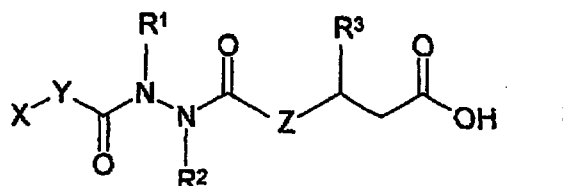


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Diacylhydrazine derivatives

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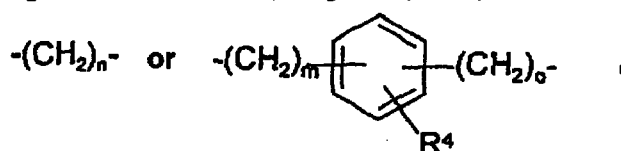
The invention relates to diacylhydrazine derivatives of the formula I



5

in which

X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$, $\text{H}_3\text{C}-\text{C}(=\text{NH})-\text{NH}-$ or $\text{Het}^1-\text{NH}-$,



Y is

- Z is $\text{N}-\text{R}^2$ or $\text{CH}-\text{R}^2$,
- 10 R^1, R^2 are each independently of one another H or A,
- R^3 is H, Ar or Het,
- R^4 is H, A, Ar, OH, OA, OAr, arylalkyl, Hal, CN, NO_2 , CF_3 or OCF_3
- A is alkyl having 1 to 6 carbon atoms,
- 15 Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA, CF_3 , OCF_3 , CN, NO_2 or Hal and which may be substituted by a phenyl which is mono-, di- or trisubstituted by A, OH, OA, CF_3 , OCF_3 , CN, NO_2 or Hal such that
- 20 an unsubstituted or substituted biphenyl is formed or naphthyl which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA, CF_3 , OCF_3 , CN, NO_2 or Hal,
- Hal is F, Cl, Br or I,
- 25 Het is a saturated, partially or fully unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, wherein 1 or 2 nitrogen and/or 1 or 2 sulfur or oxygen atoms may be present and wherein the heterocyclic radical

may be mono- or disubstituted by CN, Hal, OH, OA, CF₃, A, NO₂ or OCF₃,
Het¹ is a 5- or 6-membered aromatic heterocycle
having 1 to 4 nitrogen atoms which may be
5 unsubstituted or mono- or disubstituted by Hal,
A, OA, Ar, OAr, arylalkyl, CN, NO₂, CF₃ or OCF₃,
n is 2, 3, 4, 5 or 6,
m, o are 0, 1 or 2,
and their physiologically acceptable salts and
10 solvates.

Partially similar compounds are known from EP 0 632 016,
WO 97/26250, WO 97/24124 or DE 198 31 710.

- 15 The invention was based on the object of discovering novel compounds having valuable properties, in particular those which can be used for preparing medicaments.
- 20 It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties, coupled with a good tolerability. Above all, they act as integrin inhibitors, and in particular inhibit the interactions of the α v-, β 3-, β 5- or β 6-
- 25 integrin receptors with ligands, such as, for example, binding of fibrinogen to the integrin receptor.

Integrins belong to the family of heterodimeric class I - transmembrane receptors which play an important role
30 in numerous cell-matrix or cell-cell adhesion processes (Tuckwell et al., 1996, Symp. Soc. Exp. Biol. 47). Roughly, they can be divided into three classes: the β 1-integrins, which are receptors for the extracellular matrix, the β 2-integrins, which are activatable on
35 leukocytes and are triggered during inflammatory processes, and the α v-integrins, which influence the cellular response during wound healing and other pathological processes (Marshall and Hart, 1996, Semin.

Cancer Biol. 7, 191). The relative affinity and specificity for ligand binding is determined by the combination of the various α - and β -subunits.

- 5 The compounds according to the invention are particularly effective in the case of the integrins $\alpha v \beta 1$, $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha I I b \beta 3$ and also $\alpha v \beta 6$ and $\alpha v \beta 8$, preferably of $\alpha v \beta 3$, $\alpha v \beta 5$ and $\alpha v \beta 6$, and also $\alpha I I b \beta 3$.
- 10 $\alpha v \beta 6$ is a relatively rare integrin (Busk et al., J. Biol. Chem. 1992, 267(9), 5790) which is increasingly formed during reparation processes in epithelial tissue and which preferably binds the natural matrix molecules fibronectin and tenascin
- 15 (Wang et al., Am. J. Respir. Cell Mol. Biol. 1996, 15(5), 664). The physiological and pathological functions of $\alpha v \beta 6$ are not yet known in detail; however, it is assumed that this integrin plays an important role in physiological processes and disorders (for
- 20 example inflammations, wound healing, tumours) in which epithelial cells are involved. Thus, $\alpha v \beta 6$ is expressed on keratinocytes in wounds (Haapasalmi et al., J. Invest. Dermatol. 1996, 106(1), 42), which indicates that, in addition to wound-healing processes and
- 25 inflammations, other pathological processes in the skin, such as, for example, psoriasis, bullous pemphigus, dermatitis and erythema, and also cystic fibrosis, endometriosis, cirrhosis of the liver or periodontitis, can also be influenced by agonists or
- 30 antagonists of said integrin. Furthermore, $\alpha v \beta 6$ plays a role in the epithelium of the respiratory tract (Weinacker et al., Am. J. Respir. Cell Mol. Biol. 1995, 12(5), 547) so that it may be possible to use appropriate agonists/antagonists of this integrin
- 35 successfully for disorders of the respiratory tract, such as bronchitis, asthma, pulmonary fibrosis and tumours of the respiratory tract. Finally, it is known that $\alpha v \beta 6$ also plays a role in the intestinal

epithelium, so that appropriate integrin agonists/antagonists could be used for treating inflammations, tumours and wounds of the gastrointestinal tract.

5

It has been found that the compounds of the formula I according to the invention and their salts, as soluble molecules, act on cells carrying the receptor mentioned, or, if they are attached to surfaces, they are artificial ligands for the $\alpha v \beta 6$ -mediated cell adhesion. Especially, they act as $\alpha v \beta 6$ integrin inhibitors, inhibiting in particular the interactions of the receptor with other ligands, such as, for example, binding of fibronectin.

15

In particular, the compounds according to the invention are potent inhibitors of the vitronectin receptor $\alpha v \beta 3$ and/or potent inhibitors of the $\alpha v \beta 6$ -receptor.

20 The $\alpha v \beta 3$ integrin is expressed on a number of cells, for example endothelial cells, smooth vascular muscle cells, for example of the aorta, cells which degrade the bone matrix, (osteoclasts) or tumour cells.

25 The action of the compounds according to the invention can be demonstrated, for example, using the method described by J.W. Smith et al. in J. Biol. Chem. **1990**, 265, 12267-12271.

In Curr. Opin. Cell. Biol. **1993**, 5, 864, B. Felding-Habermann and D.A. Cheresh describe the importance of the integrins as adhesion receptors for various phenomena and symptoms, specifically with respect to the vitronectin receptor $\alpha v \beta 3$.

35 The dependence of the formation of angiogenesis on the interaction between vascular integrins and extracellular matrix proteins is described by P.C. Brooks,

R.A. Clark and D.A. Cheresh in Science 1994, 264, 569-671.

P.C. Brooks, A.M. Montgomery, M. Rosenfeld,
5 R.A. Reisfeld, T. Hu, G. Klier and D.A. Cheresh
describe, in Cell 1994, 79, 1157-1164 the possibility
of inhibiting this interaction, thus initiating
apoptosis (programmed cell death) of angiogenic
vascular cells by a cyclic peptide. They describe, for
10 example, $\alpha_v\beta_3$ antagonists or antibodies against $\alpha_v\beta_3$
which cause tumours to shrink, by initiating apoptosis.

The experimental proof that the compounds according to
the invention also prevent adhesion of living cells on
15 the corresponding matrix proteins and, accordingly,
also adhesion of tumour cells to matrix proteins can be
obtained in a cell adhesion test, analogously to the
method of F. Mitjans et al., J. Cell Science 1995, 108,
2825-2838.

20

In J. Clin. Invest. 1995, 96, 1815-1822, P.C. Brooks
et al. describe $\alpha_v\beta_3$ antagonists for controlling cancer
and for treating tumour-induced angiogenic disorders.

The compounds are capable of inhibiting binding of
25 metal proteinases to integrins, thus preventing the
cells from utilizing the enzymatic activity of the
proteinase. An example is given by the inhibition of
MMP-2 (matrix metalloproteinase 2) binding to the
vitronectin receptor $\alpha_v\beta_3$ by a cyclo-RGD peptide, as
30 described in P.C. Brooks et al., Cell 1996, 85,
683-693.

It is therefore possible to use the compounds of the
formula I according to the invention as medicinally
35 active compounds, in particular for treating tumour
disorders, osteoporoses, osteolytic disorders, and for
suppressing angiogenesis.

Compounds of the formula I which block the interaction of integrin receptors and ligands, such as, for example, of fibrinogen on the fibrinogen receptor (glycoprotein IIb/IIIa), inhibit, as GPIIb/IIIa
5 antagonists, the spreading of tumour cells by metastasis. This is demonstrated by the following observations:

tumour cells spread from a localized tumour into the vascular system by forming microaggregates (micro-
10 thrombi) by interaction of the tumour cells with platelets. Protected in the microaggregate, the tumour cells are shielded and are not recognized by the cells of the immune system. These microaggregates can establish themselves at the walls of blood vessels,
15 thus facilitating further penetration of tumour cells into the tissue. Since the formation of the microthrombi is mediated by fibrinogen binding to the fibrinogen receptors on activated platelets, the GPIIb/IIIa antagonists can be considered to be
20 effective metastasis inhibitors.

In addition to binding of fibrinogen, fibronectin and the von-Willebrand factor to the platelet fibrinogen receptor, compounds of the formula I also inhibit
25 binding of further adhesive proteins, such as vitronectin, collagen and laminin, to the corresponding receptors on the surface of various cell types. In particular, they inhibit the formation of platelet thrombi and can therefore be used for treating
30 thromboses, apoplexy, myocardial infarction, inflammations and arteriosclerosis.

The inhibitory effect on thrombocyte aggregation can be demonstrated in vitro using the method of Born (Nature
35 1962, 4832, 927-929).

A measure for the uptake of a medicinally active compound into an organism is its bioavailability.

If the medicinally active compound is administered to the organism intravenously, in the form of a solution for injection, its absolute bioavailability, i.e. the percentage of the pharmaceutical which enters the systemic circulation unchanged, i.e. the greater
5 circulation, is 100%.

If a therapeutically active compound is administered orally, the active compound is generally present in the formulation as a solid and, accordingly, first has to
10 pass into solution to be able to overcome the entry barriers, for example the gastrointestinal tract, the mucosa of the mouth, nasal membranes or the skin, in particular the stratum corneum, or to be resorbed by the body. Pharmacokinetic data, i.e. data on the
15 bioavailability, can be obtained analogously to the method of J. Shaffer et al, J. Pharm. Sciences, 1999, 88, 313-318.

The invention provides compounds of the formula I
20 according to Claim 1 and their physiologically acceptable salts and/or solvates for use as therapeutically active compounds.

Accordingly, the invention provides compounds of the
25 formula I according to Claim 1 and their physiologically acceptable salts and/or solvates for use as integrin inhibitors.

The invention provides compounds of the formula I
30 according to Claim 1 and their physiologically acceptable salts and/or solvates for use in the control of diseases.

The compounds of the formula I can be employed as
35 medicinally active compounds in human and veterinary medicine, in particular for the prophylaxis and/or therapy of cardiovascular disorders, thrombosis, myocardial infarction, arteriosclerosis, apoplexy,

angina pectoris, tumour diseases, such as tumour growth or tumour metastasis, osteolytic diseases, such as osteoporosis, pathological angiogenic diseases, such as, for example, inflammations, ophthalmological diseases, diabetic retinopathy, macular degeneration, myopia, ocular histoplasmosis, rheumatoid arthritis, osteoarthritis, rubeotic glaucoma, ulcerative colitis, Crohn's disease, atherosclerosis, psoriasis, bullous pemphigus, dermatitis, erythema, pulmonary fibrosis, cystic fibrosis, endometriosis, cirrhosis of the liver, periodontitis, restenosis after angioplasty, multiple sclerosis, viral infection, bacterial infection, fungal infection, in cases of acute renal failure and in cases of wound healing to assist the healing process.

The compounds of the formula I can be employed as antimicrobially acting substances during operations where biomaterials, implants, catheters or cardiac pacemakers are used.

Here, they have an antiseptic action. The efficacy of the antimicrobial activity can be demonstrated by the method described by P. Valentin-Weigund et al. in *Infection and Immunity*, **1988**, 2851-2855.

Since the compounds of the formula I are inhibitors of fibrinogen binding and thus ligands of the fibrinogen receptors on platelets, they can be used as diagnostic aids for the detection and localization of thrombi in the vascular system *in vivo* if they are substituted, for example, by a radioactive or UV-detectable radical.

As inhibitors of fibrinogen binding, the compounds of the formula I can also be employed as effective auxiliaries for the study of the metabolism of platelets in different activation stages or of intracellular signal mechanisms of the fibrinogen receptor. The detectable unit of a "label" which is to

be incorporated, for example isotope labelling by ^3H , permits the investigation of the abovementioned mechanisms after receptor binding.

5 The following abbreviations are used:

	Ac	acetyl
	Aza-Gly	$\text{H}_2\text{N-NH-COOH}$
	BOC	tert-butoxycarbonyl
10	CBZ or Z	benzyloxycarbonyl
	DCCI	dicyclohexylcarbodiimide
	DCM	dichloromethane
	DIPEA	diisopropylethylamine
	DMF	dimethylformamide
15	EDCI	N-ethyl-N,N'-(dimethylaminopropyl)carbo- diimide
	Et	ethyl
	Fmoc	9-fluorenylmethoxycarbonyl
	Gly	glycine
20	HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'- tetramethyluronium hexafluorophosphate
	HOBt	1-hydroxybenzotriazole
	Me	methyl
	MBHA	4-methylbenzhydramine
25	Mtr	4-methoxy-2,3,6-trimethylphenylsulfonyl
	NMP	N-methylpyrrolidone
	NMR	nuclear magnetic resonance
	HONSu	n-hydroxysuccinimide
	OBzl	benzyl ester
30	OtBu	tert-butyl ester
	Oct	octanoyl
	OMe	methyl ester
	OEt	ethyl ester
	Pbf	2,2,4,6,7-pentamethyldihydrobenzofuran- 5-sulfonyl
35	β -Phe	β -phenylalanine
	POA	phenoxyacetyl
	R_f value	retention factor

RP reversed phase
RT retention time
Sal salicyloyl
TBTU O-(1H-benzotriazol-1-yl)-N,N,N',N'-
5 tetramethyluronium tetrafluoroborate
TFA trifluoroacetic acid
Trt trityl (triphenylmethyl).

10 The compounds of the formula I have at least one chiral centre and can therefore be present in a plurality of stereoisomeric forms. All of these forms (for example D- and L-forms) and their mixtures (for example the DL forms) are embraced by the formula I.

15 The compounds according to the invention of Claim 1 also include so-called prodrug derivatives, i.e. compounds of the formula I which are derivatized with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the
20 organism to the active compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 1995, 115, 61-67.

25 The compounds according to the invention of Claim 1 also include derivatives of the compounds of the formula I whose carboxyl group has been converted into a pharmaceutically acceptable metabolically labile ester or an amide.

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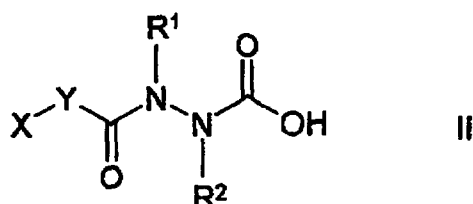
Furthermore, free amino groups or free hydroxyl groups as substituents of compounds of the formula I may carry appropriate protective groups.

35 Solvates of the compounds of the formula I are understood to be addition compounds of the compounds of the formula I with inert solvent molecules, which are formed owing to their mutual attraction. Examples of

solvates are mono- or dihydrates or adducts with alcohols, such as, for example, with methanol or ethanol.

5 The invention furthermore provides a process for preparing compounds of the formula I according to Claim 1 and their salts, characterized in that

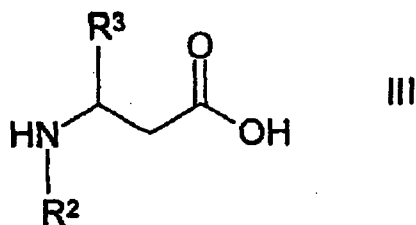
a) to prepare a compound of the formula I in which Z is
10 N-R², a compound of the formula II



in which X, Y, R¹ and R² are as defined in Claim 1 and in which free amino groups are protected by a suitable amino protective group,

15

is reacted with a compound of the formula III

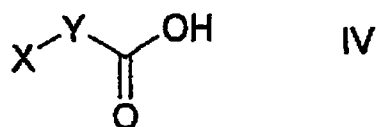


in which R² and R³ are as defined in Claim 1 and in which a free hydroxyl group is protected by a suitable
20 hydroxyl protective group or attached to a solid phase,

and the protective groups and/or the solid phase are subsequently removed,

25 or

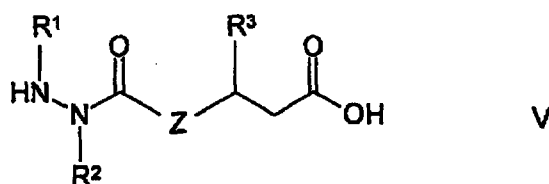
b) a compound of the formula IV



in which X and Y are as defined in Claim 1 and in which free amino groups are protected by a suitable amino protective group

5

is reacted with a compound of the formula V



in which R¹, R², R³ and Z are as defined in Claim 1 and in which a free hydroxyl group is protected by a suitable hydroxyl protective group or attached to a solid phase,

10

and the protective groups and/or the solid phase are subsequently removed;

15

or

c) a compound of the formula I is liberated from one of its functional derivatives by treatment with a solvolysing or hydrogenolysing agent,

20

and/or in that a basic or acidic compound of the formula I is converted into one of its salts by treatment with an acid or base.

25

For the entire invention, it applies that all radicals which are present more than once, such as, for example, R², can be identical or different, i.e. are independent of one another.

30

In the above formulae, A is alkyl which is linear or branched and has 1 to 6, preferably 1, 2, 3, 4, 5 or 6,

carbon atoms. A is preferably methyl, furthermore ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec-butyl or tert-butyl, furthermore also n-pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl. A is particularly preferably methyl.

Amino protective group is preferably acetyl, propionyl, butyryl, phenylacetyl, benzoyl, toluoyl, POA, methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC, 2-iodoethoxycarbonyl, CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl, Fmoc, Mtr or benzyl.

Fmoc is particularly preferred.

Ar is preferably unsubstituted phenyl, furthermore preferably phenyl which is mono-, di- or trisubstituted by A, OH, OA, CF₃, OCF₃, CN, NO₂ or Hal and which may also be substituted by a phenyl which is mono-, di- or trisubstituted by A, OH, OA, CF₃, OCF₃, CN, NO₂ or Hal such that an unsubstituted or substituted biphenyl is formed. A and Hal have the preferred or particularly preferred meanings listed above or below.

Ar is furthermore preferably unsubstituted naphthyl or naphthyl which is mono-, di- or trisubstituted by A, OH, OA, CF₃, OCF₃, CN, NO₂ or Hal, where A and Hal have one of the preferred or particularly preferred meanings listed above or below.

Accordingly, Ar is preferably phenyl, o-, m- or p-methylphenyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m-, p-trifluoromethylphenyl, o-, m-, p-trifluoromethoxy-

phenyl, o-, m- or p-fluorophenyl, o-, m- or p-chlorophenyl, o-, m- or p-bromophenyl, o-, m-, p-nitrophenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dihydroxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-ditrifluoromethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-ditrifluoromethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dinitrophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl. However, preference is furthermore also given to unsubstituted biphenyl or else substituted biphenyl, specifically preferably to 4-biphenyl or 3-biphenyl, 4'-(2-methylbiphenyl), 4'-(3-methylbiphenyl), 4'-(4-methylbiphenyl), 3'-(2-methylbiphenyl), 3'-(3-methylbiphenyl), 3'-(4-methylbiphenyl), 4-(2-methylbiphenyl), 4-(3-methylbiphenyl), 3-(2-methylbiphenyl), 3-(4-methylbiphenyl), 4'-(2-fluorobiphenyl), 4'-(3-fluorobiphenyl), 4'-(4-fluorobiphenyl), 3'-(2-fluorobiphenyl), 3'-(3-fluorobiphenyl), 3'-(4-fluorobiphenyl), 4-(2-fluorobiphenyl), 4-(3-fluorobiphenyl), 3-(2-fluorobiphenyl) or 3-(4-fluorobiphenyl). However, preference is furthermore also given to unsubstituted naphthalin-1-yl or naphthalin-2-yl.

Ar is particularly preferably phenyl, p-chlorophenyl, p-bromophenyl, p-fluorophenyl, 3,5-dichlorophenyl, o- or m-nitrophenyl, p-trifluoromethoxyphenyl, p-methoxyphenyl, 3,5-dichloro-2-hydroxyphenyl, naphthalin-1-yl, biphenyl-4-yl or 4'-(4-fluorobiphenyl).

Aralkyl is preferably benzyl, phenylethyl, phenylpropyl or naphthylmethyl, particularly preferably benzyl.

Hal is preferably F, Cl or Br.

Het is a saturated, partially or fully unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, wherein 1 or 2 nitrogen and/or 1 or 2 sulfur or oxygen atoms may be present and the heterocyclic radical may be mono- or disubstituted by CN, Hal, OH, OA, CF₃, A, NO₂ or OCF₃.

- 10 Het is preferably substituted or unsubstituted 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -4- or -5-yl, 1- or -5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-1H-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl. The heterocyclic radicals can also be partially or fully hydrogenated. Het can therefore also be 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or

- 3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or
-5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or
-5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-,
-2- or -3-pyrrolyl, tetrahydro-1-, -2- or 4-imidazolyl,
5 2,3-dihydro-1-, -2-, -3-, -4-, -5-, -6-, -7-1H-indolyl,
2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl,
tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-,
-2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-,
-3-, -4-, -5- or -6-pyridyl, 1,2,3,6-tetrahydro-1-,
10 -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or
4-piperidinyl, 1-, 2-, 3- or 4-azepanyl, 2-, 3- or
4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl,
1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl,
hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-,
15 -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl,
1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or
-8-quinolinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-,
-5-, -6-, -7- or -8-isoquinolinyl.
- 20 Het is particularly preferably 2-, 3- or 4-pyridyl or
1-, 2-, 3-, 4-, 5-, 6- or 7-1H-indolyl.

Het¹ is a 5- or 6-membered aromatic heterocycle having
1 to 4 nitrogen atoms which may be unsubstituted or
25 mono- or disubstituted by Hal, A, OA, Ar, OAr,
arylalkyl, CN, NO₂, CF₃ or OCF₃, wherein Hal, A,
arylalkyl and Ar have one of the meanings given above.

Het¹ is preferably unsubstituted or substituted 2- or
30 3-pyrrolyl, 2, 4- or 5-imidazolyl, 3-, 4- or
5-pyrazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or
6-pyrimidinyl, 3- or 4-pyridazinyl, 2- or 3-pyrazinyl.
Particular preference is given to pyridin-2-yl,
imidazol-2-yl or 4-methylpyridin-2-yl.

35 Het¹-NH is preferably pyrrol-2- or pyrrol-3-ylamine,
imidazol-2-, imidazol-4- or imidazol-5-ylamine,
pyrazol-3-, pyrazol-4- or pyrazol-5-ylamine, pyrid-2-,

pyrid-3- or pyrid-4-ylamine, pyrimidin-2-,
pyrimidin-4-, pyrimidin-5- or pyrimidin-6-ylamine,
pyridazin-3- or pyridazin-4-ylamine, pyrazin-2- or
pyrazin-3-ylamine, where the heterocyclic rings
5 mentioned may be substituted, preferably by alkyl.
Het¹-NH is particularly preferably pyrid-2-ylamine,
imidazol-2-ylamine or 4-methylpyridin-2-ylamine.

10 OA is preferably methoxy, ethoxy, propoxy or butoxy,
furthermore also pentyloxy or hexyloxy.

R¹ is preferably H or A, where A has one of the
meanings given above, and is in particular H.

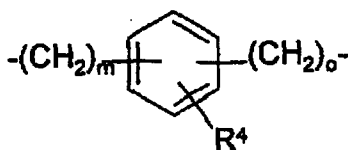
15 R² is preferably H or A, where A has one of the
meanings given above, and is in particular H.

R³ is preferably H, Ar or Het, where Ar and Het have
one of the meanings given above, and is in particular
20 H, phenyl, p-chlorophenyl, p-bromophenyl,
p-fluorophenyl, 3,5-dichlorophenyl, o- or m-nitro-
phenyl, p-trifluoromethoxyphenyl, p-methoxyphenyl,
3,5-dichloro-2-hydroxyphenyl, naphthalin-1-yl,
biphenyl-4-yl or 4'-(4-fluorobiphenyl).

25 R⁴ is preferably H, A, Ar, OH, OA, OAr, arylalkyl, Hal,
CN, NO₂, CF₃ or OCF₃, wherein A, arylalkyl, Ar and Hal
have one of the meanings given above, and is in
particular H and methyl.

30 X is H₂N-C(=NH)-NH-, H₃C-C(=NH)-NH- or Het¹-NH wherein
Het¹-NH has one of the meanings given above, and in
particular, X is H₂N-C(=NH)-NH-, H₃C-C(=NH)-NH-,
pyridin-2-ylamino, imidazol-2-ylamino or
35 4-methylpyridin-2-ylamino.

Y is -(CH₂)_n- or



wherein n is 2, 3, 4, 5 or 6, in particular 3 or 4, and m is 0, 1 or 2, in particular 0, and o is 0, 1 or 2, in particular 0 or 1, and R^4 has one of the meanings given above.

Z is $N-R^2$ or $CH-R^2$, wherein R^2 has one of the meanings given above, and is in particular NH or CH_2 .

- 10 Accordingly, the invention provides in particular those compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings given above. Some preferred groups of compounds can be expressed by the following partial formulae Ia to Ir
- 15 which correspond to the formula I and in which the radicals that are not specified in more detail are as defined under formula I, but in which

in Ia) X is $H_2N-C(=NH)-NH-$,

in Ib) Y is

20

in Ic) Z is $N-R^2$,

in Id) Z is $CH-R^2$,

in Ie) X is $H_2N-C(=NH)-NH-$, $H_3C-C(=NH)-NH-$ or Het^1-NH- and

25

Y is $-(CH_2)_n$,

in If) X is $H_2N-C(=NH)-NH-$ and

Y is

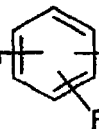
in Ig) X is $H_2N-C(=NH)-NH-$ or Het^1-NH- ,

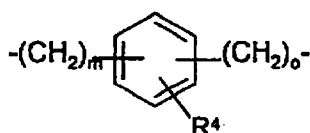
Y is $-(CH_2)_n-$,

30

R^3 is Ar,

Z is NH,

- in Ih) X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$,
 R^3 is Ar,
Z is NH and
Y is $-(\text{CH}_2)_m-$  $(\text{CH}_2)_o-$
- 5 in Ii) X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$ or $\text{Het}^1-\text{NH}-$,
 R^3 is Ar,
Y is $-(\text{CH}_2)_n-$ and
Z is CH_2 ,
- 10 in Ik) X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$,
 R^3 is Ar,
Z is CH_2 and
Y is $-(\text{CH}_2)_m-$  $(\text{CH}_2)_o-$
- 15 in Im) X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$, $\text{H}_3\text{C}-\text{C}(=\text{NH})-\text{NH}-$ or
 $\text{Het}^1-\text{NH}-$,
Y is $-(\text{CH}_2)_n-$ or
 $-(\text{CH}_2)_m-$  $(\text{CH}_2)_o-$
- 20 Z is NH or CH_2
 R^1, R^2 are H,
 R^3 is Ar,
 R^4 is H,
 Het^1 is 4-methylpyridin-2-yl, pyridin-2-yl
or imidazol-2-yl,
- 25 n is 3 or 4,
m is 0 and
o is 0 or 1,
- in In) X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$ or $\text{Het}^1-\text{NH}-$,
30 Y is $-(\text{CH}_2)_n-$ or



Z is NH

R¹, R² are H,

R³ is phenyl which is unsubstituted or mono-, di- or trisubstituted by OH, OA, OCF₃, NO₂ or Hal and which may be substituted by a phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal such that an unsubstituted or substituted biphenyl is formed or unsubstituted naphthyl,

R⁴ is H,

Het¹ is 4-methylpyridin-2-yl, or pyridin-2-yl or imidazol-2-yl,

n is 3 or 4 and

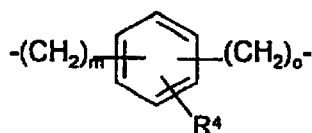
m is 0 and

o is 0 or 1,

in Io)

X is H₂N-C(=NH)-NH- or Het¹-NH-,

Y is -(CH₂)_n- or



Z is CH₂,

R¹, R² are H,

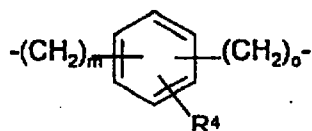
R⁴ is H,

R³ is phenyl which is unsubstituted or mono-, di- or trisubstituted by OH, OA, OCF₃, NO₂ or Hal and which may be substituted by a phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal such that an unsubstituted or substituted biphenyl is formed or unsubstituted naphthyl,

Het¹ is 4-methylpyridin-2-yl, pyridin-2-yl or imidazol-2-yl,

n is 4 and
m, o are 0,

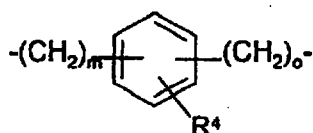
5 in Ip) X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$ or $\text{Het}^1-\text{NH}-$,
Y is $-(\text{CH}_2)_n-$ or



Z is NH or CH_2 ,
 R^1, R^2 are H ,
 R^4 is H ,
 10 R^3 is phenyl which is unsubstituted or
 mono-, di- or trisubstituted by OH ,
 OA , OCF_3 , NO_2 or Hal and which may be
 15 substituted by a phenyl which is
 unsubstituted or mono-, di- or
 trisubstituted by Hal such that an
 unsubstituted or substituted biphenyl
 is formed or unsubstituted naphthyl,
 Het^1 is 4-methylpyridin-2-yl, pyridin-2-yl
 or imidazol-2-yl,
 20 n is 3 or 4,
 m is 0 and
 o is 0 or 1,

25 in Iq) R^3 is unsubstituted biphenyl-4-yl or is
 phenyl which is mono-, di- or
 trisubstituted by Hal ,

in Ir) X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$ or $\text{Het}^1-\text{NH}-$,
 Y is $-(\text{CH}_2)_n-$ or



30 Z is NH or CH_2 ,
 R^1, R^2 are H ,
 R^4 is H ,

- R³ is biphenyl-4-yl, 4-chlorophenyl or 3,5-dichlorophenyl,
Het¹ is 4-methylpyridin-2-yl, pyridin-2-yl or imidazol-2-yl,
5 n is 3 or 4,
m is 0 and
o is 0 or 1.

The compounds of the formula I and also the starting
10 materials for their preparation are otherwise prepared by methods known per se, such as are described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of organic chemistry], Georg-Thieme-Verlag, Stuttgart),
15 and more specifically under reaction conditions which are known and suitable for the reactions mentioned. In these reactions, variants which are known per se and are not mentioned here in more detail can also be employed.

20 If desired, the starting materials can also be formed in situ, so that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of the formula I.

25 Compounds of the formula I can preferably be obtained under the conditions of a peptide synthesis. It is advantageous to employ customary methods of peptide synthesis, as described, for example, in Houben-Weyl,
30 1.c., Volume 15/II, pages 1 to 806 (1974).

The direct precursors of the compounds of the formula I can also be synthesized on a solid phase, for example a swellable polystyrene resin, for example according to
35 Merrifield (Angew. Chem. 97, 801-812, 1985).

Suitable for use as solid phase are, in principle, all supports as known, for example, from solid-phase peptide chemistry or nucleic acid synthesis.

Suitable polymeric support materials are polymeric solid phases preferably having hydrophilic properties, for example crosslinked polysugars, such as cellulose, sepharose or Sephadex®, acrylamides, polymers based on
5 polyethylene glycols or Tentakelpolymere®. The solid phase used is preferably trityl chloride polystyrene resin, 4-methoxytrityl chloride resin, Merrifield resin and Wang resin.

10 Thus, compounds of the formula I can be obtained by reacting a compound of the formula II with a compound of the formula III, followed by removal of the protective groups or the solid phase.

15 It is also possible to obtain the compounds of the formula I by reacting a compound of the formula IV with a compound of the formula V, followed by removal of the protective groups.

20 The coupling reaction is preferably carried out in the presence of a dehydrating agent, for example a carbodiimide such as DCCI or EDCI, furthermore, for example, propanephosphonic anhydride (cf. Angew. Chem. 1980, 92, 129), diphenylphosphoryl azide or 2-ethoxy-
25 N-ethoxycarbonyl-1,2-dihydroquinoline, in an inert solvent, for example a halogenated hydrocarbon such as dichloromethane, in an ether such as tetrahydrofuran or dioxane, in an amide such as DMF or dimethylacetamide, in a nitrile such as acetonitrile, in dimethyl
30 sulfoxide or in the presence of these solvents, at temperatures between approximately -10 and 40, preferably between 0 and 30°. It is advantageous to work in dilute solutions to promote intramolecular cyclization rather than intermolecular peptide
35 formation.

Depending on the conditions employed, the reaction time is between some minutes and 14 days.

Instead of compounds of the formula II and/or IV, it is also possible to employ derivatives of compounds of the formula II and/or IV, preferably a pre-activated carboxylic acid, or a carbonyl halide, a symmetric or mixed anhydride or an activated ester. Such radicals for the activation of the carboxyl group in typical acylation reactions are described in the literature (for example in the standard works such as Houben-Weyl, Methoden der organischen Chemie, Georg-Thieme-Verlag, Stuttgart).

Activated esters are advantageously formed in situ, for example by addition of HOBT or N-hydroxysuccinimide.

The reaction is generally carried out in an inert solvent, if a carbonyl halide is used in the presence of an acid binder, preferably of an organic base, such as triethylamine, dimethylaniline, pyridine or quinoline.

It may also be favourable to add an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate, or another salt of a weak acid of the alkali metals or alkaline earth metals, preferably of potassium, sodium, calcium or caesium.

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

Preferred starting materials for the solvolysis or hydrogenolysis are those which otherwise correspond to the formula I but, instead of one or more free amino and/or hydroxyl groups, contain corresponding protected amino and/or hydroxyl groups, in particular those which, instead of an H-N group, carry a PG¹-N group, in which PG¹ is an amino protective group, and/or those which, instead of the H atom of a hydroxyl group, carry a hydroxyl protective group, for example those which

correspond to the formula I but carry, instead of a group -COOH, a group -COOPG², in which PG² is a hydroxyl protective group.

- 5 It is also possible for several - identical or different - protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If the protective groups present differ from one another, in many cases they can be split off selectively
- 10 (cf.: T.W. Greene, P.G.M. Wuts, *Protective Groups in Organic Chemistry*, 2nd Ed., Wiley, New York 1991 or P.J. Kocienski, *Protecting Groups*, 1st Ed., Georg Thieme Verlag, Stuttgart - New York, 1994, H. Kunz, H. Waldmann in *Comprehensive Organic Synthesis*, Vol. 6
- 15 (Eds. B.M. Trost, I. Fleming, E. Winterfeldt), Pergamon, Oxford, 1991, pages 631-701).

The term "amino protective group" is generally known and relates to groups which are suitable for protecting

20 (blocking) an amino group from chemical reactions. Typical such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino protective groups are removed after the desired reaction (or reaction sequence),

25 their nature and size is otherwise not critical; however, those having 1-20 carbon atoms are preferred. The term "acyl group" is to be interpreted in the broadest sense in connection with the present process. It includes acyl groups derived from aliphatic,

30 araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and in particular alkoxycarbonyl, alkenyloxycarbonyl, aryloxycarbonyl and, above all, aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl, butyryl;

35 aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or toluoyl; aryloxyalkanoyl, such as phenoxyacetyl; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, Boc,

2-iodoethoxycarbonyl; alkenyloxycarbonyl, such as allyloxycarbonyl (Aloc), aralkyloxycarbonyl such as CBZ (synonymous with Z), 4-methoxybenzyloxycarbonyl (MOZ), 4-nitrobenzyloxycarbonyl or 9-fluorenylmethoxycarbonyl (Fmoc); 2-(phenylsulfonyl)ethoxycarbonyl; trimethylsilylethoxycarbonyl (Teoc), or arylsulfonyl, such as 4-methoxy-2,3,6-trimethylphenylsulfonyl (Mtr). Preferred amino protective groups are Boc, Fmoc and Aloc, furthermore Z, benzyl and acetyl.

10

The term "hydroxyl protective group" is also generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions. Typical such groups are the abovementioned unsubstituted or substituted aryl, aralkyl, aroyl or acyl groups, and furthermore also alkyl groups, alkyl-, aryl- or aralkylsilyl groups or O,O- or O,S-acetals. The nature and size of the hydroxyl protective groups are not critical, since they are removed again after the desired chemical reaction or reaction sequence; preference is given to groups having 1-20, in particular 1-10, carbon atoms. Examples of hydroxyl protective groups are, inter alia, aralkyl groups, such as benzyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl, aroyl groups, such as benzoyl or p-nitrobenzoyl, acyl groups, such as acetyl or pivaloyl, p-toluenesulfonyl, alkyl groups, such as methyl or tert-butyl, but also allyl, alkylsilyl groups, such as trimethylsilyl (TMS), triisopropylsilyl (TIPS), tert-butyldimethylsilyl (TBS) or triethylsilyl, trimethylsilylethyl, aralkylsilyl groups, such as tert-butyldiphenylsilyl (TBDPS), cyclic acetals, such as isopropylidene, cyclopentylidene, cyclohexylidene, benzylidene, p-methoxybenzylidene or o,p-dimethoxybenzylidene acetal, acyclic acetals, such as tetrahydropyranyl (Thp), methoxymethyl (MOM), methoxyethoxymethyl (MEM), benzyloxymethyl (BOM) or methylthiomethyl (MTM). Particularly preferred hydroxyl

35

protective groups are benzyl, acetyl, tert-butyl and TBS.

5 The liberation of the compounds of the formula I from their functional derivatives is, for the protective group employed in each case, known from the literature (for example T.W. Greene, P.G.M. Wuts, *Protective Groups in Organic Chemistry*, 2nd Ed., Wiley, New York, 1991 or P.J. Kocienski, *Protecting Groups*, 1st Ed., 10 Georg Thieme Verlag, Stuttgart - New York, 1994). It is also possible to employ variants known per se which are not mentioned in more detail here.

15 A base of the formula I can be converted into the associated acid addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, and subsequent evaporation. Acids which give physiologically acceptable salts are particularly suitable for 20 this reaction. It is thus possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as, for example, orthophosphoric acid, 25 sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, hexanoic acid, octanoic acid, decanoic 30 acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, 35 methane- or ethanesulfonic acid, benzenesulfonic acid, trimethoxybenzenesulfonic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic

acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and -disulfonic acids, or lauryl sulfuric acid. Salts with
5 physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted with bases (for example sodium hydroxide or potassium hydroxide or
10 sodium carbonate or potassium carbonate) into the corresponding metal, in particular alkali metal or alkaline earth metal, or into the corresponding ammonium salts. Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-,
15 diethyl- or diisopropylammonium salts, monoethanol-, diethanol- or diisopropylammonium salts, cyclohexyl-, dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

20 The invention furthermore provides the use of the compounds of the formula I and/or their pharmaceutically acceptable salts for preparing a pharmaceutical preparation.

25 The invention furthermore provides pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts or solvates prepared, in particular, by a non-
30 chemical route. For this purpose, the compounds of the formula I can be brought into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or auxiliary, and, if appropriate, in combination with one or more further active compounds.

35 These preparations can be used as medicaments in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral

(for example oral), parenteral or topical administration and which do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates, such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used, in particular, for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, and furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilizates can be used, for example, for the production of injection preparations. The preparations mentioned can be sterilized and/or comprise auxiliaries, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, dyes, flavourings and/or several other active compounds, for example one or more vitamins. For administration as an inhalation spray, it is possible to use sprays which contain the active compound either dissolved or suspended in a propellant or propellant mixture (for example CO₂ or chlorofluorocarbons). Here, the active compound is expediently employed in micronized form, wherein one or more additional physiologically acceptable solvents may be present, for example ethanol. Solutions for inhalation can be administered with the aid of customary inhalators.

The compounds of the formula I and their physiologically acceptable salts can be employed as integrin inhibitors for controlling diseases, in particular

thromboses, myocardial infarction, coronary heart diseases, arteriosclerosis, tumours, osteoporosis, inflammations and infections.

- 5 The compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts are also used for pathological processes which are maintained or propagated by angiogenesis, in particular for tumours or rheumatoid arthritis.

10

- For this purpose, the substances according to the invention are generally preferably administered in dosages between approximately 0.05 and 500 mg, in particular between 0.5 and 100 mg, per dosage unit, analogously to other known, commercially available peptides, and in particular analogously to the compounds described in US-A-4 472 305. The daily dosage is preferably between approximately 0.01 and 2 mg/kg of body weight. However, the specific dose for each patient depends on the most diverse factors, for example on the activity of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the administration time and route, and on the rate of excretion, medicament combination and severity of the particular disease to which the therapy applies. Parenteral administration is preferred.

- 30 The compounds of the formula I can furthermore be employed as integrin ligands for preparing affinity chromatography columns for the preparation of pure integrins.

- To this end, the ligand, that is to say a compound of the formula I, is covalently coupled to a polymer support via an anchor function, for example the carboxyl group of Asp.

35

The affinity chromatography materials for the purification of integrin are prepared under conditions like those which are customary for the condensation of amino acids and known per se.

5

The compounds of the formula I contain one or more chiral centres and may therefore be present in racemic or optically active form. Racemates that are obtained can be separated into the enantiomers by methods which are known per se, mechanically or chemically. Preferably, the racemic mixture is converted into diastereomers by reaction with an optically active resolving agent. Suitable resolving agents are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the different optically active camphorsulfonic acids, such as β -camphorsulfonic acid. Also advantageous is an enantiomer separation with the aid of a column filled with an optically active resolving agent (for example dinitrobenzoylphenylglycine); a suitable mobile phase is, for example, a hexane/isopropanol/acetonitrile mixture, for example in a ratio by volume of 82:15:3.

25

It is of course also possible to obtain optically active compounds of the formula I by the methods described above by using starting materials which are already optically active.

30

All temperatures above and below are given in °C. In the following examples, "customary work-up" means: water is added, if necessary, the pH is brought to values of between 2 and 10, if necessary, depending on the structure of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium

35

sulfate and evaporated and the residue is purified by silica gel chromatography and/or crystallization.

RT = retention time (minutes) for HPLC in the following
5 systems:

Columns from Omnicrom YMC:

1. 4.6×250 mm, 5 μ m, C₁₈ (for analysis);
2. 30×250 mm, 7 μ m, C₁₈ (for preparations).

The mobile phases used were gradients of acetonitrile (B) with 0.1% TFA and water (A) with 0.1% TFA (data in each case in per cent by volume of acetonitrile). The retention time RT was determined at a flow rate of 1 ml/min.

Detection at 220 nm.

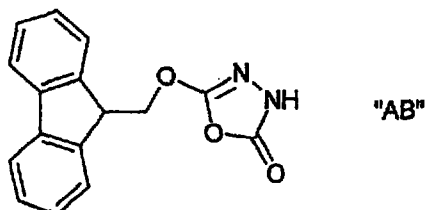
15

The diastereomers are preferably separated under the given conditions.

Mass spectrometry (MS): ESI (electron spray ionization)
 (M+H)⁺
 FAB (fast atom bombardment)
 (M+H)⁺.

Example 1:

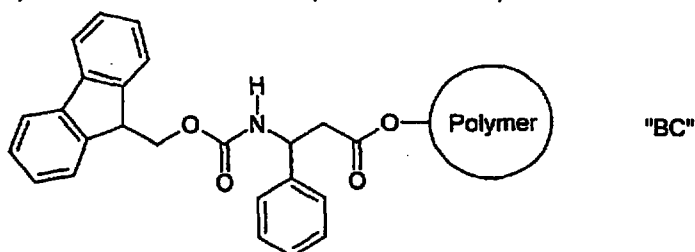
25 1. 5-(9H-fluoren-9-ylmethoxy)-3H-[1,3,4]oxadiazol-2-one:
2 equivalents of phosgene (1.89M in toluene; 4.2 ml)
are added to a solution of 3.91 mmol of 9H-fluoren-
9-ylmethyl hydrazinecarboxylate in 40 ml of
dichloromethane and 40 ml of saturated aqueous NaHCO₃
30 solution. The mixture is stirred for 15 minutes and
then worked up as usual, giving 5-(9H-fluoren-
9-ylmethoxy)-3H-[1,3,4]oxadiazol-2-one ("AB")



58 mg; IR (KBr): 3300s, 1780s, 1650s, 1451m, 1426m, 1347m, 1224m, 918m, 758w, 740m cm^{-1} .

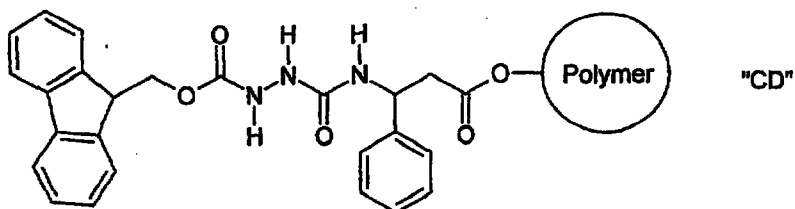
2. Resin-bonded Fmoc- β -Phe-OH ("BC"):

- 5 2.0 g of trityl chloride polystyrene resin (theoretical load 1.8 mmol) are washed in 20 ml of DMF. The resin is then admixed with a solution of 2.7 mmol Fmoc- β -Phe-OH and 2.25 mmol DIPEA in 20 ml of DMF, the mixture is shaken at room temperature for 2 hours and 1 ml of
- 10 methanol is then added. The mixture is washed with DCM (5 $\times$ 20 ml) and methanol (3 $\times$ 20 ml) and dried



3. Resin-bonded Fmoc-azaGly- β -Phe("CD"):

- 15 0.48 mmol/g of "BC" is washed with DCM (2 $\times$ 7 ml) and NMP (1 $\times$ 7 ml) and then deprotected twice using 20% piperidine in 7 ml of DMF, first for 5 min and then for 15 min. The deprotected resin is washed with NMP (5 $\times$ 7 ml) and absolute DCM (5 $\times$ 7 ml), admixed with a
- 20 solution of 0.72 mmol "AB" in 7 ml of DCM and shaken at room temperature for 90 min.
- The resin is washed with DCM (5 $\times$ 7 ml) and NMP (5 $\times$ 7 ml) and dried



25

4. 3-[4-(3-guanidinobenzoyl)semicarbazido]-3-phenyl-propionic acid

0.24 mmol of "CD" is washed with NMP (7 $\times$ 5 ml) and deprotected twice with 20% piperidine in 7 ml of DMF,

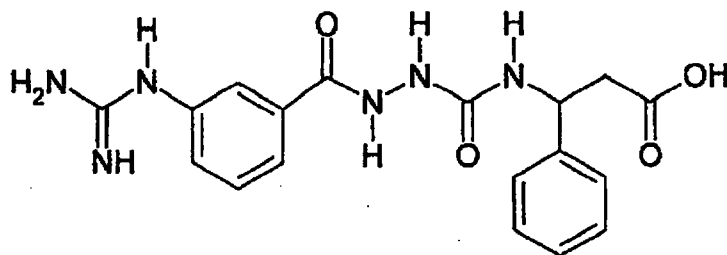
first for 5 min and then for 15 min. The resin is then washed with NMP (5 × 7 ml) and DMF (2 × 7 ml), admixed with a solution of 0.48 mmol of 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid, 0.48 mmol of
5 HATU and 2.4 mmol of collidine in 5 ml of DMF and shaken at room temperature for 90 min. The resin is washed and deprotected as described.

The resin is subsequently admixed with a solution of
10 2.4 mmol of N,N'-bis-BOC-1-guanylpurazole ("DE") in 4 ml of chloroform and left at 50° for 16 hours. The resin is washed with DCM, methanol and diethyl ether.

To remove the BOC groups, the resin is shaken with a mixture of 95% TFA and 5% triisopropylsilane (5 ml) at
15 room temperature, first for 90 min and then for 30 min. Removal of the solvent and purification by preparative RP-HPLC gives 3-[4-(3-guanidinobenzoyl)semicarbazido]-3-phenylpropionic acid, trifluoroacetate.

RT = 19.1 (0 → 50% B, 30 min)

20 MS (ESI): m/e = 385.1 ([M+H]⁺)



Example 2:

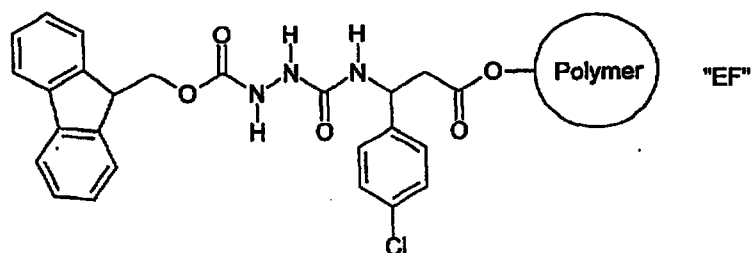
1. Analogously to Example 1, reaction of "CD" with 3-(9H-fluoren-9-ylmethoxycarbonylamino)phenylacetic acid followed by removal of the Fmoc group and reaction with "DE", removal of the BOC group and cleavage from the resin gives

3-[4-(3-guanidinophenylacetyl)semicarbazido]-3-phenylpropionic acid, trifluoroacetate.

RT = 4.3 (10 → 50% B, 30 min)

10 MS (ESI): m/e = 399.1 ([M+H]⁺).

2. Analogously to Example 1, reaction of "EF", prepared by reaction of "AB" with resin-bonded Fmoc-protected β-(4-chlorophenyl)alanine



15

with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid followed by removal of the Fmoc group and reaction with "DE", removal of the BOC group and cleavage from the resin gives

- 20 3-[4-(3-guanidinophenylacetyl)semicarbazido]-3-(4-chlorophenyl)propionic acid, trifluoroacetate.

RT = 22.8 (0 → 50% B, 30 min)

MS (ESI): m/e = 419.0 ([M+H]⁺).

25 Example 3:

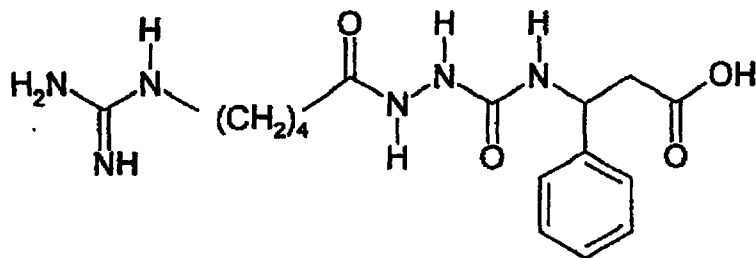
- 0.24 mmol of "CD" is washed with NMP (7 × 5 ml) and deprotected twice with 20% piperidine in 7 ml of DMF, first for 5 min and then for 15 min. The resin is then washed with NMP (5 × 7 ml) and DMF (2 × 7 ml), admixed with a solution of 0.48 mmol of 3-(9H-fluoren-9-ylmethoxycarbonylamino)valeric acid, 0.48 mmol of HATU and 2.4 mmol of collidine in 5 ml of DMF and shaken at room temperature for 90 min. The resin is washed and deprotected as described.

The resin is subsequently admixed with a solution of 2.4 mmol of N,N'-bis-BOC-1-guanylpurazole ("DE") in 4 ml of chloroform and left at 50° for 16 hours. The resin is washed with DCM.

- 5 To remove the BOC groups, the resin is shaken with a mixture of 95% TFA and 5% triisopropylsilane (5 ml) at room temperature, first for 90 min and then for 30 min. Removal of the solvent and purification by preparative RP-HPLC gives 3-[4-(3-guanidinopentanoyl)semi-
- 10 carbazido]-3-phenylpropionic acid, trifluoroacetate.

RT = 18.2 (0 → 50% B, 30 min)

MS (ESI): m/e = 365.1 ([M+H]⁺).



15

Example 4:

- Analogously to Example 3, reaction of "EF" with 3-(9H-fluoren-9-ylmethoxycarbonylamino)valeric acid followed by removal of the Fmoc group, reaction with
- 20 "DE" and removal of the BOC group and cleavage from the resin gives

3-[4-(3-guanidinopentanoyl)semicarbazido]-
3-(4-chlorophenyl)propionic acid, trifluoroacetate.

RT = 21.9 (0 → 50% B, 30 min)

- 25 MS (ESI): m/e = 399.1 ([M+H]⁺).

Example 5:

- 0.60 mmol of "EF" is washed with 20 ml of NMP and deprotected twice with 20% piperidine in 20 ml of DMF,
- 30 first for 5 min and then for 15 min. The resin is then washed with NMP (5 × 20 ml) and DMF (2 × 20 ml), admixed with a solution of 0.90 mmol of N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid, 0.90 mmol

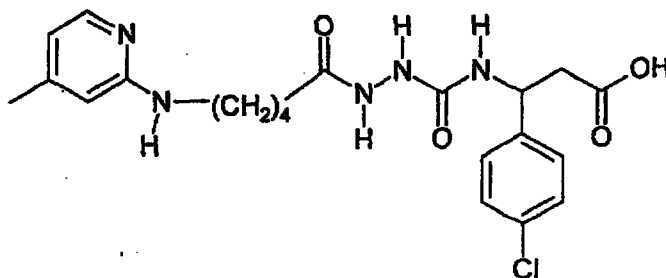
of HATU and 6.0 mmol of collidine in 5 ml of DMF and shaken at room temperature overnight. The resin is washed with DMF, NMP and DCM. To cleave the washed resin from the solid phase, it is shaken with 20 ml of
5 a mixture of DCM/acetic acid/trifluoroethanol (3:1:1) at room temperature, first for 90 min and then for 30 min.

Removal of the solvent gives 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semicarbazido}-3-(4-chlorophenyl)-
10 propionic acid, acetate.

Purification by preparative HPLC gives 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]-semicarbazido}-3-(4-chlorophenyl)propionic acid, trifluoroacetate.

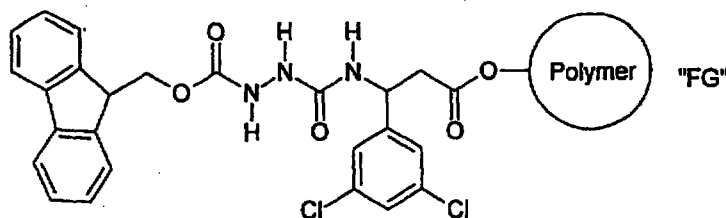
15 RT = 19.3 (10 → 60% B, 30 min)

MS (ESI): m/e = 448.1 ([M+H]⁺).



Example 6:

20 1. Analogously to Example 5, reaction of "FG", prepared by reaction of "AB" with resin-bonded Fmoc-protected β-(3,5-dichlorophenyl)alanine



with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid,
25 and cleavage from the resin, gives

3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]}-semicarbazido}-3-(3,5-dichlorophenyl)propionic acid, acetate.

Purification by preparative HPLC gives

5 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]}-semicarbazido}-3-(3,5-dichlorophenyl)propionic acid, trifluoroacetate.

RT = 19.3 (0 → 60% B, 30 min)

MS (ESI): m/e = 483.4 ([M+H]⁺).

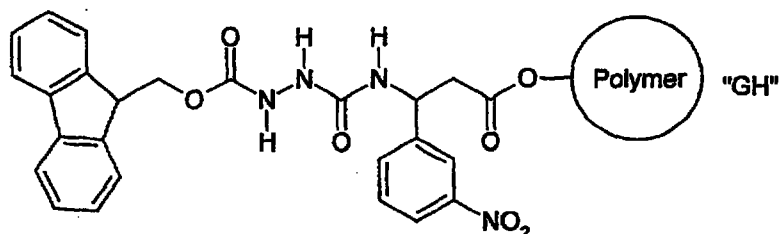
10 If the reaction solution is, after cleavage from the resin and after removal of the solid phase by filtration, acidified to pH 4.0 using hydrochloric acid, the inner salt of 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]}semicarbazido}-3-(3,5-dichloro-

15 phenyl)propionic acid is formed.

RT = 19.2 (0 → 60% B, 30 min.)

2. Analogously to Example 5, reaction of "GH", prepared by reaction of "AB" with resin-bonded Fmoc-protected

20 β-(3-nitrophenyl)alanine



with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid, and cleavage from the resin, gives

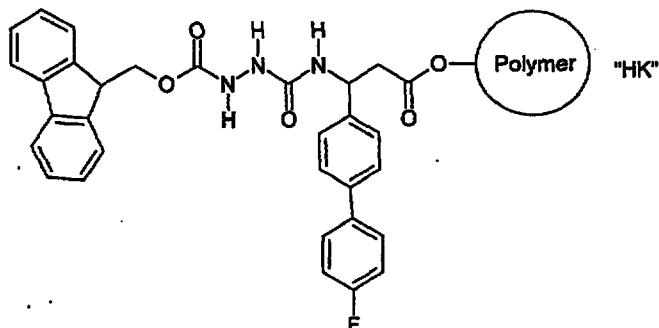
25 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]}semicarbazido}-3-(3-nitrophenyl)propionic acid, acetate.

Purification by preparative HPLC gives 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]}-semicarbazido}-3-(3-nitrophenyl)propionic acid, trifluoroacetate.

30 RT = 14.9 (0 → 60% B, 30 min)

MS (ESI): m/e = 459.5 ([M+H]⁺).

3. Analogously to Example 5, reaction of "HK", prepared by reaction of "AB" with resin-bonded Fmoc-protected β -(4-fluorophenyl)phenylalanine

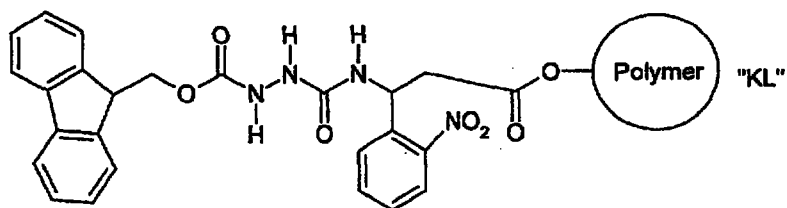


5 with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid, and cleavage from the resin, gives

3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semi-carbazido}-3-(4'-(4-fluoro)biphenyl)propionic acid, acetate.

10 Purification by preparative HPLC gives 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semi-carbazido}-3-(4'-(4-fluoro)biphenyl)propionic acid, trifluoroacetate.

15 4. Analogously to Example 5, reaction of "KL", prepared by reaction of "AB" with resin-bonded Fmoc-protected β -(2-nitrophenyl)alanine



20 with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid, and cleavage from the resin, gives

3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semi-carbazido}-3-(2-nitrophenyl)propionic acid, acetate.

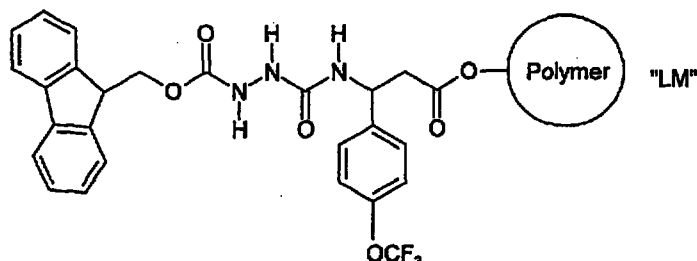
Purification by preparative HPLC gives 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semi-carbazido}-3-(2-nitrophenyl)propionic acid, trifluoro-

25 acetate.

RT = 14.7 (0 $\rightarrow$ 60% B, 30 min)

MS (ESI): $m/e = 459.5$ ($[M+H]^+$).

5. Analogously to Example 5, reaction of "LM", prepared by reaction of "AB" with resin-bonded Fmoc-protected β -(4-trifluoromethoxyphenyl)alanine



with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid, and cleavage from the resin, gives

- 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]-semicarbazido}-3-(4-trifluoromethoxyphenyl)propionic acid, acetate.

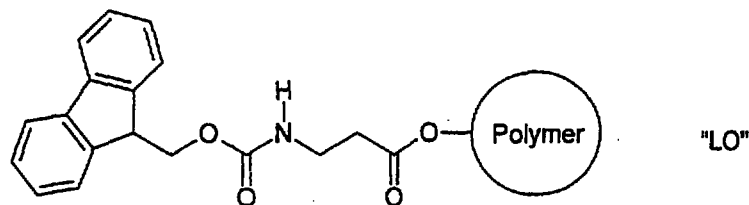
- Purification by preparative HPLC gives 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semicarbazido}-3-(4-trifluoromethoxyphenyl)propionic acid, trifluoroacetate.

RT = 19.8 (0 → 60% B, 30 min)

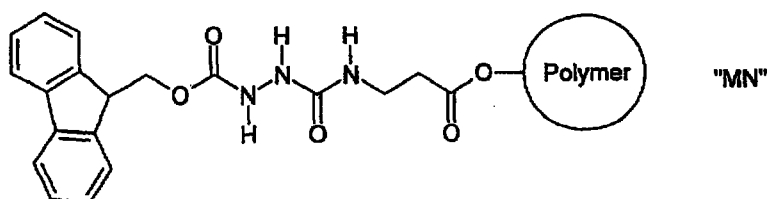
MS (ESI): $m/e = 498.5$ ($[M+H]^+$).

Example 7:

- 20 Analogously to Example 1.2, reaction of trityl chloride polystyrene resin with Fmoc-protected 3-aminopropionic acid gives the resin "LO"



- which is deprotected analogously to Example 1.3 and reacted with "AB" to give "MN"

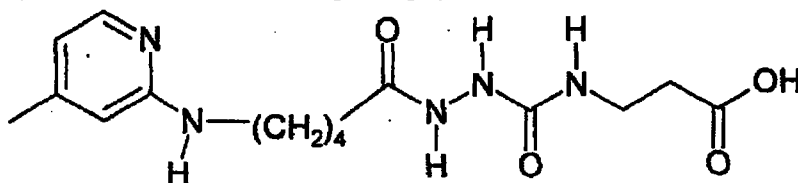


Analogously to Example 5, "MN" is reacted with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid. After
 5 cleavage from the resin, 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semicarbazido}-3-propionic acid, acetate, is obtained.

Purification by preparative HPLC gives
 10 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semi-carbazido}-3-propionic acid, trifluoroacetate.

RT = 7.3 (0 → 60% B, 30 min)

MS (ESI): $m/e = 338.4$ ($[M+H]^+$).



15 Example 8:

1. **3-phenylglutaric anhydride**

10 mmol of 3-phenylglutaric acid and 30 mmol of acetic anhydride are heated under reflux until they have dissolved completely. After cooling, 3 ml of diethyl
 20 ether are added and the precipitate is filtered off and washed with diethyl ether. This gives 3-phenylglutaric anhydride.

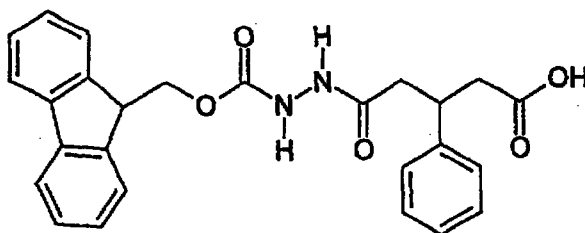
$^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 2.85$ (dd, 2H, $\text{CH}(\text{HCH})_2$),
 25 3.1 (dd, 2H, $\text{CH}(\text{CHH})_2$), 3.4 (m, 1H, $\text{CH}(\text{CH}_2)_2$), 7.15-7.45 (m, 5H, arom. H).

2. **5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-phenylpentanoic acid**

30 2.0 mmol of 3-phenylglutaric anhydride and 2.0 mmol of Fmoc-hydrazine are dissolved in 30 ml of THF and heated

under reflux for 16 hours. The product is then extracted with 50 ml of DCM and 50 ml of 1N HCl solution and the organic phase is dried with MgSO_4 and filtered off. Removal of the solvent gives
5 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-phenylpentanoic acid.

RT = 10.4 (30 $\rightarrow$ 80% B, 30 min); MS (ESI): m/e = 910.8 ($[2\text{M}+\text{Na}]^+$).



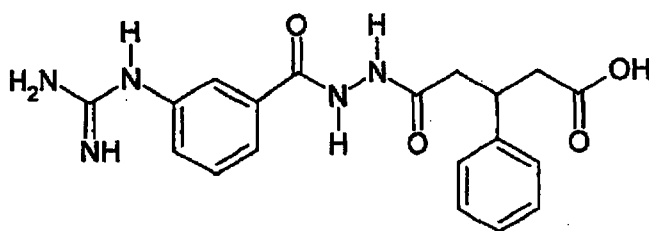
10

3. 5-[N'-(3-guanidinobenzoyl)hydrazino]-5-oxo-3-phenylpentanoic acid

5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
15 3-phenylpentanoic acid is deprotected analogously to the method described in Example 1. The deprotected compound is then admixed with a solution of 2.0 mmol of N,N'-bis-BOC-1-guanylpurazole ("DE") in 4 ml of chloroform and left at 50° for 16 hours. The solvent is
20 removed under reduced pressure. To remove the BOC groups, the residue is stirred with a mixture of 95% TFA and 5% triisopropylsilane (5 ml) at room temperature, first for 90 min and then for 30 min. Removal of the solvent and purification by preparative RP-HPLC
25 give 5-[N'-(3-guanidinobenzoyl)hydrazino]-5-oxo-3-phenylpentanoic acid, trifluoroacetate.

RT = 17.0 (10 $\rightarrow$ 50% B, 30 min)

MS (ESI): m/e = 384.1 ($[M+H]^+$).

Example 9:

1. Analogously to Example 5, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-

5 3-phenylpentanoic acid with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid gives

4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]}-hydrazinocarbonyl}-3-phenylbutyric acid, acetate.

RT = 22.1 (10 → 60% B, 30 min)

10 MS (ESI): m/e = 413.1 ([M+H]⁺).

2. Analogously to Example 5, reaction of (3R)-5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-chlorophenyl)pentanoic acid

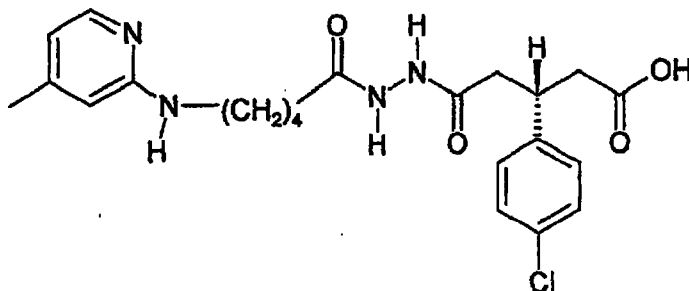
15 with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid gives

(3R)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]}-hydrazinocarbonyl}-3-(4-chlorophenyl)butyric acid, acetate.

20 MS (FAB): m/e = 447.9 ([M+H]⁺).

If the reaction solution is, after cleavage from the resin and after removal of the solid phase by filtration, acidified to pH 4.0 using hydrochloric acid, the inner salt of

25 (3R)-4-{N'-[5-(4-methylpyrid-2-ylamino)-pentanoyl]}hydrazinocarbonyl}-3-(4-chlorophenyl)butyric acid is formed.



Example 10:

Analogously to Example 3, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-chlorophenyl)pentanoic acid

5 with 3-(9H-fluoren-9-ylmethoxycarbonylamino)valeric acid, followed by removal of the Fmoc group, reaction with "DE" and removal of the BOC group, gives

4-[N'-(5-guanidinopentanoyl)hydrazinocarbonyl]-3-phenylbutyric acid, trifluoroacetate.

10 RT = 19.4 (0 → 50% B, 30 min)

MS (ESI): m/e = 364.2 ([M+H]⁺).

Example 11:

Analogously to Example 5, reaction of 15 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxopentanoic acid, prepared analogously to Example 8.2 by reacting glutaric anhydride with Fmoc-hydrazine,

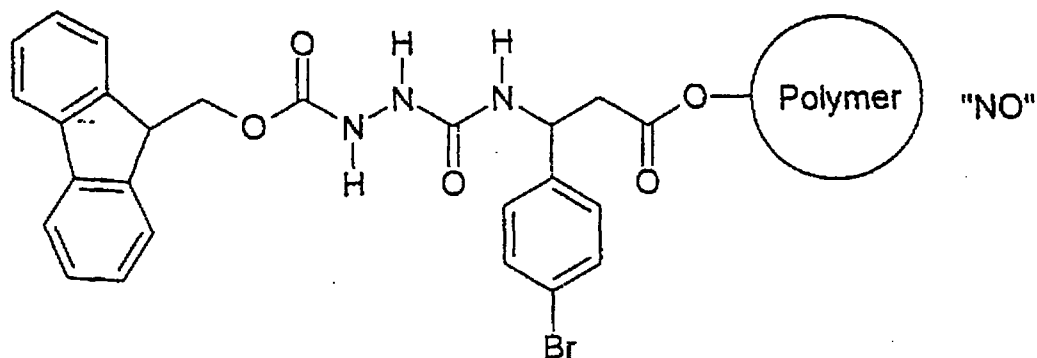
20 with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid gives

4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]-hydrazinocarbonyl}butyric acid, acetate.

MS (ESI): m/e = 337.4 ([M+H]⁺).

25 Example 12:

1. Analogously to Example 5, reaction of "NO", prepared by reaction of "AB" with resin-bound Fmoc-protected β-(4-bromophenyl)alanine,



30 with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid and cleavage from the resin gives

3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semi-carbazido}-3-(4-bromophenyl)propionic acid, acetate.

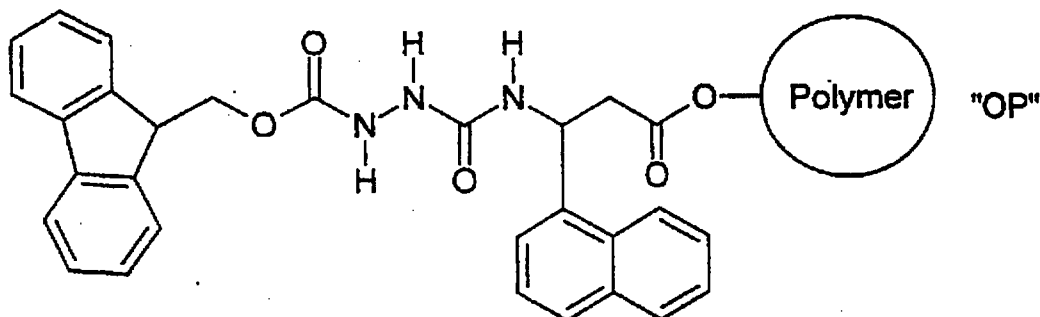
Preparative HPLC gives 3-{4-5-(4-methylpyrid-2-ylamino)pentanoyl]semicarbazido}-3-(4-bromophenyl)-

5 propionic acid, trifluoroacetate.

RT = 17.0 (0 → 60% B, 30 min.)

MS (ESI): m/e = 493.4 ([M+H]⁺).

2. Analogously to Example 5, reaction of "OP", prepared
10 by reaction of "AB" with resin-bound Fmoc-protected β-(naphthalen-1-yl)alanine,



with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid and cleavage from the resin gives

15 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semi-carbazido}-3-(naphthalin-1-yl)propionic acid, acetate.

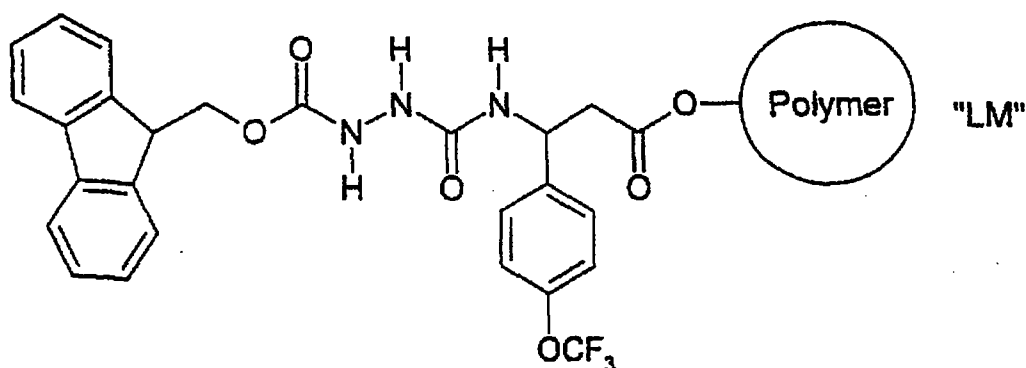
Preparative HPLC gives 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]semicarbazido}-3-(naphthalin-1-yl)propionic acid, trifluoroacetate.

20 RT = 17.6 (0 → 60% B, 30 min.)

MS (ESI): m/e = 464.5 ([M+H]⁺).

Example 13:

1. Analogously to Example 1, reaction of "LM", prepared
25 by reaction of "AB" with resin-bound Fmoc-protected β-(4-trifluoromethoxyphenyl)alanine,



with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid, followed by removal of the Fmoc group and reaction with "DE" and removal of the BOC group and
 5 cleavage from the resin gives

3-[4-(3-guanidinobenzoyl)semicarbazido]-3-(4-trifluoromethoxyphenyl)propionic acid, trifluoroacetate.

RT = 17.6 (0 → 60% B, 30 min.)

10 MS (ESI): m/e = 468.5 ([M+H]⁺).

Example 14:

1. Analogously to Example 1, reaction of "FG" with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid,
 15 followed by removal of the Fmoc group and reaction with "DE" and removal of the BOC group and cleavage from the resin gives

3-[4-(3-guanidinobenzoyl)semicarbazido]-3-(3,5-dichlorophenyl)propionic acid, trifluoroacetate.

20 RT = 17.0 (0 → 60% B, 30 min.)

MS (ESI): m/e = 454.3 ([M+H]⁺).

2. Analogously to Example 1, reaction of "OP" with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid,
 25 followed by removal of the Fmoc group and reaction with "DE" and removal of the BOC group and cleavage from the resin gives

3-[4-(3-guanidinobenzoyl)semicarbazido]-3-naphthylpropionic acid, trifluoroacetate,

30 RT = 15.9 (0 → 60% B, 30 min.)

MS (ESI): m/e = 435.5 ([M+H]⁺).

3. Analogously to Example 1, reaction of "NO" with
3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid,
followed by removal of the Fmoc group and reaction with
5 "DE" and removal of the BOC group and cleavage from the
resin gives

3-[4-(3-guanidinobenzoyl)semicarbazido]-
3-(4-bromophenyl)propionic acid, trifluoroacetate.

RT = 14.9 (0 → 60% B, 30 min.)

10 MS (ESI): m/e = 464.3 ([M+H]⁺).

4. Analogously to Example 5, reaction of "CD" with
N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid and
cleavage from the resin gives

15 3-{4-[5-(4-methylpyrid-2-ylamino)pentanoyl]-
semicarbazido}-3-phenylpropionic acid, acetate.
Preparative HPLC gives 3-{4-[5-(4-methylpyrid-2-
ylamino)pentanoyl]semicarbazido}-3-phenylpropionic
acid, trifluoroacetate.

20 RT = 13.2 (0 → 60% B, 30 min.)

MS (ESI): m/e = 414.5 ([M+H]⁺).

Example 15:

1. Analogously to Example 9, reaction of 5-[N'-(9H-
25 fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(4-bromophenyl)pentanoic acid, prepared by reaction
of 3-(4-bromophenyl)glutaric anhydride with Fmoc-
hydrazine,
with N-(2-(4-methylpyridyl)-5-aminovaleric acid gives
30 3-(4-bromophenyl)-4-{N'-[5-(4-methylpyrid-2-
ylamino)pentanoyl]hydrazinocarbonyl}butyric acid,
acetate.

Preparative HPLC gives 3-(4-bromophenyl)-4-{N'-
[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazino-
35 carbonyl}butyric acid, trifluoroacetate.

RT = 17.0 (0 → 60% B, 30 min.)

MS (ESI): m/e = 492.4 ([M+H]⁺).

2. Analogously to Example 8, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-bromophenyl)pentanoic acid with "DE" gives

3-(4-bromophenyl)-5-{N'-[1-(3-guanidino-phenyl)methanoyl]hydrazino}-5-oxopentanoic acid, tri-fluoroacetate.

RT = 15.0 (0 → 60% B, 30 min.)

MS (ESI): m/e = 463.3 ([M+H]⁺).

3. Analogously to Example 1, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-bromophenyl)pentanoic acid with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid and naphthalen-2-ylmethyl thioacetimidate gives

5-[N'-{1-(3-acetimidoylaminophenyl)methanoyl}hydrazino]-3-(4-bromophenyl)-5-oxopentanoic [sic] acid, trifluoroacetate.

RT = 15.4 (0 → 60% B, 30 min.)

MS (ESI): m/e = 462.3 ([M+H]⁺).

20

Example 16:

1. Analogously to Example 9, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-fluorophenyl)pentanoic acid, prepared by reaction of 3-(4-fluorophenyl)glutaric anhydride with Fmoc-hydrazine, with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid gives

3-(4-fluorophenyl)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazinocarbonyl}butyric acid, acetate.

Preparative HPLC gives 3-(4-fluorophenyl)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazinocarbonyl}butyric acid, trifluoroacetate.

RT = 14.1 (0 → 60% B, 30 min.)

MS (ESI): m/e = 431.5 ([M+H]⁺).

2. Analogously to Example 8, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-fluorophenyl)pentanoic acid with "DE" gives

3-(4-fluorophenyl)-5-{N'-[1-(3-guanidino-phenyl)methanoyl]hydrazino}-5-oxopentanoic acid, tri-fluoroacetate.

RT = 11.2 (0 → 60% B, 30 min.)

MS (ESI): m/e = 402.4 ([M+H]⁺).

3. Analogously to Example 1, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-fluorophenyl)pentanoic acid with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid and naphthalen-2-ylmethyl thioacetimidate gives

5-{N'-[1-(3-acetimidoylaminophenyl)methanoyl]hydrazino}-3-(4-fluorophenyl)-5-oxopentanoic acid, tri-fluoroacetate.

RT = 12.0 (0 → 60% B, 30 min.)

MS (ESI): m/e = 401.4 ([M+H]⁺).

20

Example 17:

1. Analogously to Example 9, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-chlorophenyl)pentanoic acid, prepared by reaction of 3-(4-chlorophenyl)glutaric anhydride with Fmoc-hydrazine, with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid gives

3-(4-chlorophenyl)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazinocarbonyl}butyric acid, acetate,

Preparative HPCL gives 3-(4-chlorophenyl)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazinocarbonyl}butyric acid, trifluoroacetate.

RT = 16.3 (0 → 60% B, 30 min.)

MS (ESI): m/e = 447.9 ([M+H]⁺).

2. Analogously to Example 8, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-chlorophenyl)pentanoic acid with "DE" gives

3-(4-chlorophenyl)-5-{N'-[1-(3-guanidinophenyl)-methanoyl]hydrazino}-5-oxopentanoic acid, trifluoroacetate,

RT = 13.9 (0 → 60% B, 30 min.)

MS (ESI): m/e = 418.9 ([M+H]⁺).

10 3. Analogously to Example 1, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-chlorophenyl)pentanoic acid with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid and naphthalen-2-ylmethyl thioacetimidate gives

15 5-{N'-[1-(3-acetimidoylamino)phenyl]methanoyl}-hydrazino}-3-(4-chlorophenyl)-5-oxopentanoic acid, trifluoroacetate,

MS (ESI): m/e = 417.9 ([M+H]⁺).

20 4. Analogously to Example 3, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(4-chlorophenyl)pentanoic acid with 3-(9H-fluoren-9-ylmethoxycarbonylamino)valeric acid and "DE" gives

25 3-(4-chlorophenyl)-5-[N'-(5-guanidinopentanoyl)-hydrazino]-5-oxopentanoic acid, trifluoroacetate,

RT = 13.7 (0 → 60% B, 30 min.)

MS (ESI): m/e = 398.5 ([M+H]⁺).

Example 18:

30 1. Analogously to Example 9, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3,5-dichlorophenyl)pentanoic acid, prepared by reaction of 3-(3,5-dichlorophenyl)glutaric anhydride with Fmoc-hydrazine,

35 with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid gives

3-(3,5-dichlorophenyl)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazinocarbonyl}butyric acid, acetate.

Preparative HPLC gives 3-(3,5-dichlorophenyl)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazinocarbonyl}-butyric acid, trifluoroacetate.

RT = 18.7 (0 → 60% B, 30 min.)

MS (ESI): m/e = 482.4 ([M+H]⁺).

10 2. Analogously to Example 8, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3,5-dichlorophenyl)pentanoic acid with "DE" gives

3-(3,5-dichlorophenyl)-5-{N'-[1-(3-guanidino-phenyl)methanoyl]hydrazino}-5-oxopentanoic acid, trifluoroacetate

RT = 17.7 (0 → 60% B, 30 min.)

MS (ESI): m/e = 453.3 ([M+H]⁺).

20 3. Analogously to Example 1, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3,5-dichlorophenyl)pentanoic acid with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid and naphthalen-2-ylmethyl thioacetimidate gives

25 5-{N'-[1-(3-acetimidoylaminophenyl)methanoyl]hydrazino}-3-(3,5-dichlorophenyl)-5-oxopentanoic acid, trifluoroacetate.

RT = 16.6 (0 → 60% B, 30 min.)

MS (ESI): m/e = 452.3 ([M+H]⁺).

30

4. Analogously to Example 9, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3,5-dichlorophenyl)pentanoic acid with 3-(pyrid-2-ylamino)benzoic acid gives

35 3-(3,5-dichlorophenyl)-5-oxo-5-{N'-[3-(pyrid-2-ylamino)benzoyl]hydrazino}pentanoic acid, acetate.

RT = 33.5 (0 → 60% B, 30 min.)

MS (ESI): m/e = 488.3 ([M+H]⁺).

5. Analogously to Example 3, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
5 3-(3,5-dichlorophenyl)pentanoic acid
with 3-(9H-fluoren-9-ylmethoxycarbonylamino)valeric
acid and "DE" gives
3-(3,5-dichlorophenyl)-5-[N'-
(5-guanidinopentanoyl)hydrazino]-5-oxopentanoic acid,
10 trifluoroacetate.

6. Analogously to Example 9, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(3,5-dichlorophenyl)pentanoic acid
15 with 4-(pyrid-2-ylamino)butyric acid gives
3-(3,5-dichlorophenyl)-5-oxo-5-{N'-[4-(pyrid-
2-ylamino)butanoyl]hydrazino] pentanoic acid, acetate.
Preparative HPLC gives 3-(3,5-dichlorophenyl)-
5-oxo-5-{N'-[4-(pyrid-2-ylamino)butanoyl]hydrazino]-
20 oxopentanoic acid, trifluoroacetate

7. Analogously to Example 9, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(3,5-dichlorophenyl)pentanoic acid with
25 4-(1H-imidazol-2-ylamino)butyric acid gives
3-(3,5-dichlorophenyl)-5-oxo-5-{N'-[4-(1H-
imidazol-2-ylamino)butanoyl]hydrazino]pentanoic acid,
acetate.
Preparative HPLC gives 3-(3,5-dichlorophenyl)-5-oxo-
30 5-{N'-[4-(1H-imidazol-2-ylamino)butanoyl]hydrazino]-
pentanoic acid, trifluoroacetate.
MS (ESI): m/e = 443.3 ([M+H]⁺).

Example 19:

35 1. Analogously to Example 9, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(biphenyl-4-yl)pentanoic acid, prepared by reaction

of 3-(biphenyl-4-yl)glutaric anhydride with Fmoc-hydrazine,
with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid
gives

- 5 3-(biphenyl-4-yl)-4-{N'-[5-(4-methylpyrid-2-ylamino)pentanoyl]hydrazinocarbonyl}butyric acid, acetate.

RT = 20.3 (0 → 60% B, 30 min.)

MS (ESI): m/e = 489.6 ([M+H]⁺).

10

2. Analogously to Example 8, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(biphenyl-4-yl)pentanoic acid with "DE" gives

- 15 3-biphenyl-4-yl-5-{N'-[1-(3-guanidinophenyl)-methanoyl]hydrazino}-5-oxopentanoic acid, trifluoroacetate.

RT = 19.3 (0 → 60% B, 30 min.)

MS (ESI): m/e = 460.5 ([M+H]⁺).

- 20 3. Analogously to Example 1, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(biphenyl-4-yl)pentanoic acid with 3-(9H-fluoren-9-ylmethoxycarbonylamino)benzoic acid and naphthalen-2-ylmethyl thioacetimidate gives

- 25 5-{N'-[1-(3-acetimidoethylaminophenyl)methanoyl]-hydrazino}-3-biphenyl-4-yl-5-oxopentanoic acid, trifluoroacetate.

RT = 19.6 (0 → 60% B, 30 min.)

MS (ESI): m/e = 459.5 ([M+H]⁺).

30

Example 20:

1. Analogously to Example 9, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3,5-dichloro-2-hydroxyphenyl)pentanoic acid,
35 prepared by reaction of 3-(3,5-dichloro-2-hydroxyphenyl)glutaric anhydride with Fmoc-hydrazine, with 4-(pyridin-2-ylamino)butyric acid gives

3-(3,5-dichloro-2-hydroxyphenyl)-5-oxo-{5-[4-pyrid-2-ylamino)butanoyl]hydrazino}pentanoic acid, acetate.

Preparative HPLC gives 3-(3,5-dichloro-2-hydroxyphenyl)-5-oxo-5-{N'-[4-pyrid-2-ylamino)butanoyl]hydrazino}pentanoic acid, trifluoroacetate.

MS (ESI): m/e = 470.3 ([M+H]⁺).

10 2. Analogously to Example 9, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3,5-dichloro-2-hydroxyphenyl)pentanoic acid with 4-(1H-imidazol-2-ylamino)butyric acid gives

15 3-(3,5-dichloro-2-hydroxyphenyl)-5-oxo-5-{N'-[4-(1H-imidazol-2-ylamino)butanoyl]hydrazino}pentanoic acid, acetate.

Preparative HPLC gives 3-(3,5-dichloro-2-hydroxyphenyl)-5-oxo-5-{N'-[4-(1H-imidazol-2-ylamino)butanoyl]hydrazino}pentanoic acid, trifluoroacetate

MS (ESI): m/e = 459.3 ([M+H]⁺).

Example 21:

1. Analogously to Example 9, reaction of 25 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3-nitrophenyl)pentanoic acid, prepared by reaction of 3-(3-nitrophenyl)glutaric anhydride with Fmoc-hydrazine,

with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid gives

30 3-(3-nitrophenyl)-4-{N'-[5-(4-methylpyridin-2-ylamino)pentanoyl]hydrazinocarbonyl}butyric acid, acetate.

MS (ESI): m/e = 458.5 ([M+H]⁺).

35

2. Analogously to Example 8, reaction of 5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-3-(3-nitrophenyl)pentanoic acid with "DE" gives

5-{N'-[1-(3-guanidinophenyl)methanoyl]hydrazino}-
3-(3-nitrophenyl)-5-oxopentanoic acid, trifluoro-
acetate.

RT = 11.3 (0 → 60% B, 30 min.)

5 MS (ESI): m/e = 429.4 ([M+H]⁺).

3. Analogously to Example 1, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(3-nitrophenyl)pentanoic acid with 3-(9H-fluoren-
10 9-ylmethoxycarbonylamino)benzoic acid and naphthalen-
2-ylmethyl thioacetimidate gives

5-{N'-[1-(3-acetamidoylaminophenyl)methanoyl]-
hydrazino}-3-(3-nitrophenyl)-5-oxopentanoic acid,
trifluoroacetate.

15

Example 22:

1. Analogously to Example 9, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(4-methoxyphenyl)pentanoic acid, prepared by reaction
20 of 3-(4-methoxyphenyl)glutaric anhydride with Fmoc-
hydrazine,
with N-(2-(4-methylpyridyl)-5-aminovaleric [sic] acid
gives

3-(4-methoxyphenyl)-4-{N'-[5-(4-methylpyridin-2-
25 ylamino)pentanoyl]hydrazinocarbonyl}butyric acid,
acetate.

RT = 13.7 (0 → 60% B, 30 min.)

MS (ESI): m/e = 443.4 ([M+H]⁺).

30 2. Analogously to Example 8, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(4-methoxyphenyl)pentanoic acid with "DE" gives

5-{N'-[1-(3-guanidinophenyl)methanoyl]hydrazino}-
3-(4-methoxyphenyl)-5-oxopentanoic acid, trifluoro-
35 acetate.

RT = 10.6 (0 → 60% B, 30 min.)

MS (ESI): m/e = 414.4 ([M+H]⁺).

3. Analogously to Example 1, reaction of
5-[N'-(9H-fluoren-9-ylmethoxycarbonyl)hydrazino]-5-oxo-
3-(4-methoxyphenyl)pentanoic acid with 3-(9H-fluoren-
9-ylmethoxycarbonylamino)benzoic acid and naphthalen-2-
5 ylmethyl thioacetimidate gives

5-{N'-[1-(3-
acetimidoylaminophenyl)methanoyl]hydrazino}-
3-(4-methoxyphenyl)-5-oxopentanoic acid, trifluoro-
acetate.
10 RT = 10.5 (0 → 60% B, 30 min.)
MS (ESI): m/e = 413.4 ([M+H]⁺).

The examples below relate to pharmaceutical
preparations:
15

Example A: injection vials

A solution of 100 g of an active compound of the
formula I and 5 g of disodium hydrogen phosphate in 3 l
20 of doubly distilled water is brought to pH 6.5 with 2 N
hydrochloric acid and subjected to sterile filtration,
and injection vials are filled with the solution, which
is lyophilized under sterile conditions and closed
under sterile conditions. Each injection vial contains
25 5 mg of active compound.

Example B: suppositories

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

35 **Example C: solution**

A solution is prepared from 1 g of an active compound
of the formula I, 9.38 g of NaH₂PO₄·2H₂O, 28.48 g of

$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of doubly distilled water. It is brought to pH 6.8, topped up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

5

Example D: ointment

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

10

Example E: tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed to tablets in the customary manner such that each tablet contains 10 mg of active compound.

15

Example F: coated tablets

20

Tablets are pressed analogously to Example E and are then coated in the customary manner with a coating of sucrose, potato starch, talc, tragacanth and dyestuff.

Example G: capsules

25

Hard gelatin capsules are filled with 2 kg of active compound of the formula I in the customary manner such that each capsule contains 20 mg of the active compound.

30

Example H: ampoules

A solution of 1 kg of active compound of the formula I in 60 l of doubly distilled water is subjected to sterile filtration, and ampoules are filled with the solution, which is lyophilized under sterile conditions

35

and closed under sterile conditions. Each ampoule contains 10 mg of active compound.

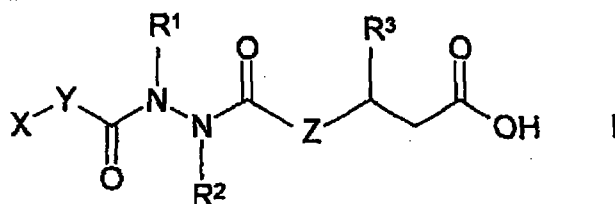
Example I: inhalation spray

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

Patent claims

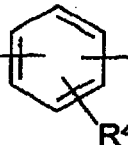


1. Compounds of the formula I



5 in which

X is $\text{H}_2\text{N}-\text{C}(=\text{NH})-\text{NH}-$, $\text{H}_3\text{C}-\text{C}(=\text{NH})-\text{NH}$ or $\text{Het}^1-\text{NH}-$,

Y is $-(\text{CH}_2)_n-$ or $-(\text{CH}_2)_m-$  $-(\text{CH}_2)_o-$

is

Z is $\text{N}-\text{R}^2$ or $\text{CH}-\text{R}^2$,

10 R^1 , R^2 are each independently of one another H or A,

R^3 is H, Ar or Het,

R^4 is H, A, Ar, OH, OA, OAr, arylalkyl, Hal, CN, NO_2 , CF_3 or OCF_3

A is alkyl having 1 to 6 carbon atoms,

15 Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA, CF_3 , OCF_3 , CN, NO_2 or Hal and which may be substituted by a phenyl which is mono-, di- or trisubstituted by A, OH, OA, CF_3 , OCF_3 , CN, NO_2 or Hal such that an unsubstituted or substituted biphenyl is formed or naphthyl which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA, CF_3 , OCF_3 , CN, NO_2 or Hal,

25 Hal is F, Cl, Br or I,

Het is a saturated, partially or fully unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 nitrogen and/or 1 or 2 sulfur or oxygen atoms



may be present and where the heterocyclic radical may be mono- or disubstituted by CN, Hal, OH, OA, CF₃, A, NO₂ or OCF₃,

Het¹ is a 5- or 6-membered aromatic heterocycle having 1 to 4 nitrogen atoms which may be unsubstituted or mono- or disubstituted by Hal, A, OA, Ar, OAr, arylalkyl, CN, NO₂, CF₃ or OCF₃,

n is 2, 3, 4, 5 or 6,

m, o are 0, 1 or 2,

and their physiologically acceptable salts and solvates.

2. Compounds of the formula I according to Claim 1

a) 5-[N'-(3-guanidinobenzoyl)hydrazino]-5-oxo-3-phenylpentanoic acid

b) 3-[4-(3-guanidinophenylacetyl)semicarbazido]-3-phenylpropionic acid,

c) 3-[4-(3-guanidinobenzoyl)semicarbazido]-3-phenylpropionic acid,

d) 4-{N'-[5-(4-methylpyridin-2-ylamino)pentanoyl]-hydrazinocarbonyl}-3-phenylbutyric acid,

e) 3-[4-(5-guanidinopentanoyl)semicarbazido]-3-phenylpropionic acid,

f) 4-[N'-(5-guanidinopentanoyl)hydrazinocarbonyl]-3-phenylbutyric acid,

g) 3-[4-(3-guanidinobenzoyl)semicarbazido]-3-(4-chlorophenyl)propionic acid,

h) 3-{4-[5-(4-methylpyridin-2-ylamino)pentanoyl]-semicarbazido}-3-(4-chlorophenyl)propionic acid,

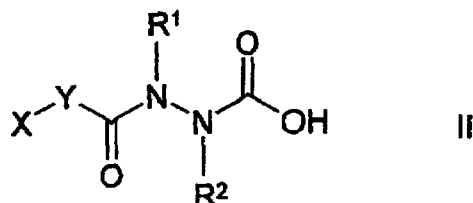
i) 3-[4-(5-guanidinopentanoyl)semicarbazido]-3-(4-chlorophenyl)propionic acid,

and their physiologically acceptable salts or solvates.

3. Process for preparing compounds of the formula I according to Claim 1 and their salts, characterized in that

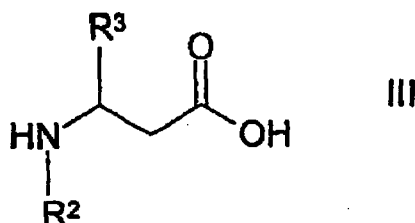


a) to prepare a compound of the formula I in which Z is N-R², a compound of the formula II



5 in which X, Y, R¹ and R² are as defined in Claim 1 and in which free amino groups are protected by a suitable amino protective group,

is reacted with a compound of the formula III

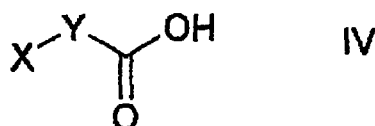


10 in which R² and R³ are as defined in Claim 1 and in which a free hydroxyl group is protected by a suitable hydroxyl protective group or attached to a solid phase,

15 and the protective groups and/or the solid phase are subsequently removed,

or

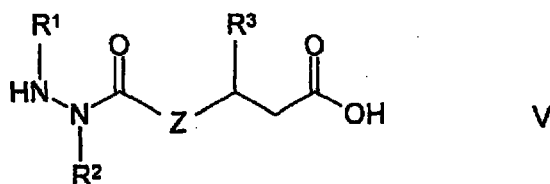
20 b) a compound of the formula IV



25 in which X and Y are as defined in Claim 1 and in which free amino groups are protected by a suitable amino protective group



is reacted with a compound of the formula V



in which R^1 , R^2 , R^3 and Z are as defined in Claim 1
and in which a free hydroxyl group is protected by
a suitable hydroxyl protective group or attached to
a solid phase,

and the protective groups and/or the solid phase
are subsequently removed;

or

c) a compound of the formula I is liberated from
one of its functional derivatives by treatment with
a solvolysing or hydrogenolysing agent,

and/or in that a basic or acidic compound of the
formula I is converted into one of its salts by
treatment with an acid or base.

20

4. Compounds of the formula I according to Claim 1 and
their physiologically acceptable salts or solvates
for use as therapeutically active compounds.

25 5. Compounds of the formula I according to Claim 1 and
their physiologically acceptable salts or solvates
for use as integrin inhibitors.

30 6. Compounds of the formula I according to Claim 1 and
their physiologically acceptable salts or solvates
for use in controlling diseases.

7. Pharmaceutical preparation, characterized in that
it comprises at least one compound of the formula I

according to Claim 1 and/or one of its physiologically acceptable salts or solvates.

- 5 8. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts or solvates for preparing a pharmaceutical preparation.
- 10 9. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts or solvates for preparing a pharmaceutical preparation for controlling thromboses, myocardial infarction, coronary heart diseases, arteriosclerosis, inflammations, tumours, osteoporosis, 15 infections and restenosis after angioplasty.
- 20 10. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts or solvates for pathological processes which are maintained or propagated by angiogenesis.

