compound.

Example C: Solution

30 A solution of 1 g of active compound of the formula I, 9.38 g of NaH₂PO₄·2H₂O, 28.48 g of Na₂HPO₄·12H₂O and 0.1 g of benzalkonium chloride is prepared in 940 ml of doubly distilled water. The solution is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

5 Example E: Tablets

A mixture of 100 g of a cyclopeptide of the formula I, 1 kg of lactose, 600 g of microcrystalline cellulose, 600 g of maize starch, 100 g of polyvinylpyrrolidone, 80 g of talc and 10 g of magnesium stearate is pressed to give tablets in a customary manner, such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

15 Tablets are pressed as stated in Example E and then coated in a customary manner with a coating of sucrose, maize starch, talc, tragacanth and colorant.

Example G: Capsules

Hard gelatin capsules are filled with an active compound of the formula I in the customary manner, so
20 that each capsule contains 5 mg of active compound.

Example H: Inhalation spray

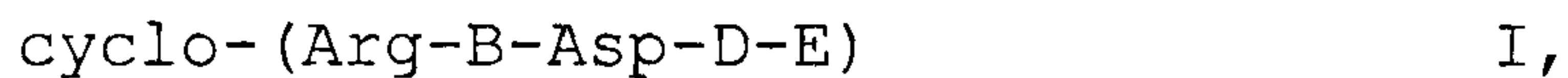
14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is filled into commercially available spray
25 containers having a pump mechanism. The solution can be sprayed into the mouth or nose. One spray burst (about 0.1 ml) corresponds to a dose of about 0.14 mg.

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CLAIMS:

1. A cyclopeptide compound of formula I



wherein:

5 B is Gly, Ala, or -HN-Q-CO-;

D is Phe, 4-Hal-Phe, Nal, or Phg;

E is Gly, Ala, Lys, Lys(Ac), Lys(AcNH₂), or
Lys(AcSH);

Hal is F, Cl, Br, or I;

10 Q is alkylene having 1-6 C atoms; and

Ac is alkanoyl having 1-10 C atoms,

wherein critically active amino acids or amino acid
derivatives can be in either the D or L form, or a
physiologically acceptable salt thereof, with the proviso
15 that said compound is not cyclo-(Arg-Gly-Asp-Phe-Val) or
cyclo-(Arg-Ala-Asp-Phe-Val) in which optically active amino
acids can be in either the D or L form.

2. A compound or salt according to claim 1, wherein B
is Gly, -NH-(CH₂)₂-CO-, -NH-(CH₂)₃-CO-, -NH-(CH₂)₅-CO-, or
20 Ala.

3. A compound or salt according to claim 1 or
claim 2, wherein D is D-Phe or 4-I-Phe.

4. A compound or salt according to claim 1, wherein B
is Gly, -HN-(CH₂)₂-CO-, -HN-(CH₂)₃-CO-, -HN-(CH₂)₅-CO-, or
25 Ala; D is Phe, D-Nal, D-Phg, or 4-I-Phe; and E is Lys, Gly,
Ala, or Lys(Ac).

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5. A compound or salt according to claim 1, wherein B is Gly; D is D-Phe; and E is Lys or Gly.
6. A compound or salt according to claim 1, wherein B is Gly and D is D-Phe.
- 5 7. A compound or salt according to any one of claims 1 to 3 and 6, wherein E is Lys, Gly, Ala, or Lys(AcSH).
8. Cyclo-(Arg-Gly-Asp-D-Phe-Gly) or a physiologically acceptable salt thereof.
- 10 9. Cyclo-(Arg-Gly-Asp-D-Phe-Lys) or a physiologically acceptable salt thereof.
10. Cyclo-(Arg-Gly-Asp-D-Phe-Phe) or a physiologically acceptable salt thereof.
11. Cyclo-(Arg-Gly-Asp-Phe-Gly) (SEQ ID NO:1) or a
15 physiologically acceptable salt thereof.
12. A pharmaceutical composition comprising a compound or salt of any one of claims 1 to 11, and a pharmaceutically acceptable carrier.
13. A composition according to claim 12, wherein said
20 composition contains 0.05-500 mg of said compound or salt.
14. A composition according to claim 12, wherein said composition contains 0.5-100 mg of said compound or salt.
15. A composition according to any one of claims 12 to 14 for treatment of thrombosis.
- 25 16. A composition according to any one of claims 12 to 14 for inhibition of binding of a ligand to a β -3 integrin receptor.

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17. A use of a compound or salt according to any one of claims 1 to 11 in manufacture of a composition for treating thrombosis.

18. A use of a compound or salt according to any one
5 of claims 1 to 11 in manufacture of a composition for inhibition of binding of a ligand to a β -3 integrin receptor.

19. A use of a compound or salt according to any one of claims 1 to 11 for treating thrombosis.

10 20. A use of a compound or salt according to any one of claims 1 to 11 for inhibition of binding of a ligand to a β -3 integrin receptor.

21. A method for the purification of integrins by affinity chromatography, comprising introducing a sample
15 containing integrins into a chromatographic column, said column containing a polymeric support to which a compound or salt according to any one of claims 1 to 11 is bonded via an anchor function.

22. A process for the preparation of a compound
20 according to claim 1, said process comprising:

treating with a cyclizing agent a peptide of formula II, H-Z-OH, wherein Z is -Arg-B-Asp-D-E, and B, D and E are as defined in claim 1, and optionally converting a basic or acidic compound of formula I into one of its salts
25 by treatment with an acid or base.

23. A compound according to claim 1, wherein B is Gly.

24. A cyclopeptide compound of formula I

cyclo-(Arg-B-Asp-D-E)

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wherein

B is Gly, Ala, or -NH-Q-CO;

D is Nal, Phe, 4-Hal-Phe, or Phg;

E is Gly, Ala, Lys, Lys(Ac), Lys(AcNH₂), or
5 Lys(AcSH);

Hal is F, Cl, Br, or I;

Q is alkylene having 1-6 C atoms; and

Ac is alkanoyl having 1-10 C atoms,

or a physiologically acceptable salt thereof, with the
10 proviso that said compound is not cyclo-(Arg-Gly-Asp-Phe-
Val) or cyclo-(Arg-Ala-Asp-Phe-Val), in which optically
active amino acids can be either the D or L form for
prophylaxis or treatment of cardiac infarct, arterial
sclerosis, apoplexy, angina pectoris, osteoporosis,
15 angiogenesis, or restenosis after angioplasty.

25. The compound or salt of claim 24, wherein B is
Gly, -NH-(CH₂)₂-CO-, -NH-(CH₂)₃-CO-, -NH-(CH₂)₅-CO-, or Ala.

26. The compound or salt of claim 24 or 25, wherein D
is Phe or 4-Hal-Phe.

20 27. The compound or salt of claim 24 or 25, wherein D
is D-Phe.

28. The compound or salt of claim 24, wherein B is
Gly; D is D-Phe; and E is Lys, or Gly.

29. The compound or salt of claim 24, wherein B is Gly
25 and D is D-Phe.

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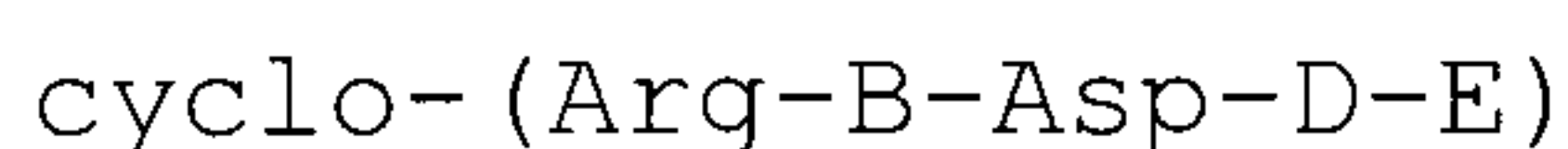
30. The compound or salt of any one of claims 24 to 27 and 29, wherein E is Lys, Gly, or Lys(AcSH).

31. Cyclo-(Arg-Gly-Asp-D-Phe-Lys) or a physiologically acceptable salt thereof, for prophylaxis or treatment of
5 cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

32. Cyclo-(Arg-Gly-Asp-D-Phe-Gly) or a physiologically acceptable salt thereof, for prophylaxis or treatment of
10 cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

33. A compound or salt according to any one of claims 24 to 32, in a dosage form adapted for administration
15 to a patient in an amount of 0.01 to 2 mg/kg body weight of the patient.

34. A use of a cyclopeptide compound of formula I



wherein

20 B is Gly, Ala, or -NH-Q-CO;

D is Nal, Phe, 4-Hal-Phe, or Phg;

E is Gly, Ala, Lys, Lys(Ac), Lys(AcNH₂), or
Lys(AcSH);

Hal is F, Cl, Br, or I;

25 Q is alkylene having 1-6 C atoms; and

Ac is alkanoyl having 1-10 C atoms,

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or a physiologically acceptable salt thereof, with the proviso that said compound is not cyclo-(Arg-Gly-Asp-Phe-Val) or cyclo-(Arg-Ala-Asp-Phe-Val), in which optically active amino acids can be either the D or L form for
5 prophylaxis or treatment of cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

35. The use of claim 34, wherein B is Gly, -NH-(CH₂)₂-CO-, -NH-(CH₂)₃-CO-, -NH-(CH₂)₅-CO-, or Ala.

10 36. The use of claim 34 or 35, wherein D is Phe or 4-Hal-Phe.

37. The use of claim 34 or 35, wherein D is D-Phe.

38. The use of claim 34, wherein B is Gly; D is D-Phe; and E is Lys, or Gly.

15 39. The use of claim 34, wherein B is Gly and D is D-Phe.

40. The use of any one of claims 34 to 37 and 39, wherein E is Lys, Gly, or Lys(AcSH).

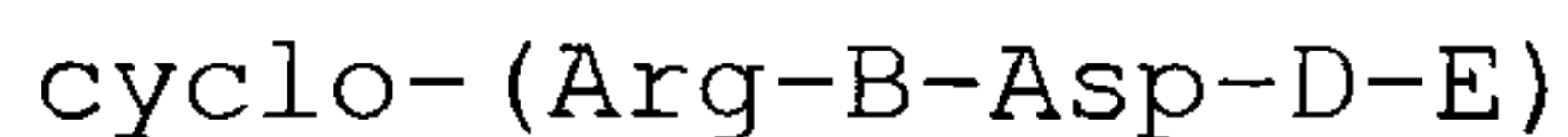
41. A use of cyclo-(Arg-Gly-Asp-D-Phe-Lys) or a
20 physiologically acceptable salt thereof, for prophylaxis or treatment of cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

42. A use of cyclo-(Arg-Gly-Asp-D-Phe-Gly) or a
25 physiologically acceptable salt thereof, for prophylaxis or treatment of cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

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43. A use of a cyclopeptide compound of formula I



wherein

B is Gly, Ala, or $-\text{NH}-\text{Q}-\text{CO}-$;

5 D is Nal, Phe, 4-Hal-Phe, or Phg;

E is Gly, Ala, Lys, Lys(Ac), Lys(AcNH₂), or
Lys(AcSH);

Hal is F, Cl, Br, or I;

Q is alkylene having 1-6 C atoms; and

10 Ac is alkanoyl having 1-10 C atoms,

or a physiologically acceptable salt thereof, with the proviso that said compound is not cyclo-(Arg-Gly-Asp-Phe-Val) or cyclo-(Arg-Ala-Asp-Phe-Val), in which optically active amino acids can be either the D or L form in
15 preparation of a pharmaceutical composition for prophylaxis or treatment of cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

44. The use of claim 43, wherein B is Gly, $-\text{NH}-(\text{CH}_2)_2-$
20 $\text{CO}-$, $-\text{NH}-(\text{CH}_2)_3-\text{CO}-$, $-\text{NH}-(\text{CH}_2)_5-\text{CO}-$, or Ala.

45. The use of claim 43 or 44, wherein D is Phe or 4-Hal-Phe.

46. The use of claim 43 or 44, wherein D is D-Phe.

47. The use of claim 43, wherein B is Gly; D is D-Phe;
25 and E is Lys, or Gly.

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48. The use of claim 43, wherein B is Gly and D is D-Phe.

49. The use of any one of claims 43 to 46 and 48, wherein E is Lys, Gly, or Lys(AcSH).

5 50. A use of cyclo-(Arg-Gly-Asp-D-Phe-Lys) or a physiologically acceptable salt thereof, in manufacture of a pharmaceutical composition for prophylaxis or treatment of cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after
10 angioplasty.

51. A use of cyclo-(Arg-Gly-Asp-D-Phe-Gly) or a physiologically acceptable salt thereof, in manufacture of a pharmaceutical composition for prophylaxis or treatment of cardiac infarct, arterial sclerosis, apoplexy, angina
15 pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.

52. A pharmaceutical composition comprising a compound or salt as defined in any one of claims 24 to 33, with the proviso that said compound or salt is not selected from the
20 group consisting of cyclo-(Arg-Gly-Asp-Phe-Val), cyclo-(Arg-Ala-Asp-Phe-Val), a salt of cyclo-(Arg-Gly-Asp-Phe-Val) and a salt of cyclo-(Arg-Ala-Asp-Phe-Val), in which optically active amino acids can be either the D or L form, and a pharmaceutically acceptable carrier for prophylaxis or
25 treatment of cardiac infarct, arterial sclerosis, apoplexy, angina pectoris, osteoporosis, angiogenesis, or restenosis after angioplasty.