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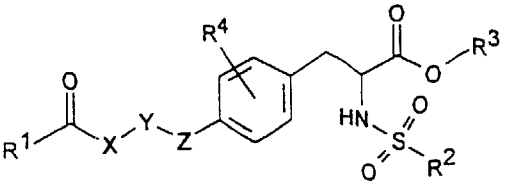
(54) **DERIVES DE PHENYLALANINE UTILISES COMME INHIBITEURS DE L'INTEGRINE**

(54) **PHENYLALAMINE DERIVATIVES AS INTEGRIN INHIBITORS**



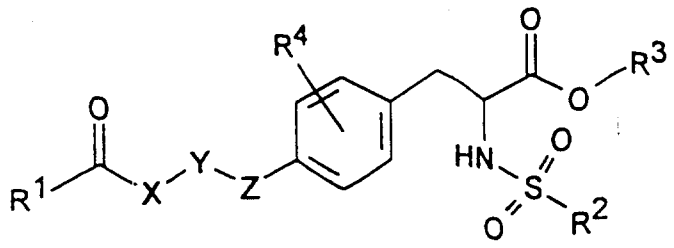
I

(57) Les composés de formule (I), dans laquelle X, Y, Z, R^1, R^2, R^3 et R^4 ont la signification donnée dans la revendication (1), à condition qu'au moins un élément choisi dans le groupe X, Y, Z soit CH_2, ainsi que leurs sels physiologiquement inoffensifs, peuvent être utilisés comme inhibiteurs de l'intégrine, en particulier pour la prophylaxie et le traitement de maladies du système circulatoire, en cas de thrombose, d'infarctus du myocarde, de maladie cardiaque coronarienne, d'artérioslérose, d'ostéoporose, lors de processus pathologiques qui sont maintenus ou propagés par angiogenèse, et également pour le traitement des tumeurs.

(57) Compounds of formula (I) wherein X, Y, Z, R^1, R^2, R^3 and R^4 have the meaning stated in claim 1, with the proviso that at least one element chosen from the group X, Y, Z must be CH_2, as well as their physiologically harmless salts, can be used as integrin inhibitors, particularly for prophylaxis and treatment of circulatory diseases, in case of thrombosis, heart infarct, coronary heart diseases, arteriosclerosis, osteoporosis, in pathological processes which are maintained or propagated by angiogenesis, and in tumor therapy.

Abstract

Compounds of the formula I



I

in which

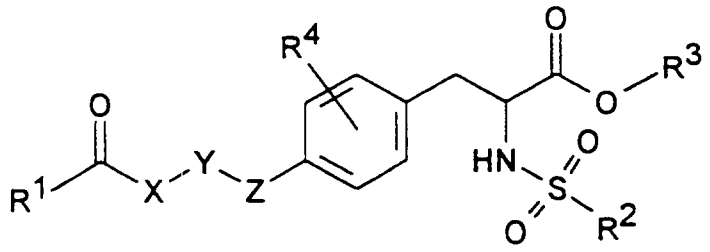
X, Y, Z, R^1, R^2, R^3 and R^4
have the meaning given in Claim 1,
with the proviso that at least one element selected from the group X, Y and Z must be CH_2

and the physiologically harmless salts thereof,

can be employed as integrin inhibitors, in particular for treating tumour diseases, osteoporoses and osteolytic diseases, and also for suppressing pathologically angiogenic diseases.

Phenylalanine derivatives

The invention relates to compounds of the formula I



I

in which

X is absent, or is alkylene, arylene, cycloalkylene having 4-8 carbon atoms, or heterocycloalkylene having from 1 to 3 N, O and/or S atoms which is unsubstituted or substituted once, twice or three times by A, oxo and/or R^4,

Y and Z are, in each case, independently of each other, absent, or are alkylene, O, S, NH, C(=O), CONH, NHCO, C(=S), SO_2NH, CA=CA' or -C≡C-,

R^1 is H_2N-C(=NH) or H_2N(C=NH)-NH, where the primary amino groups can also be provided with conventional amino protecting groups or can be substituted once, twice or three times by A, Ar or R^5,

R^2 is A, Ar or aralkylene,

R^3 is H or A,

R^4 is H, Hal, OA, NHA, NAA', CN, NO_2, SA, SOA, SO_2A, SO_2Ar or SO_3H,

R^5 is alkanoyl or cycloalkanoyl having 1-18 carbon atoms, in which one, two or three methylene groups can be replaced with N, O and/or S,
Ar-CO- or Ar-alkylene-CO-,

A and A' are, in each case, independently of each other, H, or alkyl or cycloalkyl having 1-15 carbon atoms which is unsubstituted or substituted once, twice or three times by R^4 and in which one, two or three methylene groups can be replaced with N, O and/or S,

Ar is a mononuclear or binuclear aromatic ring system having 0, 1, 2, 3 or 4 N, O and/or S atoms which is unsubstituted or substituted once, twice or three times by A and/or R^4,

Hal is F, Cl, Br or I,

with the proviso that at least one element selected from the group X, Y and Z must be CH_2,

and the physiologically harmless salts thereof.

Similar compounds are known, for example, from EP 0 478 363, EP 0 478 328, WO 94/12181 and WO 95/32710.

The underlying object of the invention was to discover novel compounds possessing valuable properties, in particular such compounds as can be used to prepare pharmaceuticals.

It has been found that the compounds of the formula I, and their salts, possess very valuable pharmacological properties while being well tolerated. In particular, they act as integrin inhibitors, in connection with which they inhibit, in particular, the interactions of

the α_v integrin receptors with ligands. The compounds exhibit particular activity in the case of the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. The compounds are very particularly active as adhesion receptor antagonists for the vitronectin receptor $\alpha_v\beta_3$. This effect can be demonstrated, for example, using the method which is described by J.W. Smith et al. in J. Biol. Chem. 265, 11008-11013 and 12267-12271 (1990).

The ability of some representative compounds of the formula I to inhibit the binding of vitronectin to receptors was proven experimentally. The pharmacological test data are summarized in Table I.

In Curr. Opin. Cell. Biol. 5, 864 (1993), B. Felding-Habermann and D.A. Cheresh describe the importance of the integrins, as adhesion receptors, for a very wide range of phenomena and syndromes, especially in relation to the vitronectin receptor $\alpha_v\beta_3$.

The dependence of the development 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 264 569-71 (1994).

The possibility of using a cyclic peptide to inhibit this interaction and thereby institute apoptosis (programmed cell death) of angiogenic vascular cells is reported by P.C. Brooks, A.M. Montgomery, M. Rosenfeld, R.A. Reisfeld, T.-Hu, G. Klier and D.A. Cheresh in Cell 79, 1157-64 (1994).

The experimental demonstration that the novel compounds also prevent adherence of living cells to the corresponding matrix proteins, and accordingly also prevent adherence of tumour cells to matrix proteins, can be provided in a cell adhesion test, which is carried out

in analogy with the method of F. Mitjans et al., J. Cell Science 108, 2825-2838 (1995).

In J. Clin. Invest. 96, 1815-1822 (1995), P.C. Brooks et al. describe $\alpha_v\beta_3$ antagonists for controlling cancer and for treating tumour-induced angiogenic diseases. The novel compounds of the formula I can therefore be employed as pharmaceutical active compounds, in particular for treating tumour diseases, osteoporoses and osteolytic diseases, and also for suppressing angiogenesis.

Compounds of the formula I which block the interaction of integrin receptors and ligands, for example of fibrinogen to (sic) the fibrinogen receptor (glycoprotein IIb/IIIa), prevent, as GPIIb/IIIa antagonists, the dissemination of tumour cells by means of metastasis. This is substantiated by the following observations:
Tumour cells are spread into the vascular system from a local tumour by the formation of microaggregates (microthrombi) as a result of interaction of the tumour cells with blood platelets. The tumour cells are shielded by being protected in the microaggregate and are not recognized by the cells of the immune system. The microaggregates can become attached to vessel walls, thereby 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 blood platelets, GPIIa/IIIb antagonists can be regarded as being effective metastasis inhibitors.

In addition to inhibiting the binding of fibrinogen, fibronectin and the Willebrand factor to the fibrinogen receptor of the blood platelets, compounds of the formula I also inhibit the binding of other adhesive proteins, such as vitronectin, collagen and laminin, to the corresponding receptors on the surface of different

cell types. They prevent, in particular, the development of blood platelet thrombi and can therefore be employed for treating thromboses, stroke, cardiac infarction, inflammations and arteriosclerosis.

The properties of the compounds can also be demonstrated using methods which are described in EP-A1-0 462 960. The inhibition of the binding of fibrinogen to the fibrinogen receptor can be demonstrated by the method which is given in EP-A1-0 381 033.
The experimental (sic) fact that the novel compounds, too, block inhibition of the binding of fibrinogen to the corresponding receptors was demonstrated experimentally in the case of some representative compounds of the formula I. The pharmacological test data are summarized in Table II.

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

Accordingly, the invention relates to compounds of the formula I according to Claim 1, and/or their physiologically harmless salts, for preparing a pharmaceutical for use as integrin inhibitors [sic]. The invention relates, in particular, to compounds of the formula I according to Claim 1, and/or their harmless salts, in which R^2 has the meaning of camphor-10-yl, for preparing a pharmaceutical for controlling pathologically angiogenic diseases, tumours, osteoporosis, inflammations and infections.

The compounds of the formula I may be employed, as pharmaceutical active compounds in humans and veterinary medicine, for the prophylaxis and/or therapy of thrombosis, myocardial infarction, arteriosclerosis, inflammations, stroke, angina pectoris, tumour diseases, osteolytic diseases such as osteoporosis, patho-

logically angiogenic diseases such as inflammations, ophthalmological diseases, diabetic retinopathy, macular degeneration, myopia, ocular histoplasmosis, rheumatoid arthritis, osteoarthritis, rubeotic glaucoma, ulcerative colitis, Crohn's disease, atherosclerosis, psoriasis, restenosis after angioplasty, viral infection, bacterial infection, fungal infection, in acute renal failure and in wound healing, to support the healing processes.

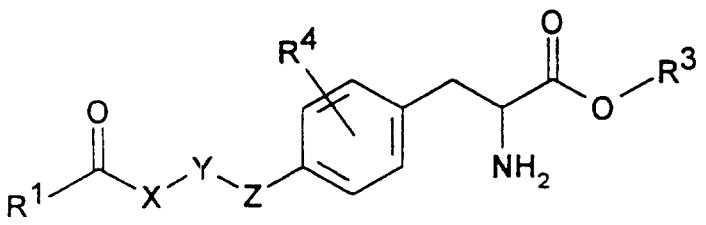
The compounds of the formula I may be employed as antimicrobial substances in operations where biomaterials, implants, catheters or cardiac pacemakers are used. In this context, they have an antiseptic effect. The antimicrobial activity can be demonstrated by the method described by P. Valentin-Weigund et al., in Infection and Immunity, 2851-2855 (1988).

The invention furthermore relates to a process for preparing compounds of the formula I according to Claim 1, and also their salts, which process is characterized in that

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

or

b) a compound of the formula II



II

in which R^1, R^3, R^4, X, Y and Z have the meanings given in Claim 1,
is reacted with a compound of the formula III

R^2-SO_2-L III

in which

R^2 has the meaning given in Claim 1
and L is Cl, Br, I, OH or an OH group which has been esterified to make it capable of reacting,

or

c) an ester of the formula I is hydrolysed,

or

d) a radical R^1 and/or R^3 is/are converted into another radical R^1 and/or R^3,

and/or

e) a basic or acidic compound of the formula I is converted into one of its salts by treating it with an acid or base.

The compounds of the formula I possess at least one chiral centre and can therefore occur in several stereoisomeric forms. All these forms (e.g. D and L forms) and their mixtures (e.g. the DL forms) are included in formula I.
So-called prodrug derivatives, i.e. compounds of the formula I which are modified with, for example, alkyl or acyl groups, sugars or oligopeptides, and which are rapidly cleaved in the organism to form the active novel compounds, are also included in the novel compounds.

The abbreviations which are listed above and in that which follows have the following meanings:

Ac	acetyl
BOC	tert-butoxycarbonyl
CBZ or Z	benzyloxycarbonyl
DCCl	dicyclohexylcarbodiimide
DMF	dimethylformamide
EDCl	N-ethyl-N,N'-(dimethylaminopropyl)carbodiimide
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
HOBt	1-hydroxybenzotriazole
Me	methyl
Mtr	4-methoxy-2,3,6-trimethylphenylsulfonyl
HONSu	N-hydroxysuccinimide
OBut	tert-butyl ester
Oct	octanoyl
OMe	methyl ester
OEt	ethyl ester
POA	phenoxyacetyl
TFA	trifluoroacetic acid
Trt	trityl(triphenylmethyl).

For the whole invention, it holds that all the radicals which occur several times, such as A and A', can be identical or different, i.e. are independent of each other.

In the above formulae, alkyl is preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, and also 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, heptyl, octyl, nonyl or decyl.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cylopentyl [sic], cyclohexyl, cycloheptyl or 3-menthyl. Cycloalkyl is, in particular, the radical of a bicyclic terpene; the camphor-10-yl radical is very particularly preferred.

Alkylene is preferably methylene, ethylene, propylene, butylene or pentylene, and also hexylene, heptylene, ocytylene [sic], nonylene or decylene. Aralkylene is preferably alkylenephenyl and is, for example, preferably benzyl or phenethyl.

Cycloalkylene is preferably cyclopropylene, 1,2- or 1,3-cyclobutylene, 1,2- or 1,3-cyclopentylene or 1,2-, 1,3- or 1,4-cyclohexylene, and also 1,2-, 1,3- or 1,4-cycloheptylene.

Alkanoyl is preferably formyl, acetyl, propionyl, butyryl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl or octadecanoyl.

Preferred substituents for alkyl, alkylene, cycloalkyl, cycloalkylene, alkanoyl and cycloalkanoyl are, for example, Hal, OA, NHA, NAA', CN, NO_2, SA, SOA, SO_2A, SO_2Ar and/or SO_3H, in particular, for example, F, Cl, hydroxyl, methoxy, ethoxy, amino, dimethylamino, methylthio, methylsulfinyl, methylsulfonyl or phenylsulfonyl.

Preferred substituents for Ar and arylene are, for example, A and/or Hal, OA, NHA, NAA', CN, NO_2, SA, SOA, SO_2A, SO_2Ar and/or SO_3H, in particular, for example, F, Cl, hydroxyl, methoxy, ethoxy, amino, dimethylamino, methylthio, methylsulfinyl, methylsulfonyl or phenylsulfonyl.

In the radicals alkyl, alkylene, cycloalkyl, cycloalkylene, alkanoyl and cycloalkanoyl, one, two or three methylene groups can in each case be replaced with N, O and/or S.

Ar-CO is aroyl and is preferably benzoyl or naphthoyl.

Ar is unsubstituted, preferably - as indicated - monosubstituted phenyl, preferably and specifically phenyl, o-, m- or p-tolyl, 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-cyanophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-methylthiophenyl, o-, m- or p-methylsulfinylphenyl, o-, m- or p-methylsulfonylphenyl, o-, m- or p-aminophenyl, o-, m- or p-methylaminophenyl, o-, m- or p-dimethylaminophenyl or o-, m- or p-nitrophenyl,

and also, preferably, 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, 2-chloro-3-methyl-, 2-chloro-4-methyl-, 2-chloro-5-methyl-, 2-chloro-6-methyl-, 2-methyl-3-chloro-, 2-methyl-4-chloro-, 2-methyl-5-chloro-, 2-methyl-6-chloro-, 3-chloro-4-methyl-, 3-chloro-5-methyl- or 3-methyl-4-chlorophenyl, 2-bromo-3-methyl-, 2-bromo-4-methyl-, 2-bromo-5-methyl-, 2-bromo-6-methyl-, 2-methyl-3-bromo-, 2-methyl-4-bromo-, 2-methyl-5-bromo-, 2-methyl-6-bromo-, 3-bromo-4-methyl-, 3-bromo-5-methyl- or 3-methyl-4-bromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or 3,4,5-trichlorophenyl, 2,4,6-tri-tert-butylphenyl, 2,5-dimethylphenyl, p-iodophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3,5-dimethylphenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 2,4-dichloro-5-methylphenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 2-methoxy-5-methylphenyl, 2,4,6-triisopropylphenyl, naphthyl, 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, benzothiadiazol-5-yl or benzoxadiazol-5-yl.

In addition, Ar is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 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 or 2-, 4-, 5- or 6-pyrimidinyl, and also, preferably, 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- 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 4-4-H-thiopyranyl [sic], 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-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-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl or 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl.

Arylene has the same meanings as given for Ar, with the proviso that a further bond of the aromatic system is linked to the nearest bonding neighbour.

Heterocycloalkylene is preferably 1,2-, 2,3- or 1,3-pyrrolidinyl, 1,2-, 2,4-, 4,5- or 1,5-imidazolidinyl, 1,2-, 2,3- or 1,3-pyrazolidinyl, 2,3-, 3,4-, 4,5- or 2,5-oxazolidinyl, 1,2-, 2,3-, 3,4- or 1,4-isoxazolidinyl, 2,3-, 3,4-, 4,5- or 2,5-thiazolidinyl, 2,3-, 3,4-, 4,5- or 2,5-isothiazolidinyl, 1,2-, 2,3-, 3,4- or 1,4-piperidinyl, 1,4- or 1,2-piperazinyl, and also, preferably, 1,2,3-tetrahydrotriazol-1,2- or -1,4-yl, 1,2,4-tetrahydrotriazol-1,2- or -3,5-yl, 1,2- or 2,5-tetrahydrotetrazolyl, 1,2,3-tetrahydrooxadiazol-2,3-, -3,4-, -4,5- or -1,5-yl, 1,2,4-tetrahydrooxadiazol-2,3-, -3,4- or -4,5-yl, 1,3,4-tetrahydrothiadiazol-2,3-, -3,4-, -4,5- or -1,5-yl, 1,2,4-tetrahydrothiadiazol-2,3-, -3,4-, -4,5- or -1,5-yl, 1,2,3-thiadiazol-2,3-, -3,4-, -4,5- or -1,5-yl,

2,3- or 3,4-morpholinyl or 2,3-, 3,4- or 2,4-thiomorpholinyl.

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

Correspondingly, the invention relates, in particular, to those compounds of the formula I in which at least one of the said radicals has one of the abovementioned preferred meanings. Some preferred groups of compounds can be expressed by the following part formulae Ia to Ie, which conform to formula I and in which the radicals which are not designated more precisely have the meaning given in formula I, but in which

in a)	R^1	is	$H_2N-C(=NH)$
	X	is	alkylene having 1-6 carbon atoms,
	Y	is	O,
	R^2	is	A,
	R^3 and R^4	are	H;
in b)	R^1	is	$H_2N-(C=NH)-NH$,
	X		alkylene having 1-6 carbon atoms,
	Y		O,
	R^2		A,
	R^3 and R^4	are	H;
in c)	X	is	alkylene having 1-6 carbon atoms,
	Y	is	absent,
	R^3 and R^4	are	H, and
	R^2	is	aryl;
in d)	R^1	is	$H_2N-(C=NH)-NH$,
	X	is	alkylene having 1-6 carbon atoms,
	Y	is	CONH,

	R^3 and R^4	are H, and
	R^2	is A;
in e)	X	is alkylene having 1-6 carbon atoms,
	Y	is O or CO-NH,
	Z	is absent,
	R^2	is camphor-10-yl,
	R^3	is H or A, and
	R^4	is H.

The compounds of the formula I, and also the starting compounds for their preparation, are otherwise prepared in accordance with methods known per se and as 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;), using reaction conditions which are known and suitable for the said reactions. In this context, use can also be made of variants which are known per se but which are not mentioned in detail here.

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

Compounds of the formula I can preferably be obtained by liberating compounds of the formula I from one of their functional derivatives, by means of treating the latter with a solvolysing or hydrogenolysing agent.

Starting compounds which are preferred for the solvolysis or hydrogenolysis are those which conform to the formula I except that, instead of one or more free amino groups and/or hydroxyl groups, they contain corresponding, protected amino groups and/or hydroxyl groups, preferably those starting compounds which carry an amino protecting group instead of an H atom which is

linked to a N atom, in particular those starting compounds which carry an R'-N group, in which R' is an amino protecting group, instead of an HN group, and/or those starting compounds which carry a hydroxyl protecting group instead of the H atom of a hydroxyl group, for example those starting compounds which conform to the formula I except that they carry a -COOR" group, in which R" is a hydroxyl protecting group, instead of a -COOH group.

Several - identical or different - protected amino groups and/or hydroxyl groups can also be present in the molecule of the starting compound. If the protecting groups which are present differ from each other, they can in many cases be eliminated selectively.

The expression "amino protecting group" is generally known and refers to groups which are suitable for protecting (blocking) an amino group from chemical reactions but which can readily be removed after the desired chemical reaction has been carried out at other sites in the molecule. Unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups are, in particular, typical of such groups. Since the amino protecting groups are removed after the desired reaction (or sequence of reactions), their nature and size is otherwise not critical; however, those having 1-20, in particular 1-8, carbon atoms are preferred. In connection with the present process, the expression "acyl group" is to be understood in the widest sense. It encompasses acyl groups which are derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and also, in particular, alkoxycarbonyl, aryloxycarbonyl and, especially, aralkoxycarbonyl groups. Examples of acyl groups of this nature are alkanoyl, such as acetyl, propionyl and butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or toluyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as

methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC and 2-iodoethoxycarbonyl; aralkyloxycarbonyl, such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl and FMOC; and arylsulfonyl, such as Mtr. Amino protecting groups which are preferred are BOC and Mtr and also CBZ, Fmoc, benzyl and acetyl.

Depending on the protecting group which is used, the amino protecting group is eliminated, for example, with strong acids, expediently with TFA or perchloric acid, or else 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 benzenesulfonic acid or p-toluenesulfonic acid. It is possible, but not always necessary, for an additional inert solvent to be present. Suitable inert solvents are preferably organic, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as DMF, or halogenated hydrocarbons, such as dichloromethane, and also alcohols, such as methanol, ethanol or isopropanol, and also water. Mixtures of the abovementioned solvents are also suitable. TFA is preferably used in excess without the addition of any further solvent while perchloric acid is used in the form of a mixture of acetic acid and 70% perchloric acid in a ratio of 9:1. Expediently, the reaction temperatures for the cleavage are between about 0 and about 50°, preferably between 15 and 30° (room temperature).

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

Protecting groups which can be removed by hydrogenolysis (for example CBZ or benzyl) can be eliminated, for example, by treatment with hydrogen in the presence of a catalyst (for example a precious metal catalyst such as palladium, expediently on a support such as charcoal). The abovementioned solvents, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF, are suitable as solvents in this context. As a rule, the hydrogenolysis is carried out at temperatures of between about 0 and 100° and under pressures of between about 1 and 200 bar, preferably at 20-30° and under 1-10 bar. The CBZ group is hydrogenolysed satisfactorily on, for example, 5 to 10% Pd/C in methanol or with ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

Compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III. As a rule, the starting compounds of the formula II and III are novel. However, they can be prepared using methods which are known per se.

In the compounds of the formula III, L is preferably Cl, Br, I or an OH group which has been modified so as to make it capable of reaction, such as alkylsulfonyloxy having 1-6 carbon atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy).

As a rule, the compounds of the formula II are reacted in an inert solvent and in the presence of an acid-binding agent, preferably an organic base such as triethylamine, dimethylaniline, pyridine or quinoline.

It can also be advantageous to add an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of (sic) alkali metals or alkaline earth metals, preferably potassium, sodium, calcium or caesium.

Depending on the conditions which are used, the reaction time is between a few minutes and 14 days, while the reaction temperature is between about -30° and 140°, normally between -10° and 90°, in particular between about 0° and about 70°.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl ether or ethylene glycol monoethyl ether (methyl glycol or ethyl glycol), or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or water, or mixtures of the said solvents.

It is furthermore possible to hydrolyse an ester of the formula I. This is expediently effected by means of solvolysis or hydrogenolysis, as indicated above, for example using NaOH or KOH in dioxane/water at temperatures of between 0 and 60°C, preferably of between 10 and 40°C.

It is also possible to convert a radical R^1 and/or R^3 into another radical R^1 and/or R^3.
In particular, a carboxylic acid can be converted into a carboxylic ester.
A cyano group is converted into an amidino group by reaction, for example, with hydroxylamine and subse-

quent reduction of the N-hydroxyamidine with hydrogen in the presence of a catalyst such as Pd/C.

It is also possible to replace a conventional amino protecting group with hydrogen by eliminating the protecting group solvolytically or hydrogenolytically, as described above, or for an amino group which is protected by a conventional protecting group to be liberated by solvolysis or hydrogenolysis.

A base of the formula I can be converted with an acid into the associated acid addition salt, for example by reacting equivalent quantities of the base and the acid in an inert solvent, such as ethanol, and then concentrating by evaporation. Acids which yield physiologically harmless salts are particularly suitable for this reaction. Thus, inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid can be used, as can organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example 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, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and disulfonic acids, or laurylsulfuric acid. Salts with acids which are not physiologically harmless, for example picrates, can be used for isolating and/or purifying the compounds of the formula I.

On the other hand, an acid of the formula I can be converted into one of its physiologically harmless metal salts or ammonium salts by reaction with a base.

Suitable salts in this context are, in particular, the sodium, potassium, magnesium, calcium and ammonium salts, and also substituted ammonium salts, for example the dimethyl-, diethyl- or diisopropylammonium salts, monoethanol-, diethanol- or diisopropylammonium salts, cyclohexyl- or dicyclohexylammonium salts or dibenzylethylenediammonium salts, and also, for example, salts with arginine or lysine.

The compounds of the formula I contain one or more chiral centres and can therefore be present in racemic form or in optically active form. Racemates which have been obtained can be resolved mechanically or chemically into the enantiomers using methods which are known per se. Preferably, diastereomers are formed from the racemic mixture by means of reaction with an optically active separating agent. Examples of suitable separating agents are optically active acids such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid or lactic acid, or the different optically active camphorsulfonic acids, such as β-camphorsulfonic acid. Enantiomer resolution using a column which is filled with an optically active separating agent (for example dinitrobenzoylphenylglycine) is also advantageous; a suitable mobile phase is, for example, a hexane/isopropanol/acetonitrile mixture, for example in a volume ratio of 82:15:3.

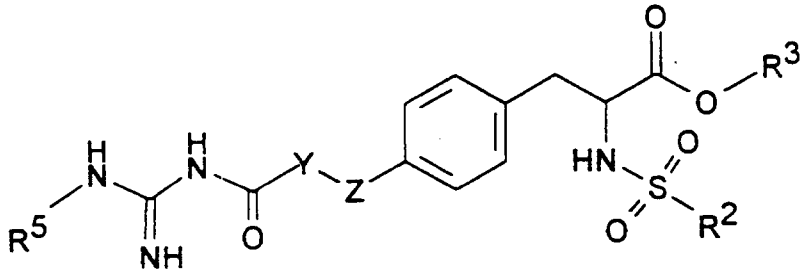
Naturally, it is also possible to use the above described methods to obtain optically active compounds of the formula I by employing starting compounds which are already optically active.

The test results obtained for $\alpha_v\beta_3$ and $\alpha_v\beta_5$ inhibitions with some representative compounds of the formula I are summarized in Table I below. The table gives the IC_{50} values, i.e. the concentrations in nmol/litre which inhibit 50% of the binding of vitronectin to the

corresponding isolated receptor, for the vitronectin binding tests.

Table I

IC_{50} values (concentrations in nmol/litre which inhibit 50% of the binding of vitronectin to the isolated receptor) of representative compounds of the formula I, which were obtained in analogy with the method of Smith et al., J. Biol. Chem. 265, 12267-71 (1990), and the measured FAB values of the substances.



I

R	R^2	R^3	Y	Z	FAB	IC_{50} $\alpha_v\beta_3$	IC_{50} $\alpha_v\beta_5$
(1)	Butyl	H	Propyl	O	471	6.5	55
H	Butyl	H	Propyl	O	429	1.1	2.1
(2)	Butyl	H	Propyl	O	563	92	
(2)	(A)	H	Propyl	O	657	61	136
H	(A)	H	Propyl	O	523	0.13	0.16
H	(A)	Ethyl	Propyl	O	551	16	13
Ethyl	Butyl	H	Propyl	O	457	0.81	
(2)	(A)	H	Butyl	O	671	252	
H	4-Tolyl	H	Butyl	O	477	4.6	
H	Butyl	H	Butyl	O	443	6.2	
H	(A)	H	Butyl	O	537	0.45	

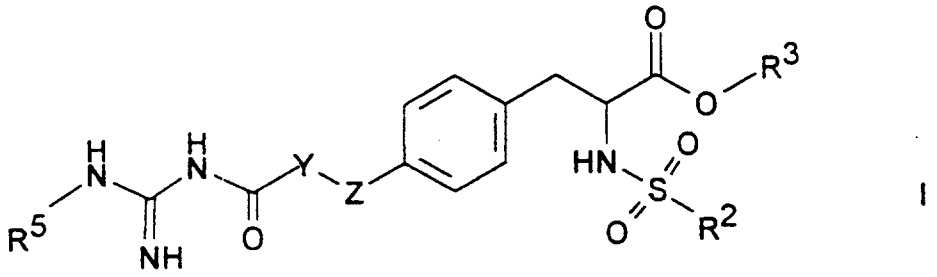
(1) = acetyl; (2) = benzyloxycarbonyl;
(A) = (S)-camphor-10-yl

The pharmacological data provide proof of the antagonistic activity of the novel compounds of the formula I for the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ vitronectin receptors.

The results obtained for GPIIb/IIIa inhibition with some representative compounds of formula I are summarized in Table II below. The table gives the IC_{50} values, i.e. the concentrations in nmol/litre which inhibit 50% of the binding of fibrinogen to the corresponding isolated receptor.

Table II

IC_{50} values (ccncentrations in nmol/litre which isolate [sic] 50% of the binding of fibrinogen to the isolated receptor) of representative compounds of the formula I, and the FAB values which were measured.



I

R^1	R^2	R^3	Y	Z	FAB	IC_{50} GPIIb/IIIa
(1)	Butyl	H	Propyl	O	471	1860
H	Butyl	H	Propyl	O	429	16
(2)	Butyl	H	Propyl	O	563	5600
(2)	(A)	H	Propyl	O	657	167
H	(A)	H	Propyl	O	523	1.3
H	(A)	Ethyl	Propyl	O	551	78

(1) = acetyl; (2) = benzyloxycarbonyl;
(A) = (S)-camphor-10-yl

The pharmacological data provide proof of the antagonistic activity of the novel compounds of the formula I for the GPIIb/IIIa fibrinogen receptor.

The invention furthermore relates to the use of the compounds of the formula I, and/or their physiologically harmless salts, for producing pharmaceutical preparations, in particular by a non-chemical route. In this context, they can be brought into a suitable dosage form together with at least one solid, liquid and/or semiliquid carrier substance or auxiliary substance and, where appropriate, in combination with one or more additional active compounds.

The invention furthermore relates to pharmaceutical preparations which comprise at least one compound of the formula I and/or one of its physiologically harmless salts.

These preparations can be used as pharmaceuticals in human or veterinary medicine. Suitable carrier substances are organic or inorganic substances which are appropriate for enteral (e.g. oral), parenteral or topical administration, or for administration in the form of an inhalation spray, 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 or vaseline. For oral applications, use is made, in particular, of tablets, pills, coated tablets, capsules, powders, granulates, syrups, juices or drops, for rectal applications, of suppositories, for parenteral applications, of solutions, preferably oily or aqueous solutions, and also suspensions, emulsions or implants, and for topical applications, of ointments, creams or powders. The novel compounds can also be lyophilized and the resulting lyophilizates used, for example, for producing preparations for injection. The indicated

preparations can be sterilized and/or comprise auxiliary substances such as glidants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffering substances, dyes, flavorings and/or several additional active compounds, for example one or more vitamins.

For administration as an inhalation spray, sprays can be used which comprise the active compound either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO_2 or fluorochlorohydrocarbons). In this context, the active compound is expediently used in micronized form, with it being possible for one or more additional physiologically tolerated solvents, for example ethanol, to be present. Solutions for inhalation can be administered using customary inhalers.

The compounds of the formula I, and their physiologically harmless salts, can be used as integrin inhibitors in the control of diseases, in particular of pathologically angiogenic diseases, thromboses, cardiac infarction, coronary heart diseases, arteriosclerosis, tumours, inflammations and infections.
For controlling pathologically angiogenic diseases, tumours, osteoporosis, inflammations and infections, preference is given to using compounds of the formula I according to Claim 1, and/or their harmless salts, in which R^2 has the meaning camphor-10-yl.

In this context, the novel substances can as a rule be administered in analogy with other known peptides which are on the market, in particular, however, in analogy with the compounds described in US-A-4 472 305, preferably in doses of between about 0.05 and 500 mg, in particular between 0.5 and 100 mg, per dose unit. The daily dose is preferably between about 0.01 and 2 mg/kg of body weight. However, the particular dose for each patient depends on a very wide variety of factors, for

example on the activity of the particular compound employed, on the age, bodyweight, general state of health and sex, on the diet, on the time and route of administration, on the speed of excretion, on the drug combination and on the severity of the particular disease to which the therapy applies. Parenteral administration is preferred.

Both above and in that which follows, all the temperatures are given in °C. In the following examples, "customary working-up" denotes: water is, if necessary, added, the pH is, if necessary, adjusted to values of between 2 and 10, depending on the constitution of the end product, extraction takes place with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and purification takes place by means of chromatography on silica gel and/or by means of crystallization.

Mass spectrometry (MS):

EI (electron impact ionization) M^+

FAB (fast atom bombardment) $(M+H)^+$

Example 1

A solution of 25 g of benzyloxycarbonyl-L-tyrosine tert-butyl ester, 29 ml of ethyl 4-bromobutyrate, 18.7 g of potassium carbonate and 1.8 g of 18-Crown-6 in 300 ml of toluene is stirred at 85° for 12 hours. Following customary working-up, 25.3 g of tert-butyl (2S)-2-benzyloxycarboxamido-3-[4-(4-ethoxy-4-oxobutyloxy)phenyl]propionate ("A") are obtained as a colourless syrup; FAB 486.

1 g of 10% palladium on active charcoal is added to a solution of 10 g of "A" in 70 ml of ethyl acetate, 20 ml of methanol, 10 ml of water us [sic] 2 ml of TFA and the mixture is hydrogenated with hydrogen at room temperature for 4 hours. After the catalyst has been

removed, and after customary working-up, 8.8 g of tert-butyl (2S)-2-amino-3-[4-(4-ethoxy-4-oxobutyloxy)-phenyl]propionate, trifluoroacetate ("B") are obtained; FAB 352.

5.5 ml of triethylamine and 3.9 ml of 1-butanesulfonyl chloride are added, at room temperature, to a solution of 8.8 g of "B" in 100 ml of dichloromethane and the whole is stirred for 5 hours. Following customary working-up, 7.9 g of tert-butyl (2S)-2-butyl-sulfonamido-3-[4-(4-ethoxy-4-oxobutyloxy)phenyl]-propionate are obtained; FAB 472.

The following are obtained in an analogous manner by reacting "B"

with (S)-(+)-camphor-10-sulfonyl chloride,
tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-ethoxy-4-oxobutyloxy)phenyl]propionate; FAB 566

with 4-tolylsulfonyl chloride,
tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-ethoxy-4-oxobutyloxy)phenyl]propionate; FAB 506.

A solution of 7.9 g of tert-butyl (2S)-2-butyl-sulfonamido-3-[4-(4-ethoxy-4-oxobutyloxy)phenyl]-propionate and 10 ml of 2 N sodium hydroxide solution in 75 ml of methanol is stirred at room temperature for 12 hours. Following customary working-up, tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-carboxypropyloxy)-phenyl]propionate is obtained as a colourless syrup; FAB 444.

The following are obtained in an analogous manner by cleaving the ethyl ester:

from tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-ethoxy-4-oxobutyloxy)phenyl]propionate,
tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-carboxypropyloxy)phenyl]propionate; FAB 538, and

from tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-ethoxy-4-oxobutyloxy)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-carboxypropyloxy)phenyl]propionate; FAB 478.

1.1 g of 2-chloro-1-methylpyridinium iodide, 3.9 ml of ethyl diisopropylamine and 2.8 g of Z-guanidine are added to a solution of 1.3 g of tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-carboxypropyloxy)phenyl]-propionate in 15 ml of DMF and the mixture is stirred at room temperature for 12 hours. Following customary working-up, 1.0 g of tert-butyl (2S)-2-butyl-sulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]propionate is obtained; FAB 619.

The following are obtained in an analogous manner:

from tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-carboxypropyloxy)phenyl]propionate,

tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)-phenyl]propionate; FAB 713

and from tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-carboxypropyloxy)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]-propionate; FAB 653.

Example 2

250 mg of palladium (10% on active charcoal) are added to a solution of 1 g of tert-butyl (2S)-2-butyl-sulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]propionate in 18 ml of dioxane and 2 ml of water and the mixture is hydrogenated at room temperature for 3 hours. After separating off the catalyst and after customary working-up, 0.78 g of tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionate is obtained; FAB 485.

The following are obtained in an analogous manner:

from tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)-phenyl]propionate,

tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionate; FAB 579

and from tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]-propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionate; FAB 519.

Example 3

2 ml of TFA are added to a solution of 0.78 g of tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionate in 20 ml of dichloromethane and the mixture is stirred for 12 hours. Following customary working-up and freeze drying, 0.87 g of (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate is obtained as a white amorphous powder; FAB 429.

The following are obtained in an analogous manner:

from tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionate,

(2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate; FAB 523

and from tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionate,

(2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate; FAB 463.

Example 4

10 µl of acetyl chloride are added, at 0°, to a solution of 50 mg of (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroaceate, in 5 ml of pyridine and the mixture is stirred for 2 hours. Following customary working-up, 0.027 g of (2S)-2-butylsulfonamido-3-[4-(4-N-acetylguanidino-4-oxobutyloxy)phenyl]propionic acid is obtained; FAB 471.

The following are obtained in an analogous manner:

from (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate,

(2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-acetylguanidino-4-oxobutyloxy)phenyl]propionic acid; FAB 565

and from (2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate,

(2S)-2-tolylsulfonamido-3-[4-(4-N-acetylguanidino-4-oxobutyloxy)phenyl]propionic acid; FAB 505.

Example 5

1 ml of TFA is added to a solution of 0.05 g of tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]propionate in 5 ml of dichloromethane and the mixture is stirred at room temperature for 12 hours. Following customary working-up, 0.045 g of (2S)-2-butylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]-propionic acid is obtained; FAB 563.

The following are obtained in an analogous manner:

from tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)-phenyl]propionate,

(2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]-propionic acid; FAB 657

and from tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyloxy)phenyl]-propionate,

(2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxy-carbonylguanidino-4-oxobutyloxy)phenyl]propionic acid; FAB 597.

Example 6

5 mg of p-toluenesulfonic acid are added to a solution of 0.1 g of (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate, in 10 ml of ethanol and the mixture is stirred at room temperature for 72 hours. Following customary working-up and freeze drying, 0.055 mg of ethyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid is obtained; FAB 551.

The following are obtained in an analogous manner:

from (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxo-butyloxy)phenyl]propionic acid, trifluoroacetate,

ethyl (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid; FAB 457

and from (2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate,

ethyl (2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid; FAB 491.

Example 7

The compound tert-butyl (2S)-2-benzyloxycarboxamido-3-[4-(3-ethoxy-3-oxopropylcarboxamido)phenyl]propionate is obtained in an analogous manner by reacting benzyloxycarbonyl-L-p-aminophenylalanine tert-butyl ester and 1-chloro-4-ethoxybutane-1,4-dione. Tert-butyl (2S)-2-amino-3-[4-(3-ethoxy-3-oxopropylcarboxamido)phenyl]-propionate ("C") is obtained by eliminating the Z protecting group.

The following are obtained by the subsequent reaction of "C"

with 1-butanesulfonyl chloride,
tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-ethoxy-3-oxopropylcarboxamido)phenyl]propionate,

with 4-tolylsulfonyl chloride,
tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-ethoxy-3-oxopropylcarboxamido)phenyl]propionate,

and with (S)-(+)-camphor-10-sulfonyl chloride,
tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-ethoxy-3-oxopropylcarboxamido)phenyl]propionate.

The following are obtained from the above by cleaving the ethyl ester:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(2-carboxyethylcarboxamido)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(2-carboxyethylcarboxamido)phenyl]propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-carboxyethylcarboxamido]phenyl]propionate.

In analogy with Example 1, the following are obtained from these by reaction with Z-guanidine:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]-propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]-propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]propionate.

The Z protecting group is eliminated in analogy with Example 2, and the following compounds are obtained:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-guanidino-3-oxopropylcarboxamido)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-guanidino-3-oxopropylcarboxamido)phenyl]propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-guanidino-3-oxopropylcarboxamido)phenyl]-propionate.

In analogy with Example 3, the tert-butyl ester is cleaved with TFA, and the following are obtained;

(2S)-2-butylsulfonamido-3-[4-(3-guanidino-3-oxopropyl-carboxamido)phenyl]propionic acid, trifluoroacetate,

(2S)-2-tolylsulfonamido-3-[4-(3-guanidino-3-oxopropyl-carboxamido)phenyl]propionic acid, trifluoroacetate

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-guanidino-3-oxopropylcarboxamido)phenyl]propionic acid, trifluoroacetate.

In analogy with Example 4, the following compounds are obtained form these by reaction with acetyl chloride:

(2S)-2-butylsulfonamido-3-[4-(3-N-acetylguanidino-3-oxopropylcarboxamido)phenyl]propionic acid,

(2S)-2-tolylsulfonamido-3-[4-(3-N-acetylguanidino-3-oxopropylcarboxamido)phenyl]propionic acid,

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-N-acetylguanidino-3-oxopropylcarboxamido)phenyl]propionic acid.

In analogy with Example 5, treatment with TFA converts

tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]-propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]-propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]propionate

into the following compounds

(2S)-2-butylsulfonamido-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]propionic acid,

(2S)-2-tolylsulfonamido-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)phenyl]propionic acid,

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-N-benzyloxycarbonylguanidino-3-oxopropylcarboxamido)-phenyl]propionic acid.

Example 8

The compound tert-butyl (2S)-2-benzyloxycarboxamido-3-[4-(4-ethoxy-4-oxobutylcarboxamido)phenyl]propionate is obtained, in analogy with Example 1, by reacting benzyloxycarbonyl-L-p-aminophenylalanine tert-butyl ester and 1-chloro-5-ethoxypentane-1,5-dione. Tert-butyl (2S)-2-amino-3-[4-(4-ethoxy-4-oxobutylcarboxamido)phenyl]propionate ("D") is obtained by eliminating the Z protecting group.

The following are obtained by the subsequent reaction of "D"

with 1-butanesulfonyl chloride,
tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-ethoxy-4-oxobutylcarboxamido)phenyl]propionate,

with 4-tolylsulfonyl chloride,
tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-ethoxy-4-oxobutylcarboxamido)phenyl]propionate

and with (S)-(+)-camphor-10-sulfonyl chloride,
tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-ethoxy-4-oxobutylcarboxamido)phenyl]propionate.

The following are obtained from these by cleaving the ethyl ester:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-carboxy-propylcarboxamido)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-carboxy-propylcarboxamido)phenyl]propionate

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido-3-[4-(3-carboxypropylcarboxamido)phenyl]propionate.

In analogy with Example 1, the following are obtained from these by reaction with Z guanidine:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutylcarboxamido)phenyl]-propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutylcarboxamido)phenyl]-propionate

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyl-carboxamido)phenyl]propionate.

The Z protecting group is eliminated in analogy with Example 2, and the following compounds are obtained:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutylcarboxamido)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutylcarboxamido)phenyl]propionate

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutylcarboxamido)phenyl]-propionate.

In analogy with Example 3, the tert-butyl ester is cleaved with TFA, and the following are obtained:

(2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutyl-carboxamido)phenyl]propionic acid, trifluoroacetate,

(2S)-2-tolylsulfonamido-3-[4-(4-guanidino-4-oxobutyl-carboxamido)phenyl]propionic acid, trifluoroacetate

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-guanidino-4-oxobutylcarboxamido)phenyl]propionic acid, trifluoroacetate.

In analogy with Example 4, the following compounds are obtained from these by reaction with acetyl chloride:

(2S)-2-butylsulfonamido-3-[4-(4-N-acetylguanidino-4-oxobutylcarboxamido)phenyl]propionic acid,

(2S)-2-tolylsulfonamido-3-[4-(4-N-acetylguanidino-4-oxobutylcarboxamido)phenyl]propionic acid,

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-acetylguanidino-4-oxobutylcarboxamido)phenyl]propionic acid.

In analogy with Example 5, treatment with TFA converts

tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutylcarboxamido)phenyl]-propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutylcarboxamido)phenyl]-propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutyl-carboxamido)phenyl]propionate

into the following compounds

(2S)-2-butylsulfonamido-3-[4-(4-N-benzyloxycarbonyl-guanidino-4-oxobutylcarboxamido)phenyl]proponic acid,

(2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxycarbonyl-guanidino-4-oxobutylcarboxamido)phenyl]proponic acid

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutylcarboxamido)-phenyl]propionic acid.

Example 9

The compound tert-butyl (2S)-2-benzyloxycarboxamido-3-[4-(2-ethoxy-2-oxoethylcarboxamido)phenyl]propionate is obtained, in analogy with Example 1, by reacting benzyloxycarbonyl-L-p-aminophenylalanine tert-butyl ester and 1-chloro-3-ethoxypropane-1,3-dione. Tert-butyl (2S)-2-amino-3-[4-(2-ethoxy-2-oxobutylcarboxamido)phenyl]propionate ("E") is obtained by eliminating the Z protecting group.

The following are obtained by subsequent reaction of "E"

with 1-butanesulfonyl chloride,
tert-butyl (2S)-2-butylsulfonamido-3-[4-(2-ethoxy-2-oxoethylcarboxamido)phenyl]propionate,

with 4-tolylsulfonyl chloride,
tert-butyl (2S)-2-tolylsulfonamido-3-[4-(2-ethoxy-2-oxoethylcarboxamido)phenyl]propionate

and with (S)-(+)-camphor-10-sulfonyl chloride,
tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-ethoxy-2-oxoethylcarboxamido)phenyl]propionate.

The following are obtained from these by cleaving the ethyl ester:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(carboxy-methylcarboxamido)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(carboxy-methylcarboxamido)phenyl]propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(carboxymethylcarboxamido)phenyl]propionate.

In analogy with Example 1, the following are obtained from these by reaction with Z-guanidine:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(2-N-benzyloxycarbonylguanidino-2-oxoethylcarboxamido)phenyl]-propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(2-N-benzyloxycarbonylguanidino-2-oxoethylcarboxamido)phenyl]-propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-N-benzyloxycarbonylguanidino-2-oxoethylcarboxamido)phenyl]propionate.

The Z protecting group is eliminated in analogy with Example 2, and the following compounds are obtained:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(2-guanidino-2-oxoethylcarboxamido)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(2-guanidino-2-oxoethylcarboxamido)phenyl]propionate

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-guanidino-2-oxoethylcarboxamido)phenyl]-propionate.

In analogy with Example 3, the tert-butyl ester is cleaved with TFA, and the following are obtained:

(2S)-2-butylsulfonamido-3-[4-(2-guanidino-2-oxoethylcarboxamido)phenyl]propionic acid, trifluoroacetate,

(2S)-2-tolylsulfonamido-3-[4-(2-guanidino-2-oxoethylcarboxamido)phenyl]propionic acid, trifluoroacetate

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-guanidino-2-oxoethylcarboxamido)phenyl]propionic acid, trifluoroacetate.

In analogy with Example 4, the following compounds are obtained from these by reaction with acetyl chloride:

(2S)-2-butylsulfonamido-3-[4-(2-N-acetylguanidino-2-oxoethylcarboxamido)phenyl]propionic acid,

(2S)-2-tolylsulfonamido-3-[4-(2-N-acetylguanidino-2-oxoethylcarboxamido)phenyl]propionic acid,

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-N-acetylguanidino-2-oxoethylcarboxamido)phenyl]propionic acid.

In analogy with Example 5, treatment with TFA converts

tert-butyl (2S)-2-butylsulfonamido-3-[4-(2-N-benzyloxycarbonylguanidino-2-oxoethylcarboxamido)phenyl]-propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(2-N-benzyloxycarbonylguanidino-2-oxoethylcarboxamido)phenyl]-propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-N-benzyloxycarbonylguanidino-2-oxoethyl-carboxamido)phenyl]propionate

into the following compounds

(2S)-2-butylsulfonamido-3-[4-(2-N-benzyloxycarbonyl-guanidino-2-oxoethylcarboxamido)phenyl]propionic acid,

(2S)-2-tolylsulfonamido-3-[4-(2-N-benzyloxycarbonyl-guanidino-2-oxoethylcarboxamido)phenyl]propionic acid

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(2-N-benzyloxycarbonylguanidino-2-oxoethylcarboxamido)-phenyl]propionic acid.

Example 10

The compound tert-butyl (2S)-2-benzyloxycarboxamido-3-[4-(5-ethoxy-5-oxopentyloxy)phenyl]propionate is obtained, in analogy with Example 1, by reacting benzyloxycarbonyl-L-tyrosine tert-butyl ester and ethyl 5-bromovalerate. Tert-butyl (2S)-2-amino-3-[4-(5-ethoxy-5-oxopentyloxy)phenyl]propionate ("F") is obtained by eliminating the Z protecting group.

The following are obtained by subsequent reaction of "F"

with 1-butanesulfonyl chloride,
tert-butyl (2S)-2-butylsulfonamido-3-[4-(5-ethoxy-5-oxopentyloxy)phenyl]propionate,

with 4-tolylsulfonyl chloride,
tert-butyl (2S)-2-tolylsulfonamido-3-[4-(5-ethoxy-5-oxopentyloxy)phenyl]propionate

and with (S)-(+)-camphor-10-sulfonyl chloride,
tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(5-ethoxy-5-oxopentyloxy)phenyl]propionate.

The following are obtained from these by cleaving the ethyl ester:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-carboxy-butyloxy)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-carboxy-butyloxy)phenyl]propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-carboxybutyloxy)phenyl]propionate.

In analogy with Example 1, the following are obtained from these by reaction with Z-guanidine:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(5-N-benzyloxycarbonylguanidino-5-oxopentyloxy)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(5-N-benzyloxycarbonylguanidino-5-oxopentyloxy)phenyl]propionate

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(5-N-benzyloxycarbonylguanidino-5-oxopentyloxy)-phenyl]propionate.

The Z protecting group is eliminated in analogy with Example 2, and the following compounds are obtained:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(5-guanidino-5-oxopentyloxy)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(5-guanidino-5-oxopentyloxy)phenyl]propionate,

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(5-guanidino-5-oxopentyloxy)phenyl]propionate.

In analogy with Example 3, the tert-butyl ester is cleaved with TFA, and the following compounds are obtained:

(2S)-2-butylsulfonamido-3-[4-(5-guanidino-5-oxopentyloxy)phenyl]propionic acid, trifluoroacetate; FAB 443

(2S)-2-tolylsulfonamido-3-[4-(5-guanidino-5-oxopentyloxy)phenyl]propionic acid, trifluoroacetate; FAB 477

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(5-guanidino-5-oxopentyloxy)phenyl]propionic acid, trifluoroacetate; FAB 537.

In analogy with Example 4, the following compounds are obtained from these by reaction with acetyl chloride:

(2S)-2-butylsulfonamido-3-[4-(5-N-acetylguanidino-5-oxopentyloxy)phenyl]propionic acid,

(2S)-2-tolylsulfonamido-3-[4-(2-N-acetylguanidino-2-oxoethylcarboxamido)phenyl]propionic acid,

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(5-N-acetylguanidino-5-oxopentyloxy)phenyl]propionic acid.

In analogy with Example 5, treatment with TFA converts

tert-butyl (2S)-2-butylsulfonamido-3-[4-(5-N-benzyloxycarbonylguanidino-5-oxopentyloxy)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(5-N-benzyloxycarbonylguanidino-5-oxopentyloxy)phenyl]propionate

and tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(5-N-benzyloxycarbonylguanidino-5-oxopentyloxy)-phenyl]propionate

into the following compounds

(2S)-2-butylsulfonamido-3-[4-(5-N-benzyloxycarbonyl-guanidino-5-oxopentyloxy)phenyl]propionic acid; FAB 577

(2S)-2-tolylsulfonamido-3-[4-(5-N-benzyloxycarbonyl-guanidino-5-oxopentyloxy)phenyl]propionic acid

and (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(5-N-benzyloxycarbonylguanidino-5-oxopentyloxy)phenyl]-propionic acid; FAB 671.

Example 11

The compound tert-butyl (2S)-2-benzyloxycarboxamido-3-[4-(4-cyano-4-oxobutyloxy)phenyl]propionate is obtained, in analogy with Example 1, by reacting benzyloxycarbonyl-L-tyrosine tert-butyl ester with 5-bromo-2-oxovaleronitrile.

The compound tert-butyl (2S)-2-amino-3-[4-(4-cyano-4-oxobutyloxy)phenyl]propionate ("G") is obtained by eliminating the Z protecting group.
Tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-cyano-4-oxobutyloxy)phenyl]propionate ("H") is obtained by reacting "G" with 1-butanesulfonyl chloride.

A solution of "H" and equimolar quantities of hydroxylamine hydrochloride and sodium hydrogen carbonate in isopropanol/water 6:1 is heated under reflux for 12 hours. Following customary working-up, tert-butyl (2S)-2-butylsulfonamido-3-[4-(5-amino-5-N-hydroxylimino-4-oxopentyloxy)phenyl]propionate ("J") is obtained.

A solution of "J" in acetic acid is hydrogenated, at room temperature for 2 hours and under standard pressure, with palladium catalyst (10% on active charcoal). After separating off the catalyst, and after customary working-up, (2S)-2-butylsulfonamido-3-[4-(4-amidino-4-oxobutyloxy)phenyl]propionic acid is obtained.

Example 12

In analogy with Example 1, the following are obtained by reacting N-benzyloxycarbonyl-N-ethylguanidine

with tert-butyl (2S)-2-butylsulfonamido-3-[4-(3-carboxypropyloxy)phenyl]propionate,

tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-N-benzyloxycarbonyl-N-ethylguanidino-4-oxobutyloxy)-phenyl]propionate; FAB 647

with tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(3-carboxypropyloxy)phenyl]propionate,

tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-benzyloxycarbonyl-N-ethylguanidino-4-oxobutyl-oxy)phenyl]propionate; FAB 741

and with tert-butyl (2S)-2-tolylsulfonamido-3-[4-(3-carboxypropyloxy)phenyl]propionate,

tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-N-benzyloxycarbonyl-N-ethylguanidino-4-oxobutyloxy)-phenyl]propionate; FAB 681.

The Z protecting group is eliminated in analogy with Example 2, and the following compounds are obtained:

tert-butyl (2S)-2-butylsulfonamido-3-[4-(4-N-ethyl-guanidino-4-oxobutyloxy)phenyl]propionate; FAB 513

tert-butyl (2S)-2-[(S)-camphor-10-sulfonamido]-3-[4-(4-N-ethylguanidino-4-oxobutyloxy)phenyl]propionate; FAB 607

and tert-butyl (2S)-2-tolylsulfonamido-3-[4-(4-N-ethylguanidino-4-oxobutyloxy)phenyl]propionate; FAB 547.

In analogy with Example 3, the following compounds are obtained from these by cleaving the tert-butyl ester with TFA:

(2S)-2-butylsulfonamido-3-[4-(4-N-ethylguanidino-4-oxo-butyloxy)phenyl]propionic acid, trifluoroacetate; FAB 457

(2S)-2-[(S)-camphor-10-sulfonamido-3-[4-(4-N-ethyl-guanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate; FAB 551

and (2S)-2-tolylsulfonamido-3-[4-(4-N-ethylguanidino-4-oxobutyloxy)phenyl]propionic acid, trifluoroacetate; FAB 491.

The following examples relate to pharmaceutical preparations:

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 of double distilled water, is adjusted to a pH of 6.5 with 2 N hydrochloric acid, sterilized by filtration and aliquoted into injection vials; the solution is then lyophilized, and the vials sealed, under sterile conditions. Each injection vial comprises 5 mg of active compound.

Example B: Suppositories

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

Example C: Solution

A solution of 1 g of an active compound of formula I, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of double distilled water is prepared. It 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 an active compound of the formula I is mixed with 99.5 g of vaseline under aseptic conditions.

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 compressed into tablets in the customary manner such that each tablet comprises 10 mg of active compound.

Example F: Coated tablets

Tablets are compressed in analogy with Example E and are then coated, in a customary manner, with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

2 kg of active compound of the formula I is aliquoted, in a customary manner, into hard gelatin capsules such that each capsule comprises 20 mg of the active compound.

Example H: Ampoules

A solution of 1 kg of active compound of the formula I in 60 l of double distilled water is sterilized by filtration and aliquoted into ampoules; the solution is then lyophilized, and the vials sealed, under sterile conditions. Each ampoule comprises 10 mg of active compound.

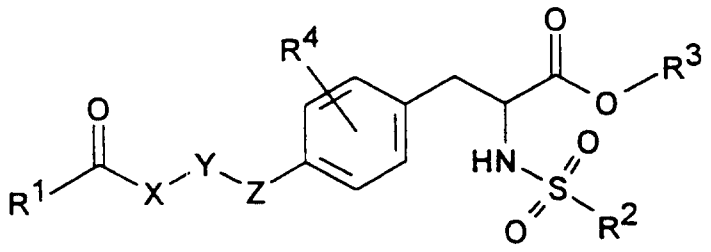
Example I: Inhalation spray

14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution, and the solution is

aliquoted into commercial spraying vessels having a pump mechanism. The solution can be sprayed into the mouth or nose. One spray pulse (approximately 0.1 ml) corresponds to a dose of about 0.14 mg.

Patent claims

1. Compounds of the formula I



I

in which

X is absent, or is alkylene, arylene, cycloalkylene having 4-8 carbon atoms, or heterocycloalkylene having from 1 to 3 N, O and/or S atoms which is unsubstituted or substituted once, twice or three times by A, oxo and/or R^4,

Y and Z are, in each case, independently of each other, absent, or are alkylene, O, S, NH, C(=O), CONH, NHCO, C(=S), SO_2NH, CA=CA' or -C≡C-,

R^1 is H_2N-C(=NH) or H_2N(C=NH)-NH, where the primary amino groups can also be provided with conventional amino protecting groups or can be substituted once, twice or three times by A, Ar or R^5,

R^2 is A, Ar or aralkylene,

R^3 is H or A,

R^4 is H, Hal, OA, NHA, NAA', CN, NO_2, SA, SOA, SO_2A, SO_2Ar or SO_3H,

R^5 is alkanoyl or cycloalkanoyl having 1-18 carbon atoms, in which one, two or three methylene groups can be replaced with N, O and/or S,
Ar-CO- or Ar-alkylene-CO-,

A and A' are, in each case, independently of each other, H, or alkyl or cycloalkyl having 1-15 carbon atoms which is unsubstituted or substituted once, twice or three times by R^4 and in which one, two or three methylene groups can be replaced with N, O and/or S,

Ar is a mononuclear or binuclear aromatic ring system having 0, 1, 2, 3 or 4 N, O and/or S atoms which is unsubstituted or substituted once, twice or three times by A and/or R^4,

Hal is F, Cl, Br or I,

with the proviso that at least one element selected from the group X, Y and Z must be CH_2,

and the physiologically harmless salts thereof.

2. Enantiomers or diastereomers of the compounds of the formula I according to Claim 1.

3. Compounds of the formula I according to Claim 1

a) (2S)-2-butylsulfonamido-3-[4-(4-N-acetyl-guanidino-4-oxobutoxy)phenyl]propionic acid;

b) (2S)-2-butylsulfonamido-3-[4-(4-guanidino-4-oxobutyloxy)phenyl]propionic acid;

c) (2S)-2-(camphor-10-sulfonamido)-3-[4-(4-N-ethylguanidino-4-oxobutoxy)phenyl]propionic acid;

d) (2S)-2-(camphor-10-sulfonamido)-3-[4-(4-N-benzyloxycarbonylguanidino-4-oxobutoxy)-phenyl]propionic acid;

e) (2S)-2-(camphor-10-sulfonamido)-3-[4-(4-guanidino-4-oxobutoxy)phenyl]propionic acid;

f) ethyl (2S)-2-(camphor-10-sulfonamido)-3-[4-(4-guanidino-4-oxobutoxy)phenyl]propionate;

g) (2S)-2-butylsulfonamido-3-[4-(4-N-ethylguanidino-4-oxobutoxy)phenyl]propionic acid;

h) (2S)-2-butylsulfonamido-3-[4-(5-guanidino-5-oxopentoxy)phenyl]propionic acid;

i) (2S)-2-(camphor-10-sulfonamido)-3-[4-(5-guanidino-5-oxopentoxy)phenyl]propionic acid;

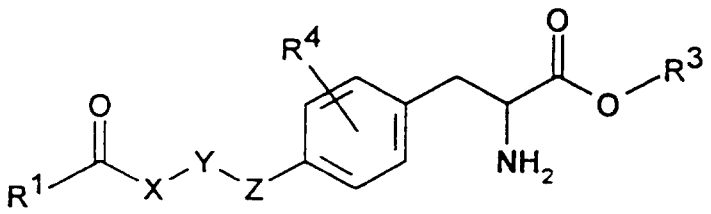
and the physiologically harmless salts thereof.

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

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

or

b) a compound of the formula II



II

in which R^1, R^3, R^4, X, Y and Z have the meanings given in Claim 1,
is reacted with a compound of the formula III

$$R^2\text{-}SO_2\text{-}L \qquad \text{III}$$

in which

R^2 has the meaning given in Claim 1
and L is Cl, Br, I, OH or an OH group which has been esterified to make it capable of reacting,

or

c) an ester of the formula I is hydrolysed,

or

d) a radical R^1 and/or R^3 is/are converted into another radical R^1 and/or R^3,

and/or

e) a basic or acidic compound of the formula I is converted into one of its salts by treating it with an acid or base.

5. Process for producing a pharmaceutical preparation, characterized in that a compound of the formula I according to Claim 1, and/or one of its physiological [sic] harmless salts, is brought into a suitable dosage form together with at least

one solid, liquid or semiliquid carrier substance or auxiliary substance.

6. Pharmaceutical preparation, characterized by a content of at least one compound of the formula I according to Claim 1 and/or one of its physiologically harmless salts.

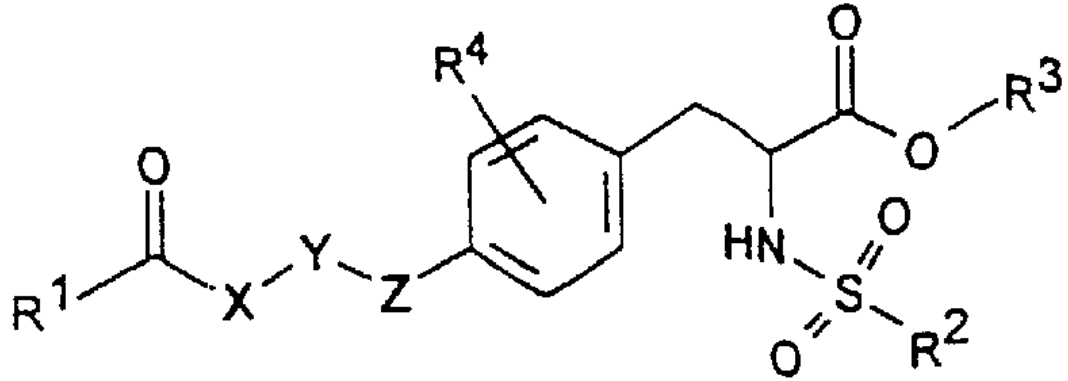
7. Compounds of the formula I according to Claim 1, and their physiologically harmless salts, as GPIIb/IIIa antagonists for controlling thromboses, cardiac infarction, coronary heart diseases and arteriosclerosis.

8. Compounds of the formula I according to Claim 1, and their physiologically harmless salts, as α_v integrin inhibitors for controlling pathologically angiogenic diseases, tumours, osteoporosis, inflammations and infections.

9. Compounds of the formula I according to Claim 1, and their physiologically harmless salts, in which R^2 has the meaning camphor-10-yl, as α_v integrin inhibitors for controlling pathologically angiogenic diseases, tumours, osteoporosis, inflammations and infections.

10. Use of compounds of the formula I according to Claim 1, and/or their physiologically harmless salts, for preparing a pharmaceutical.

11. Compounds of the formula I according to Claim 1, and/or their physiologically harmless salts, for preparing a pharmaceutical for use as an α_v integrin inhibitor.



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