(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 August 2001 (30.08.2001)

PCT

(10) International Publication Number
WO 01/62735 A1

(51) International Patent Classification[7]: C07D 217/14, A61K 31/40, 31/435, C07D 207/08, C07K 5/08, A61K 31/06

(21) International Application Number: PCT/EP01/01928

(22) International Filing Date: 21 February 2001 (21.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00104041.9 26 February 2000 (26.02.2000) EP

(71) Applicant: **AVENTIS PHARMA DEUTSCHLAND GMBH** [DE/DE]; Brüningstrasse 50, 65929 Frankfurt (DE).

(72) Inventors: **AL-OBEIDI, Fahad**; 548 E. Wine Plum Drive, Tucson, AZ 85704 (US). **WALSER, Armin**; 5900 N. Camino Miraval, Tucson, AZ 85718 (US). **WILD-GOOSE, Peter**; 21 Reid Ave., Belle Mead, NJ 08502 (US).

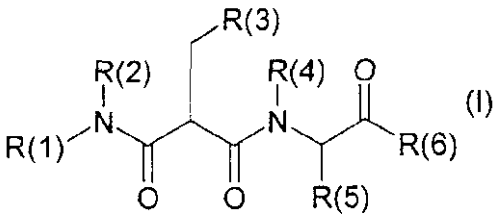
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL MALONIC ACID DERIVATIVES, PROCESSES FOR THEIR PREPARATION, THEIR USE AS INHIBITOR OF FACTOR XA ACTIVITY AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

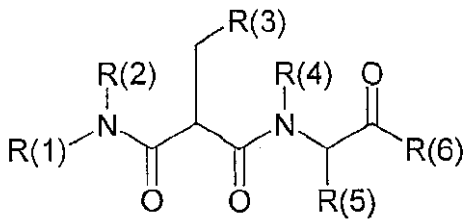
(57) Abstract: The present invention relates to new compounds for the inhibition of blood clotting proteins, and more particularly, to malonic acid derivatives of the formula (I), wherein R(1), R(2), R(3), R(4), R(5), and R(6) have the meanings indicated in the claims. The compounds of the formula (I) are inhibitors of the blood clotting enzyme factor Xa. The invention also relates to processes for the preparation of the compounds of formula (I), to methods of inhibiting factor Xa activity and of inhibiting blood clotting, to the use of the compounds of formula (I) in the treatment and prophylaxis of diseases, which can be treated or prevented by the inhibition of factor Xa activity such as thromboembolic diseases, and to the use of the compounds of formula (I) in the preparation of medicaments to be applied in such diseases. The invention further relates to compositions containing a compound of formula (I), in admixture or otherwise in association with an inert carrier, in particular pharmaceutical compositions containing a compound of formula (I) together with pharmaceutically acceptable carrier substances and auxiliary substances.

WO 01/62735 A1

NOVEL MALCONIC ACID DERIVATES, PROCESSES FOR THEIR PREPARATION, THEIR USE AS INHIBITOR OF FACTOR XA ACTIVITY AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Novel malonic acid derivatives, processes for their preparation, their use and pharmaceutical compositions containing them

The present invention relates to compounds of the formula I,



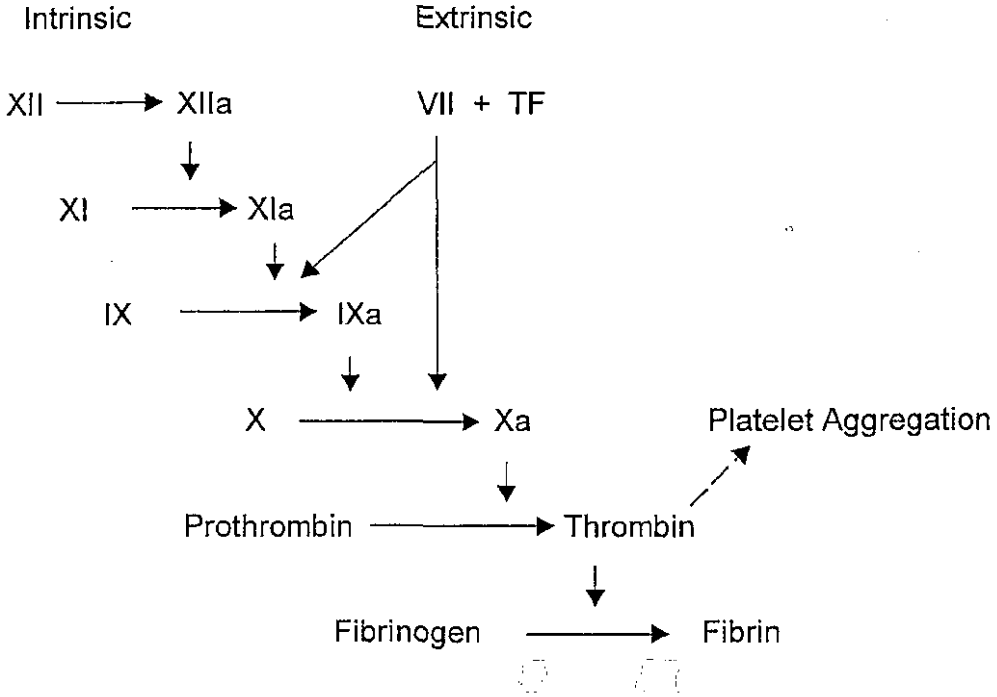
(I)

in which R(1), R(2), R(3), R(4), R(5), and R(6) have the meanings as indicated below. The compounds of formula I are valuable pharmacologically active compounds. They exhibit a strong antithrombotic effect and are suitable, for example, for the therapy and prophylaxis of cardiovascular disorders like thromboembolic diseases or restenoses. They are reversible inhibitors of the blood clotting enzyme factor Xa and can in general be applied in conditions in which an undesired activity of factor Xa is present or for the cure or prevention of which an inhibition of factor Xa is intended. The invention also relates to processes for the preparation of the compounds of formula I, to methods of inhibiting factor Xa activity and of inhibiting blood clotting, to the use of the compounds of formula I in the treatment and prophylaxis of diseases which can be treated or prevented by the inhibition of factor Xa activity such as thromboembolic diseases, and to the use of the compounds of formula I in the preparation of medicaments to be applied in such diseases. The invention further relates to compositions containing a compound of formula I in admixture or otherwise in association with an inert carrier, in particular pharmaceutical compositions containing a compound of formula I together with pharmaceutically acceptable carrier substances and auxiliary substances.

The ability to form blood clots is vital to survival. In certain disease states, however, the formation of blood clots within the circulatory system reaches an undesired extent and is itself a source of morbidity potentially leading to pathological consequences. It is nevertheless not desirable in such disease states to completely inhibit the clotting system because life threatening hemorrhage would ensue. In the treatment of such

states a well-balanced intervention into the blood clotting system is required, and there is still a need for substances exhibiting a suitable pharmacological activity profile for achieving such a result.

Blood coagulation is a complex process involving a progressively amplified series of enzyme activation reactions in which plasma zymogens are sequentially activated by limited proteolysis. Mechanistically the blood coagulation cascade has been divided into intrinsic and extrinsic pathways, which converge at the activation of factor X. Subsequent generation of the thrombin proceeds through a single common pathway (see Scheme 1).



Scheme 1: Blood coagulation cascade AVE D-2000/A012

Present evidence suggests that the intrinsic pathway plays an important role in the maintenance and growth of fibrin formation, while the extrinsic pathway is critical in the initiation phase of blood coagulation. It is generally accepted that blood coagulation is physically initiated upon formation of a tissue factor (TF)/factor VIIa complex. Once formed, this complex rapidly initiates coagulation by activating factors IX and X. The newly generated activated factor X, i. e. factor Xa, then forms a one-to-one complex

with factor Va and phospholipids to form a prothrombinase complex, which is responsible for converting soluble fibrinogen to insoluble fibrin via the activation of thrombin from its precursor prothrombin. As time progresses, the activity of the factor VIIa/tissue factor complex (extrinsic pathway) is suppressed by a Kunitz-type protease inhibitor protein, TFPI, which, when complexed to factor Xa, can directly inhibit the proteolytic activity of factor VIIa/tissue factor. In order to maintain the coagulation process in the presence of an inhibited extrinsic system, additional factor Xa is produced via the thrombin-mediated activity of the intrinsic pathway. Thus, thrombin plays a dual autocatalytic role, mediating its own production and the conversion of fibrinogen to fibrin.

The autocatalytic nature of thrombin generation is an important safeguard against uncontrolled bleeding and it ensures that, once a given threshold level of prothrombinase is present, blood coagulation will proceed to completion, effecting, for example, an end of the hemorrhage. Thus, it is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin but by inhibiting other steps in the coagulation cascade like factor Xa.

In many clinical applications there is a great need for the prevention of intravascular blood clots or for anti-coagulant therapy. For example, nearly 50 % of patients who have undergone a total hip replacement develop deep vein thrombosis (DVT). The currently approved therapies are fixed dose low molecular weight heparin (LMWH) and variable dose heparin. Even with these drug regimes 10 % to 20 % of patients develop DVT and 5 % to 10 % develop bleeding complications.

Another clinical situation for which better anticoagulants are needed concerns subjects undergoing transluminal coronary angioplasty and subjects at risk for myocardial infarction or angina. The present, conventionally accepted therapy which consists of administering heparin and aspirin, is associated with a 6 % to 8 % abrupt vessel closure rate with 24 hours of the procedure. The rate of bleeding complications requiring transfusion therapy due to the use of heparin also is approximately 7 %.

Moreover, even though delayed closures are significant, administration of heparin after termination of the procedures is of little value and can be detrimental.

The most widely used blood-clotting inhibitors are heparin and the related sulfated polysaccharides, LMWH and heparin sulfate. These molecules exert their anti-clotting effects by promoting the binding of a natural regulator of the clotting process, anti-thrombin III, to thrombin and to factor Xa. The inhibitory activity of heparin primarily is directed toward thrombin, which is inactivated approximately 100 times faster than factor Xa. Although relative to heparin, heparin sulfate and LMWH are somewhat more potent inhibitors of Xa than of thrombin, the differences in vitro are modest (3-30 fold) and effects in vivo can be inconsequential. Hirudin and hirulog are two additional thrombin-specific anticoagulants that have been tested in clinical trials. However, these anticoagulants, which inhibit thrombin, also are associated with bleeding complications.

Preclinical studies in baboons and dogs have shown that specific inhibitors of factor Xa prevent clot formation without producing the bleeding side effects observed with direct thrombin inhibitors.

Several specific inhibitors of factor Xa have been reported. Both synthetic and protein inhibitors of factor Xa have been identified, these include, for example, antistasin ("ATS") and tick anticoagulant peptide ("TAP"). ATS, which is isolated from the leech, Haementerin officinalis, contains 119 amino acids and has a Ki for factor Xa of 0.05 nM. TAP, which is isolated from the tick, Ornithodoros moubata, contains 60 amino acids and has a Ki for factor Xa of about 0.5 nM.

The effectiveness of recombinantly-produced ATS and TAP have been investigated in a number of animal model systems. Both inhibitors decrease bleeding time compared to other anticoagulants, and prevent clotting in a thromboplastin-induced, ligated jugular vein model of deep vein thrombosis. The results achieved in this model correlate with results obtained using the current drug of choice, heparin.

Subcutaneous ATS also was found to be an effective treatment in a thromboplastin-induced model of disseminated intravascular coagulation (DIC). TAP effectively prevents "high-shear" arterial thrombosis and "reduced flow" caused by the surgical placement of a polyester ("DACRON") graft at levels that produced a clinically acceptable prolongation of the activated partial thromboplastin time (aPTT), i.e. less than about two fold prolongation. By comparison, standard heparin, even at doses causing a five fold increase in the aPTT, did not prevent thrombosis and reduced flow within the graft. The aPTT is a clinical assay of coagulation which is particularly sensitive to thrombin inhibitors.

ATS and TAP have not been developed clinically. One major disadvantage of these two inhibitors is that administration of the required repeated doses causes the generation of neutralizing antibodies, thus limiting their potential clinical use. Moreover, the sizes of TAP and ATS render oral administration impossible, further restricting the number of patients able to benefit from these agents.

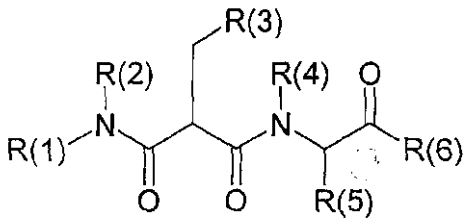
A specific inhibitor of factor Xa with a favourable property profile would have substantial practical value in the practice of medicine. In particular, a factor Xa inhibitor would be effective under circumstances where the present drugs of choice, heparin and related sulfated polysaccharides, are ineffective or only marginally effective.

Low molecular weight, factor Xa-specific blood clotting inhibitors, that are effective but does not cause unwanted side effects have been described, for example, in WO-A 95/29189). Indole derivatives as low molecular weight, factor Xa-specific blood clotting inhibitors have been described in WO-A-99/33800. However, besides being an effective factor Xa-specific blood clotting inhibitor, it is desirable that such inhibitors also have further advantageous pharmacological properties, for instance good oral bioavailabilty, high stability in plasma and liver and/or high selectivity versus other serine proteases whose inhibition is not intended, such as thrombin. Thus there exists an ongoing need for further low molecular weight factor Xa-specific blood clotting inhibitors which are effective and have the above advantages as well. Arylalkanoyl and

malonic acid derivatives, which are suitable Factor Xa inhibitors have been proposed in European application nos. 99100001, 99100002, 99119537, and 99119538.

The present invention also satisfies the above needs by providing novel compounds of the formula I which exhibit factor Xa inhibitory activity and are favourable agents for inhibiting unwanted blood clotting and thrombus formation.

Thus, a subject of the present invention are compounds of the formula I,



(I)

where

R(1) is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by R(17);

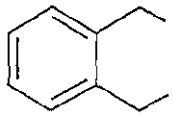
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is (C_6-C_{10})-aryl which is substituted by R(7);

R(4) is hydrogen or (C_1-C_4)-alkyl;

R(5) is (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by a residue R(20), and where alkyl is unsubstituted or substituted by a residue R(21); or

R(4) and R(5) together form a residue of the formula II



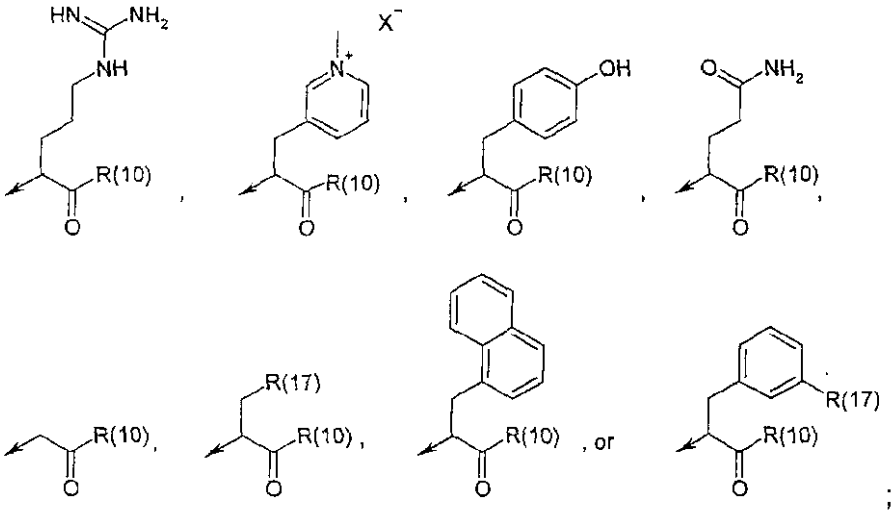
(II) ;

R(6) is NR(8)R(9) or OR(22);

R(7) is R(17) or R(20);

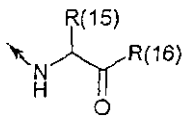
R(8) is hydrogen; (C_1-C_4)-alkyl, where alkyl is unsubstituted or substituted by a residue R(20); heteroaryl-(C_1-C_4)-alkyl; (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl is unsubstituted or substituted by a residue R(17);

R(9) is (C_6-C_{10})-aryl-(C_1-C_4)-alkyl,



;

R(10) is NR(12)R(13), OR(14), or



;

R(12) is hydrogen or (C_1-C_4)-alkyl;

R(13) is hydrogen, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, or (C_1-C_4)-alkyl;

R(14) is hydrogen, (C_1-C_4)-alkyl, (C_2-C_4)-alkenyl or (C_6-C_{10})-aryl-(C_1-C_4)-alkyl;

R(15) is (C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl;

R(16) is R(20);

R(17) is $-C(=N-R(18))-N(R(19))_2$;

R(18) is hydrogen, hydroxy, or an amino protective group;

R(19) is hydrogen, (C_1-C_4)-alkyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl, or an amino protective group;

R(20) is $N(R(19))_2$;

R(21) is hydroxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonylamino, carboxyl, or R(20);

R(22) is hydrogen or (C_1-C_4)-alkyl;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

Alkyl residues present in the compounds of formula I can be saturated or unsaturated (and therefore cover alkenyl or alkynyl residues) and straight-chain or branched. This also applies when they carry substituents or appear as substituents in other residues such as for example, in alkoxy residues, arylalkoxy residues, alkoxycarbonyl residues, cycloalkyl-alkyl residues, arylalkyl residues, heteroarylalkyl residues, and

arylalkoxycarbonyl residues. Examples of saturated alkyl residues are methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, sec-butyl, and tert-butyl, n-pentyl, n-hexyl, isopentyl, isohexyl, neopentyl, 3-methylpentyl, and tert-pentyl, examples of unsaturated alkyl residues are vinyl, 1-propenyl, 2-propenyl (i. e. allyl), butenyl, 3-methyl-2-butenyl, pentenyl, hexenyl, (alkenyl residues) or ethynyl, 1-propynyl, 2-propynyl (i. e. propargyl), butynyl, pentynyl and hexynyl (alkynyl residues).

Cycloalkyl residues present in the compounds of formula I can be mono-, di- or tricyclic and are connected in the ring. This also applies when they appear as substituents in other residues. Examples of cycloalkyl residues are cyclopropyl, methyl-cyclopropyl, ethyl-cyclopropyl, dimethyl-cyclopropyl, propyl-cyclopropyl, methyl-ethyl-cyclopropyl, butyl-cyclopropyl, methyl-propyl-cyclopropyl, diethyl-cyclopropyl, cyclobutyl, methyl-cyclobutyl, ethyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, ethyl-cyclopentyl, dimethyl-cyclopentyl, cyclohexyl, methyl-cyclohexyl, and cycloheptyl, where ethyl, propyl, and butyl, can be straight-chain or branched as described above.

Examples of aryl are phenyl or naphthyl.

Arylalkyl residues present in the compounds of formula I can consist of an alkyl residue, which can contain one to three aryl moieties. Examples of arylalkyl residues are phenyl-methyl, phenyl-ethyl, phenyl-propyl, phenyl-butyl, naphthyl-methyl, naphthyl-ethyl, naphthyl-propyl, naphthyl-butyl, diphenyl-methyl, diphenyl-ethyl, diphenyl-propyl, diphenyl-butyl, naphthyl-phenyl-methyl, naphthyl-phenyl-butyl, dinaphthyl-butyl, and triphenyl-ethyl.

Examples of heteroaryl residues are pyridyl, pyridazinyl, pyrimidyl, pyrazinyl, furanyl, pyrrolyl, imidazolyl, 1H-pyrazolyl, thiazolyl, oxazolyl, thiophenyl, 1H-benzoimidazolyl, benzothiazolyl, benzofuranyl, indolyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 3H-imidazo[4,5-c]pyridinyl, [1,2,4]oxadiazolyl, quinolinyl, and isoquinolinyl. The residues can be bound at every possible position.

Examples of pyridyl residues are 2-pyridyl, 3-pyridyl and 4-pyridyl. This also applies to pyridyl residues in which the nitrogen atom is substituted by an alkyl group etc. this substitution leading to a positively charged pyridinium group. This pyridinium group has an X^- as counterion.

In monosubstituted phenyl residues the substituent can be located in the 2-position, the 3-position or the 4-position.

Naphthyl residues can be 1-naphthyl and 2-naphthyl. In substituted naphthyl residues the substituents can be in any position, i. e. in monosubstituted 1-naphthyl residues in the 2-, 3-, 4-, 5-, 6-, 7-, or 8-position and in monosubstitued 2-naphthyl residues in the 1-, 3-, 4-, 5-, 6-, 7-, or 8-position.

A preferred $(C_6$-$C_{10})$-aryl-$(C_1$-$C_4)$-alkyl residue in compounds of formula I is benzyl (phenylmethyl).

Suitable amino protective groups are known to those skilled in the art and encompass for example those which are customarily used in peptide synthesis. Suitable amino protective groups in the residues R(18) and R(19) can be for example the following residues:

$(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkylcarbonyl, $(C_1$-$C_6)$-alkoxycarbonyl, $(C_1$-$C_{18})$-alkylcarbonyloxy-$(C_1$-$C_6)$-alkoxycarbonyl, optionally substituted $(C_6$-$C_{14})$-arylcarbonyl, optionally substituted $(C_6$-$C_{14})$-aryloxycarbonyl, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_6)$-alkoxycarbonyl which can also be substituted in the aryl moiety; cyano, nitro, amino, hydroxy, $(C_1$-$C_6)$-alkoxy, and $(C_6$-$C_{14})$-aryl-$(C_1$-$C_6)$-alkoxy which is unsubstituted or substituted in the aryl moiety for example by $(C_1$-$C_4)$-alkoxy, preferably methoxy, chloro, or $(C_1$-$C_4)$-alkyl, preferably methyl.

$(C_1$-$C_3)$-alkyl means alkyl having 1, 2, or 3 carbon atoms.
$(C_1$-$C_4)$-alkyl means alkyl having 1, 2, 3, or 4 carbon atoms.
$(C_1$-$C_6)$-alkyl means alkyl having 1, 2, 3, 4, 5, or 6 carbon atoms.
$(C_2$-$C_4)$-alkenyl means alkenyl having 2, 3, or 4 carbon atoms.

$(C_2$-$C_6)$-alkenyl means alkenyl having 2, 3, 4, 5, or 6 carbon atoms.

$(C_6$-$C_{10})$-aryl means aryl having 6, 7, 8, 9, or 10 carbon atoms.

$(C_6$-$C_{14})$-aryl means aryl having 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms.

$(C_1$-$C_4)$-alkoxy means alkoxy having 1, 2, 3, or 4 carbon atoms.

$(C_1$-$C_6)$-alkoxy means alkoxy having 1, 2, 3, 4, 5, or 6 carbon atoms.

$(C_1$-$C_6)$-alkoxycarbonyl means alkoxycarbonyl having 1, 2, 3, 4, 5, or 6 carbon atoms in the alkoxy part.

$(C_1$-$C_6)$-alkylcarbonyl means alkylcarbonyl having 1, 2, 3, 4, 5, or 6 carbon atoms in the alkyl part.

$(C_6$-$C_{10})$-aryl-$(C_1$-$C_4)$-alkyl means aryl-alkyl having independently from each other 6, 7, 8, 9, or 10 carbon atoms in the aryl part and 1, 2, 3, or 4 carbon atoms in the alkyl part.

$(C_6$-$C_{14})$-aryl-$(C_1$-$C_6)$-alkoxy means aryl-alkoxy having independently from each other 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms in the aryl part and 1, 2, 3, 4, 5, or 6 carbon atoms in the alkoxy part.$(C_6$-$C_{10})$-aryl-$(C_1$-$C_4)$-alkoxy means aryl-alkoxy having independently from each other 6, 7, 8, 9, or 10 carbon atoms in the aryl part and 1, 2, 3, or 4 carbon atoms in the alkoxy part.

Heteroaryl-$(C_1$-$C_4)$-alkyl means heteroaryl-alkyl having 1, 2, 3, or 4 carbon atoms in the alkyl part.

$(C_1$-$C_{18})$-alkylcarbonyloxy-$(C_1$-$C_6)$-alkoxycarbonyl means alkylcarbonyloxy-alkoxycarbonyl having independently from each other 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 carbon atoms in the alkyl part and 1, 2, 3, 4, 5, or 6 carbon atoms in the alkoxy part.

$(C_6$-$C_{14})$-arylcarbonyl means arylcarbonyl having 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms in the aryl part.

$(C_6$-$C_{14})$-aryloxycarbonyl means aryloxycarbonyl having 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms in the aryl part.

$(C_6$-$C_{14})$-aryl-$(C_1$-$C_6)$-alkoxy means aryl-alkoxy having independently from each other 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms in the aryl part and 1, 2, 3, 4, 5, or 6 carbon atoms in the alkoxy part.

(C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl means aryl-alkoxycarbonyl having independently from each other 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms in the aryl part and 1, 2, 3, 4, 5, or 6 carbon atoms in the alkoxy part.

(C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl means aryl-alkoxycarbonyl having independently from each other 6, 7, 8, 9, or 10 carbon atoms in the aryl part and 1, 2, 3, or 4 carbon atoms in the alkoxy part.

(C_3-C_7)-cycloalkyl means cycloalkyl having 3, 4, 5, 6, or 7 carbon atoms.

(C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl means cycloalkyl-alkyl having independently from each other 3, 4, 5, 6, or 7 carbon atoms in the cycloalkyl part and 1, 2, 3, or 4 carbon atoms in the alkyl part.

It is understood that residues present more that one time in a compound of formula I, e.g. the residues R(17), R(18), R(19), R(20) and R(21), are independent of one another and can be identical or different.

Physiologically acceptable anions X^-, which are present in the compounds of formula I if a positively charged group is present, can be anions derived from suitable inorganic acids or organic carboxylic acids or sulfonic acids. Suitable acids are, in particular, pharmaceutically utilizable or non-toxic salts. Examples of such acids are those given below as examples of acids which can form physiologically acceptable salts with the compounds of formula I containing basic groups. If a compound of formula I contains an anion X^- and simultaneously is present as an acid addition salt formed at a basic group, the anion X^- can be the same or different as the anion introduced by salt formation. The present invention also covers inner salts (or betaines) of the compounds of formula I.

Physiologically acceptable salts of the compounds of formula I are, in particular, pharmaceutically utilizable or non-toxic salts. Such salts are formed, for example, from compounds of formula I which contain acid groups, for example carboxylic acid groups. Examples of such salts are, for example, salts containing cations of alkali metals or alkaline earth metals, such as, for example, sodium, potassium, magnesium or calcium, or the unsubstituted ammonium cation or organic ammonium cations, the

latter including cations obtained from physiologically acceptable organic amines, such as, for example, methylamine, ethylamine, triethylamine, ethanolamine, tris(2-hydroxyethyl)amine or amino acids by protonation, or suitable quaternary ammonium cations like, for example, tetramethylammonium.

Compounds of formula I which contain basic groups, for example an amino group or an amidino group, form acid addition salts with, for example, inorganic acids, organic carboxylic and organic sulfonic acids. Examples of such acids the anions of which can be present in physiologically acceptable salts of the compounds of formula I are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, benzoic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, p-toluenesulfonic acid or naphthalenesulfonic acids.

Physiologically acceptable salts of the compounds of formula I can be prepared according to standard procedures, for example by combining the compound of formula I with the desired base, for example an alkaline metal hydroxide or carbonate or hydrogen carbonate or an amine, or with the desired acid in a solvent or diluent. A physiologically acceptable salt of a compound of formula I can also be prepared from another salt, for example trifluoroacetic acid salt by cation exchange or anion exchange by standard procedures. The present invention also covers in general salts of the compounds of formula I which are, for example, obtained during the chemical synthesis of the compounds and which can be used as starting materials for the subsequent preparation of a desired physiologically acceptable salt. The present invention further covers solvates of the compounds of formula I, for example hydrates or alcoholates.

The compounds of formula I according to the invention can contain optically active carbon atoms which independently of one another can have R or S configuration. They can thus be present in the form of individual enantiomers or individual diastereomers or in the form of enantiomeric mixtures including racemates, or diastereomeric mixtures. The present invention relates both to pure enantiomers and

mixtures of enantiomers in all ratios and to pure diastereomers and mixtures of diastereomers in all ratios. The invention covers mixtures of two stereoisomers as well as mixtures of more than two stereoisomers of formula I, and all ratios of stereoisomers in the mixtures.

The compounds of formula I can also be present as E isomers or Z isomers. The present invention relates to both pure E and Z isomers and to mixtures of E/Z isomers in all ratios. Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example, by chromatography. Racemates can be separated into the two enantiomers by chromatography on chiral phases or by resolution according to standard procedures. Pure enantiomers can otherwise also be obtained by employing into the synthesis optically active starting materials.

The compounds of formula I according to the invention can further contain mobile hydrogen atoms, i.e. they can be present in various tautomeric forms. The present invention also relates to all these tautomers.

The invention also includes derivatives and modifications of the compounds of the formula I, for example prodrugs, protected forms and other physiologically tolerable derivatives including esters and amides, as well as active metabolites of the compounds of the formula I. Such esters and amides are, for example, (C_1-C_4)-alkyl esters, unsubstituted amides or (C_1-C_8)-alkylamides. The invention relates in particular to prodrugs and protected forms of the compounds of the formula I which can be converted into compounds of the formula I under physiological conditions. Suitable prodrugs for the compounds of the formula I, i. e. chemically modified derivatives of the compounds of the formula I having properties which are improved in a desired manner, for example with respect to solubility, bioavailability or duration of action, are known to those skilled in the art. More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; Fleisher et al., Advanced Drug Delivery Reviews 19 (1996) 115-130; or H. Bundgaard, Drugs of the Future 16 (1991) 443 which are all incorporated herein by reference. Suitable prodrugs for the compounds of the formula I are especially ester

prodrugs and amide prodrugs of carboxylic acid groups, and also acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino group, amidino group and the guanidino group. In the acyl prodrugs and carbamate prodrugs one or more, for example one or two, hydrogen atoms on nitrogen atoms in such groups are replaced with an acyl group or an oxyacyl group. Suitable acyl groups and oxyacyl groups for acyl prodrugs and carbamate prodrugs are, for example, the groups R^{p1}-CO- and R^{p2}O-CO-, in which R^{p1} is hydrogen, (C_1-C_{18})-alkyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl-, (C_6-C_{14})-aryl which is unsubstituted or substituted by a residue (C_1-C_2)-alkyl, (C_1-C_2)-alkoxy, fluoro, or chloro; heteroaryl-, (C_6-C_{14})-aryl-(C_1-C_4)-alkyl- where aryl is unsubstituted or substituted by a residue (C_1-C_2)-alkyl, (C_1-C_2)-alkoxy, fluoro, or chloro; or heteroaryl-(C_1-C_4)-alkyl- and in which R^{p2} has the meanings indicated for R^{p1} with the exception of hydrogen.

Preferred are compounds of the formula I, wherein

R(1) is hydrogen, (C_1-C_4)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

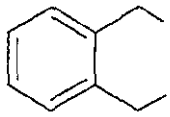
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is phenyl or naphthyl, preferably 2-naphthyl which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, preferably 4-aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II



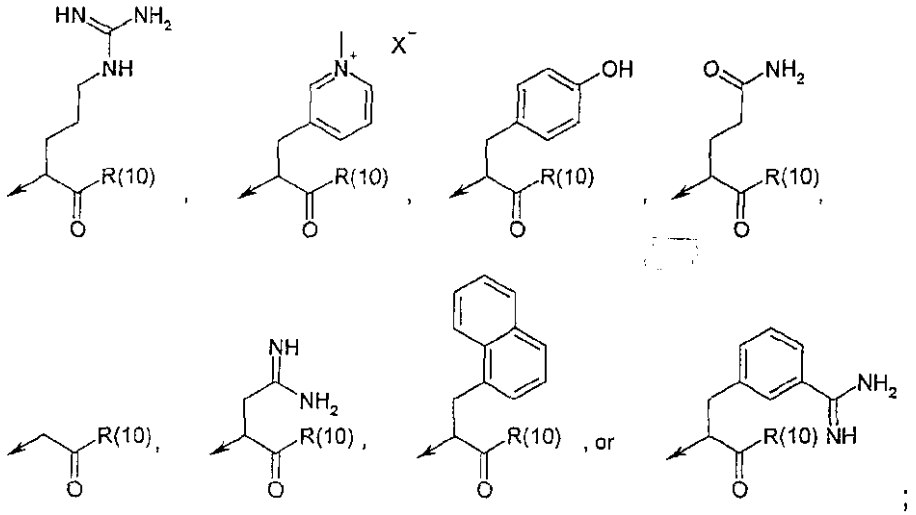
(II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

R(7) is amidino, hydroxyamidino, amino, or dimethylamino;

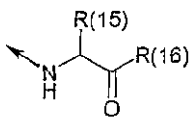
R(8) is hydrogen, pyridylmethyl, preferably 4-pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is naphthylmethyl, preferably 1-naphthylmethyl,



;

R(10) is NR(12)R(13), OR(14) or



;

R(12) is hydrogen or methyl;

R(13) is hydrogen, phenyl-(C_1-C_2)-alkyl, or methyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, benzyl, or allyl;

R(15) is cyclohexylmethyl;

R(16) is amino;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

Preferred are also compounds of the formula I where

R(1) is hydrogen, (C_1-C_3)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

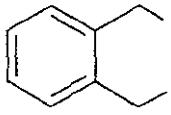
R(2) is hydrogen or (C_1-C_3)-alkyl;

R(3) is phenyl or 2-naphthyl which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, 4-aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II



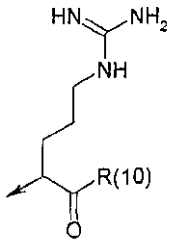
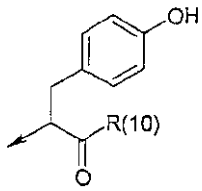
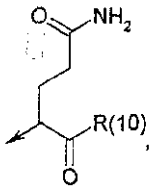
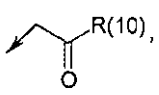
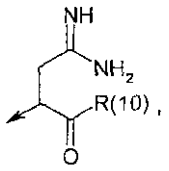
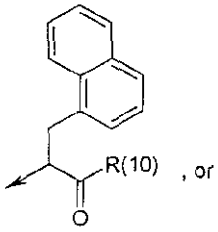
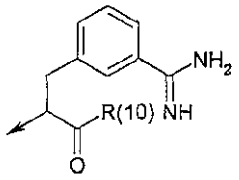
(II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

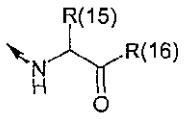
R(7) is amidino, hydroxyamidino, or dimethylamino;

R(8) is hydrogen, pyridylmethyl, preferably 4-pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is naphthylmethyl, preferably 1-naphthylmethyl,








;

R(10) is NR(12)R(13), OR(14), or


;

R(12) is hydrogen or methyl;

R(13) is hydrogen, phenyl-(C_1-C_2)-alkyl, or methyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, benzyl, or allyl;

R(15) is cyclohexylmethyl;

R(16) is amino;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

Particularly preferred are compounds of the formula I, where

R(1) is hydrogen, (C_1-C_3)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

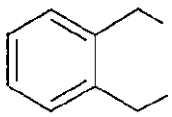
R(2) is hydrogen or (C_1-C_3)-alkyl;

R(3) is phenyl or naphthyl, preferably 2-naphthyl which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, preferably 4-aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II

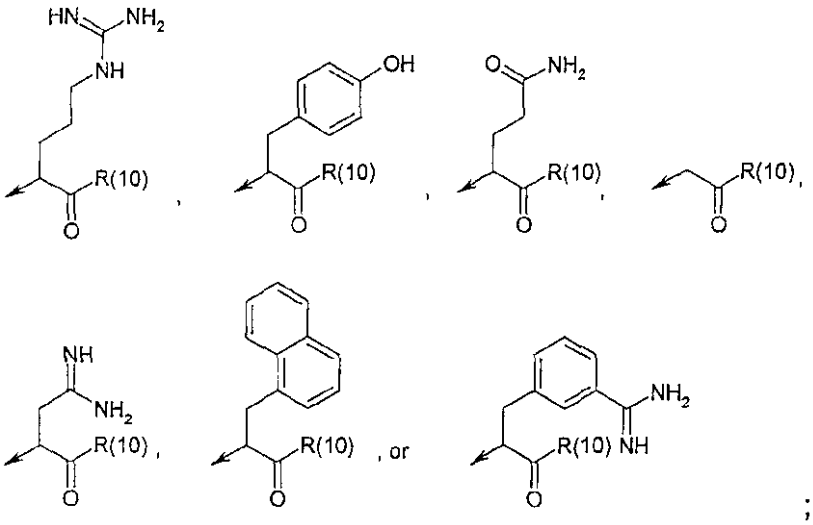
 (II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

R(7) is amidino, hydroxyamidino, or dimethylamino;

R(8) is hydrogen, pyridylmethyl, preferably 4-pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is naphthylmethyl, preferably 1-naphthylmethyl,



;

R(10) is NR(12)R(13), or OR(14);

R(12) is hydrogen or methyl;

R(13) is hydrogen, phenyl-(C_1-C_2)-alkyl, or methyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, benzyl, or allyl;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

Most particularly preferred are compounds of the formula I where

R(1) is methyl, allyl, phenyl, or benzyl, preferably methyl or benzyl;

R(2) is hydrogen or methyl;

R(3) is phenyl which is substituted by R(7);

R(4) is hydrogen;

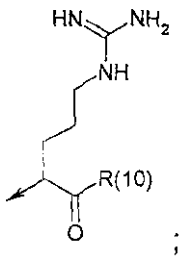
R(5) is butyl, preferably n-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, preferably 4-aminobenzyl, benzyloxymethyl, carboxymethyl, or 2-carboxy-ethyl;

R(6) is NR(8)R(9);

R(7) is amidino or hydroxyamidino;

R(8) is hydrogen;

R(9) is



;

R(10) is NR(12)R(13) or OR(14);

R(12) is hydrogen or methyl;

R(13) is hydrogen or phenyl-(C_1-C_2)-alkyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, or allyl;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

Most particularly preferred compounds of the formula I which may be mentioned are:

2-(4-Carbamimidoyl-benzyl)-N-[(1-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid allyl ester trifluoroacetic acid salt, less polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, more polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, less polar diastereomer,

N-Benzyl-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-malonamide trifluoroacetic acid salt,

N-[2-(4-Amino-phenyl)-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N'-methyl-malonamide trifluoroacetic acid salt,

4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-4-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyric acid,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-2-yl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-3-phenyl-propyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

3-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-N-(1-(S)-carbamoyl-4-guanidino-butyl)-succinamic acid trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-phenyl-methyl]-N'-methyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-phenyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

N-[2-Benzyloxy-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid; compound with trifluoro-acetic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-3-cyclohexyl-propionylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-1-yl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N'-methyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-cyclohexyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

N-Benzyl-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid ethyl ester hydrochloric acid salt,

2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid ethyl trifluoroacetic acid salt, less polar diastereomer,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-cyclohexyl-(4-guanidino-1-(S)-phenethylcarbamoyl-butylcarbamoyl)-methyl]-N',N'-dimethyl-malonamide hydrochloric acid salt,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, more polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, less polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N-methyl-malonamide trifluoroacetic acid salt,

2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid hydrochloric acid salt,

2-(S)-{2-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid methyl ester trifluoroacetic acid salt, least polar diastereomer,

N-Benzyl-N'-{[1-(S)-(benzyl-methyl-carbamoyl)-4-guanidino-butylcarbamoyl]-cyclohexyl-methyl}-2-(4-carbamimidoyl-benzyl)-N-methyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

The invention also relates to compounds of formula I, wherein

R(1) is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by R(17);

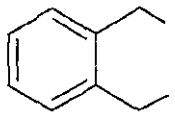
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is (C_6-C_{10})-aryl which is substituted by R(7);

R(4) is hydrogen or (C_1-C_4)-alkyl;

R(5) is (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by a residue R(20), and where alkyl is unsubstituted or substituted by a residue R(21); or

R(4) and R(5) together form a residue of the formula II

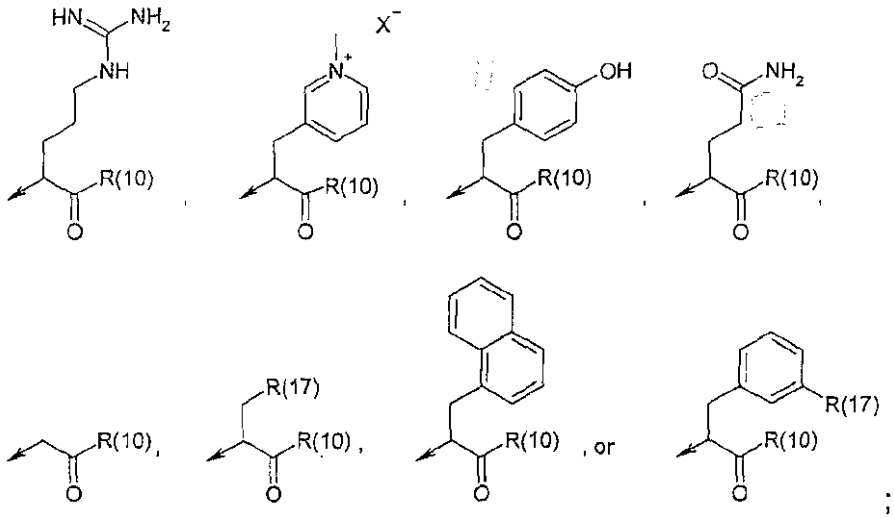
 (II) ;

R(6) is NR(8)R(9) or OR(22);

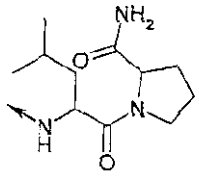
R(7) is R(17) or R(20);

R(8) is hydrogen; (C_1-C_4)-alkyl, where alkyl is unsubstituted or substituted by a residue R(20); heteroaryl-(C_1-C_4)-alkyl; (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl is unsubstituted or substituted by a residue R(17);

R(9) is



R(10) is



;

R(17) is -C(=N-R(18))-N(R(19))$_2$;

R(18) is hydrogen, hydroxy, or an amino protective group;

R(19) is hydrogen, (C_1-C_4)-alkyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl, or an amino protective group ;

R(20) is N(R(19))$_2$;

R(21) is hydroxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonylamino, carboxyl, or R(20);

R(22) is hydrogen or (C_1-C_4)-alkyl;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

The invention also relates to compounds of formula I, wherein

R(1) is hydrogen, (C_1-C_4)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

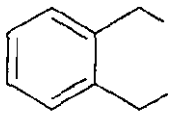
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is phenyl or 2-naphthyl which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, preferably 4-aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II

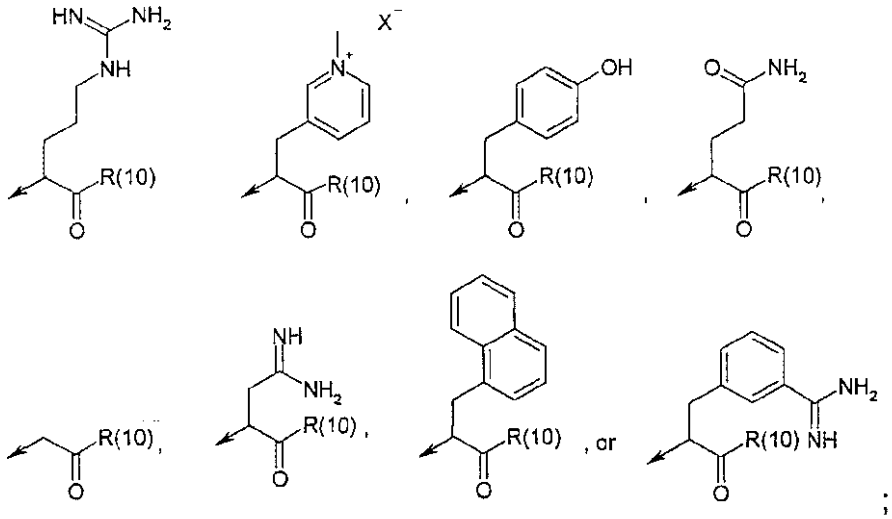
 (II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

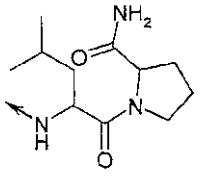
R(7) is amidino, hydroxyamidino, amino, or dimethylamino;

R(8) is hydrogen, pyridylmethyl, preferably 4-pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is



R(10) is



X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

Preferred are compounds of the formula I where

R(1) is propyl or butyl; preferably butyl;

R(2) is propyl or butyl;preferably butyl;

R(3) is phenyl which is substituted by R(7);

R(4) is hydrogen;

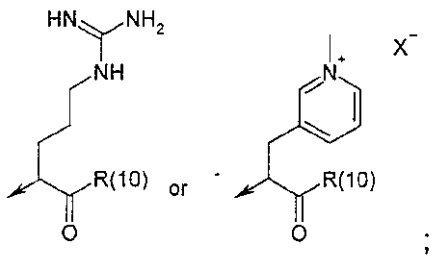
R(5) is cyclohexyl;

R(6) is NR(8)R(9);

R(7) is amidino, or amino;

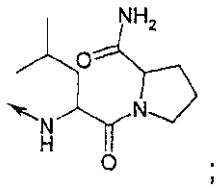
R(8) is hydrogen;

R(9) is



;

R(10) is



;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

Particular preferred compounds which may be mentioned are:

2-(4-Carbamimidoyl-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, less polar diastereomer;

3-{2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-diisopropylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-2-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-ethyl}-1-methyl-pyridinium trifluoro-acetate trifluoroacetic acid, less polar diastereomer,

2-(4-Amino-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

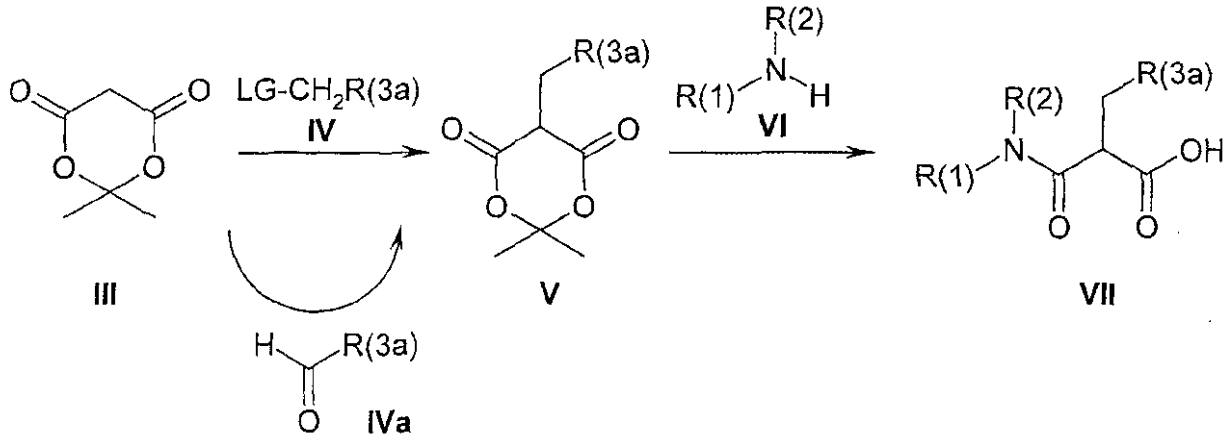
2-(4-Carbamimidoyl-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisobutyl-malonamide trifluoroacetic acid salt, more polar diasteromer,

The compounds of formula I can be prepared by utilizing procedures and techniques well known and appreciated by one of ordinary skill in the art. Starting materials or building blocks for use in the general synthetic procedures that can be applied in the preparation of the compounds of formula I are readily available to one of ordinary skill in the art. In many cases they are commercially available or have been described in the literature. Otherwise they can be prepared from readily available precursor compounds analogously to procedures described in this application.

The reactions described below that are carried out in the syntheses of the compounds of the formula I can generally be carried out according to the methods of conventional solution phase chemistry as well as according to the methods of solid phase chemistry which are well known, for example, from peptide synthesis.

Compounds of the formula I can be prepared, for example, by method A described in the schemes 2 and 3, where the residues R(1), R(2), R(3), R(4), R(5), R(6) are defined as indicated above.

Scheme 2



Meldrum acid III can be alkylated by using base for example potassium carbonate, sodium hydrate, or triethylamine and IV, wherein

LG is a leaving group like a halogen or a substituted hydroxy group like tosyloxy or mesyloxy;

R(3a) is (C_6-C_{10})-aryl which is substituted by R(23);

R(23) is $N(R(24))_2$, nitro, or cyano;

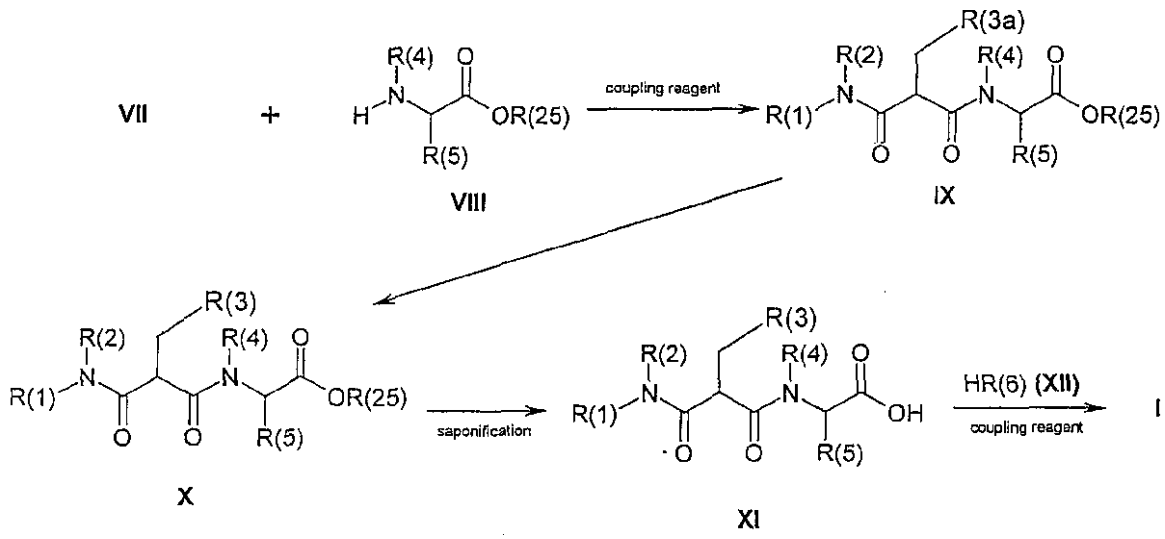
R(24) is (C_1-C_6)-alkyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, (C_1-C_6)-alkylcarbonyl, or (C_1-C_6)-alkoxycarbonyl;

to give V, or by condensation of meldrum acid III with the aldehyde IVa in presence of a reducing agent for example sodiumcyanoborohydride,

while ring opening of V can be achieved by reaction of an amine VI, preferably in the presence of a silylating agent, for example N,O-bis-(trimethylsilyl)-acetamide in an organic solvent, for example in dichloromethane under reflux to give the malonic acid amide VII.

Compounds of the formulae III, IV, IVa, and VI are commercially available or can be prepared by standard procedures, which are known to one skilled in the art.

Scheme 3



Coupling of VII with VIII, where R(25) is an easily cleavable ester (such as for example (C_1-C_4)-alkyl, benzyl, or 4-methoxybenzyl), to yield IX can be carried out by common coupling reagents used in peptide synthesis. Such coupling reagents are, for example, carbodiimides like dicyclohexylcarbodiimide (DCCI) or diisopropylcarbodiimide (DICI), carbonyldiazoles like carbonyldiimidazole and similar reagents, propylphosphonic anhydride, O-((cyano-(ethoxycarbonyl)-methylen)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU), N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU), and many others. Compounds of the formula VIII are commercially available or can be prepared by standard procedures, which are known to one skilled in the art.

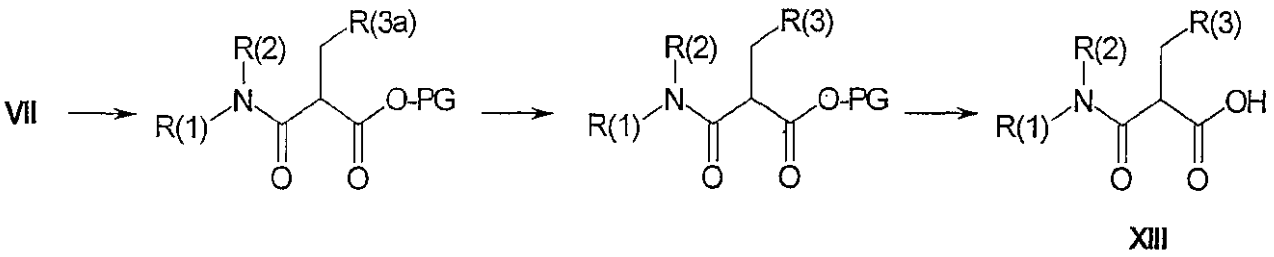
Conversion of R(3a) to R(3) (IX → X), if necessary, can be made by introduction of an amidino group as described below, or by reduction of a nitro group by hydrogenation with for example Raney-Nickel, palladium/charcoal or other catalysts in the presence of hydrogen.

Amidines can be prepared from the corresponding cyano compounds by addition of alcohols, for example methanol or ethanol, in acidic anhydrous medium, for example dioxane, methanol or ethanol, and subsequent aminolysis, for example treatment with ammonia in alcohols such as, for example, isopropanol, methanol or ethanol (G. Wagner, P. Richter and Ch. Garbe, Pharmazie 29 (1974), 12-55). Further methods of preparing amidines are the addition of hydrogen sulfide to the cyano group, followed by alkylation, for example methylation, of the resulting thioamide and subsequent reaction with ammonia (GDR Patent No. 235 866), and the addition of hydroxylamine which may be obtained from a hydroxylammonium salt with a base, to the cyano group followed by conversion of the amidoxime to the amidine, for example by catalytic hydrogenation.

Saponification of the ester of compounds of the formula X to give compounds of the formula XI can be carried out by standard methods. Coupling of XI with XII to give compounds of the formula I can be carried out with coupling reagents as described above. Compounds of the formula XII are commercially available or can be prepared by standard procedures which are known to one skilled in the art.

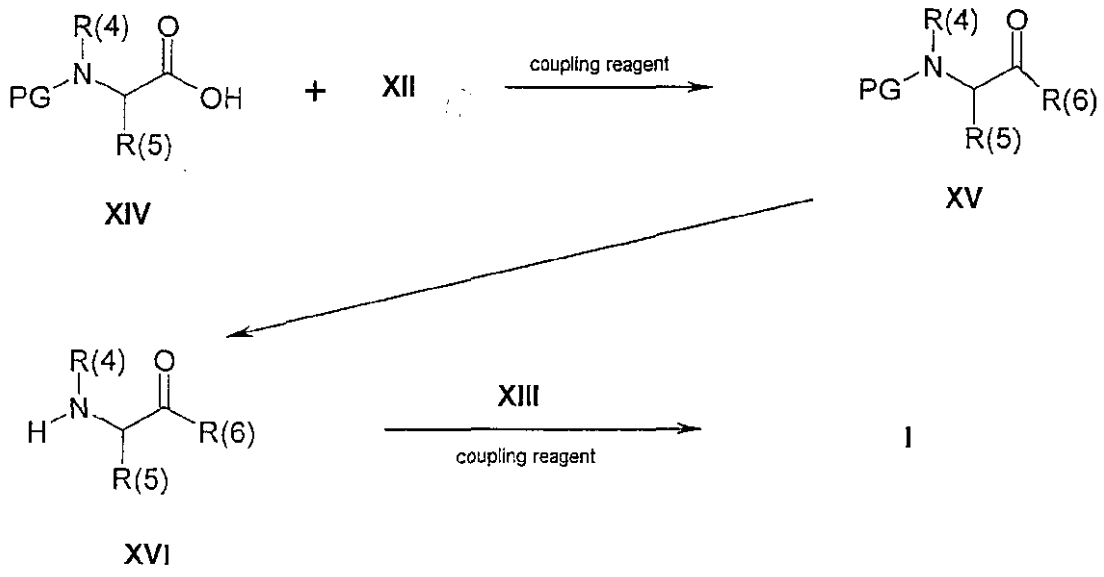
Compounds of the formula I can also be obtained by method B as drawn in schemes 4 and 5.

Scheme 4



After protection of the carboxylfunction with an easily cleavable protection group PG (such as for example (C_1-C_4)-alkyl, benzyl, or 4-methoxybenzyl) by standard methods, the residue R(3a) in compounds of the formula VII can be transformed to the residue R(3) and deprotected as outlined above to give compounds of the formula XIII.

Scheme 5



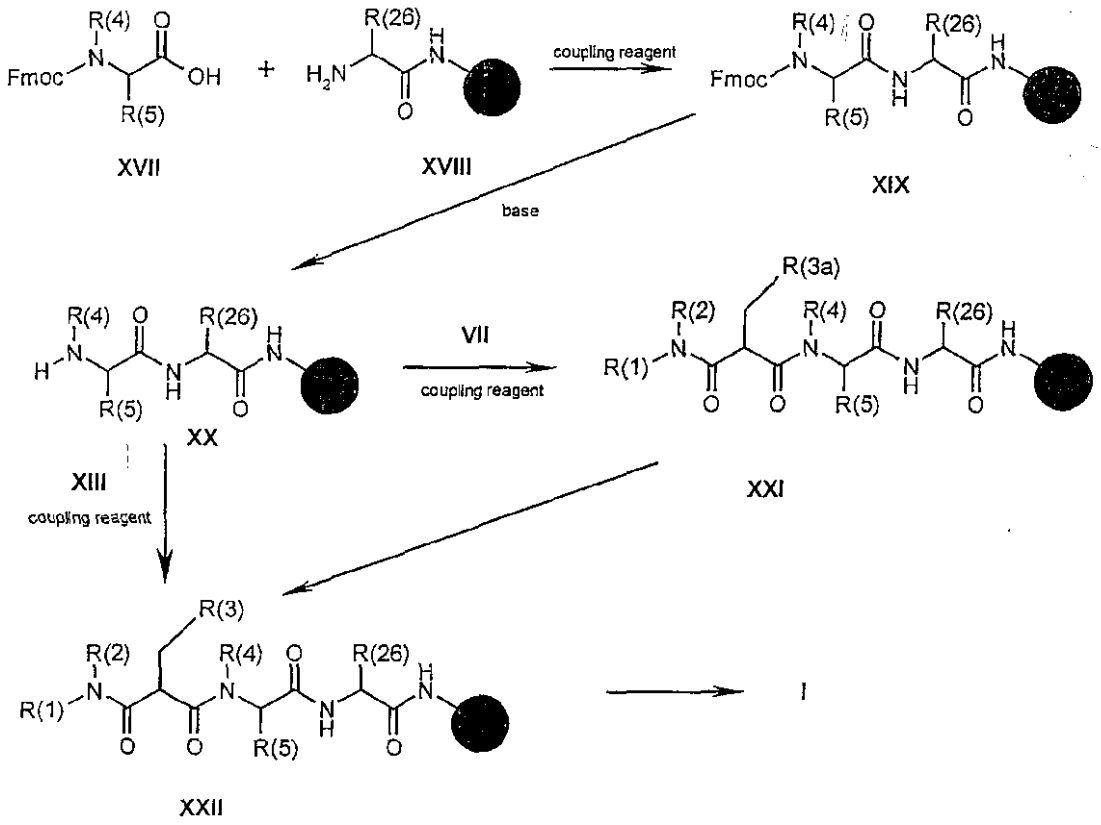
The protected amino acid XIV, wherein PG is a suitable amino protection group, for example Fmoc, benzyloxycarbonyl (Z), or Boc, preferably Fmoc, can be coupled by standard methods as described above with compounds of the formula XII to give compounds of the formula XV. Compounds of the formula XIV can be prepared by standard procedures, which are known to one skilled in the art.

Compounds of the formula XV can be deprotected by standard methods, for example by standard methods for Fmoc-deprotection (L.A. Carpino et al., J. Org. Chem. 1988, 53, 6139-44) to give compounds of the formula XVI. Compounds of the formula XVI can be coupled with compounds of the formula XIII by standard methods to give compounds of the formula I.

Compounds of the formula I can also be obtained by solid phase peptide synthesis (method C) as drawn in scheme 6. Such methods are described, for example, by Steward and Young (Solid Phase Peptide Synthesis (Freeman and Co., San Francisco, 1969), which is incorporated herein by reference.

Where solid phase synthesis methods are employed, the chemical composition of a compound can be manipulated while the nascent peptide is attached to the resin or after the peptide has been cleaved from the resin to obtain, for example, an N-terminal derivative. Similar modifications can also be made to a carboxy group of a compound, including a C-terminus carboxy group, which, for example, can be amidated. One skilled in the art can also synthesize a compound of the invention using solution phase organic chemistry.

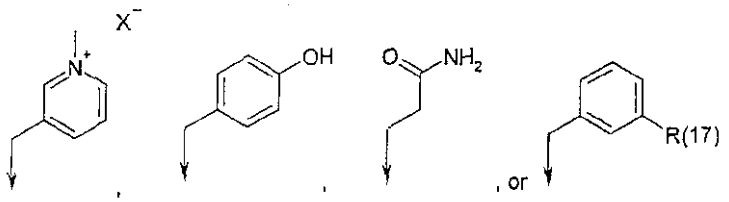
Scheme 6



bound to an acid cleavable resin

Using this method (C) (scheme 6) compounds of the formula XVIII, where an amino acid is coupled to a suitable carrier, which are for instance Wang , Trityl or Rink resin or other acid cleavable resins which are known to a person skilled in the art, and wherein

R(26) is hydrogen, $-CH_2-R(17)$, 1-naphthylmethyl, $-(CH_2)_3-NR(28)-C(=N-R(27))-NH-R(28)$



R(27) is R(28), cyano, hydroxy, (C_1-C_6)-alkoxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy which is unsubstituted or substituted in the aryl moiety, or amino;

R(28) is hydrogen, (C_1-C_6)-alkyl, or (C_1-C_6)-alkylcarbonyl;

can be coupled with an for example Fmoc-protected amino acid XVII using standard techniques. The use of other protected, for instance Boc-protected amino acid XVII is also possible, however, the use of Fmoc-protected amino acid XVII is preferred.

Compounds of the formula XVIII can be prepared by standard procedures, which are known to one skilled in the art.

The resulting dipeptide XIX can be deprotected using base, for example a solution of 20-50 % of piperidin in dimethylformamide to obtain compounds of the formula XX with a primary or secondary amino group, which can be coupled to the building blocks VII or XIII prepared using methods A and B to yield compounds of the formula XXI or XXII. Conversion of the residue R(3a) of the resulting compound XXI to the residue R(3) can be done as described above to yield compounds of the formula XXII. Compounds of the formula I can be obtained by cleaving compounds of the formula XXII under acidic conditions for example trifluoroacetic acid/water in different concentrations depending on the used resin varying from 1 % to 95 % of trifluoroacetic acid.

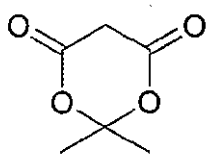
These synthesized compounds can be purified using well known methods such as reverse phase-high pressure liquid chromatography (RP-HPLC) or other methods of separation based, for example, on the size, charge or hydrophobicity of the compound. Similarly, well known methods such as amino acid sequence analysis or

mass spectrometry (MS or HPLC/ESMS) can be used for characterizing the structure of a compound of the invention (see Example 1).

Thus , the present invention also relates to a process for the preparation of a compound of formula I, which comprises

i)

a1) alkylating a compound of the formula III



III

with a compound of the formula IV,

$$LG\text{-}CH_2\text{-}R(3a) \quad (IV)$$

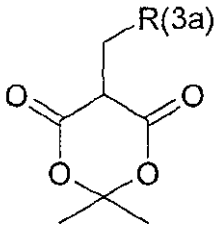
wherein LG is a leaving group like a halogen or a substituted hydroxy group like tosyloxy or mesyloxy and wherein

R(3a) is (C_6-C_{10})-aryl which is substituted by R(23);

R(23) is $N(R(24))_2$, nitro, or cyano;

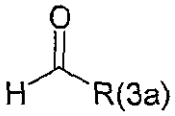
R(24) is (C_1-C_6)-alkyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, (C_1-C_6)-alkylcarbonyl, or (C_1-C_6)-alkoxycarbonyl;

in the presence of a base to give a compound of the formula V,



V

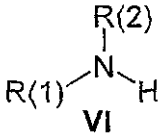
or reacting a compound of the formula III with a compound of the formula IVa,



IVa

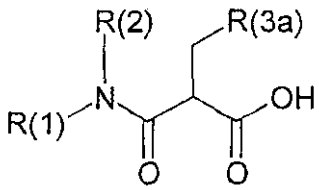
in the presence of a reducing agent to give a compound of the formula V;

b1) reacting a compound of the formula V with a compound of the formula VI,



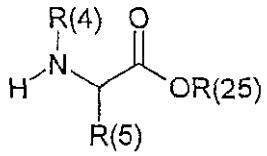
VI

wherein R(1) and R(2) are as defined above, to give a compound of the formula VII;



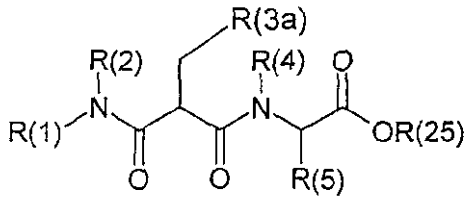
VII

c1) coupling of a compound of the formula VII with a compound of the formula VIII,



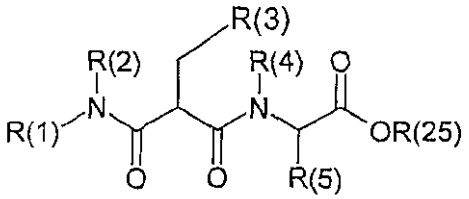
VIII

wherein R(4) and R(5) are as defined above and R(25) is an easily cleavable ester to yield a compound of the formula IX,



IX

d1) optionally introducing an amidino group or reduction of a nitro group, by converting a compound of the formula IX into a compound of the formula X,



X

wherein R(3) is as defined above;

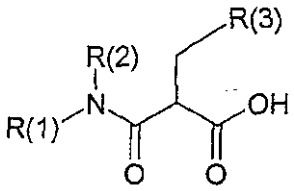
e1) saponification of the ester group R(25) and coupling the resulting compound XI according to step c1) with a compound of the formula XII

HR(6) **(XII)**

wherein R(6) is as defined above to give a compound of the formula I; or

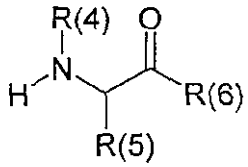
c2) protecting the carboxylfunction in a compound of the formula VII with an easily cleavable protecting group and introducing an amidino group or reduction of a nitro group according to step d1) to give after deprotection of the carboxylfunction a compound of the formula XIII; and

d2) coupling a compound of the formula XIII according to step c1)



XIII

with a compound of formula XVI;

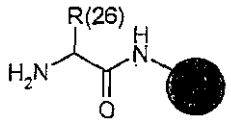


XVI

to give a compound of the formula I; or

ii)

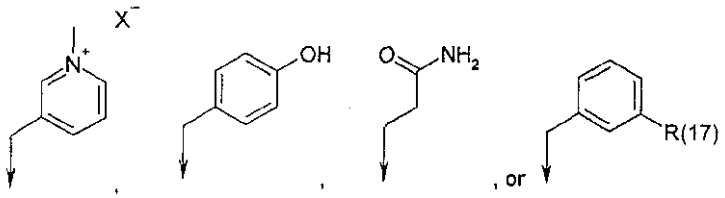
a) coupling a compound of the formula XVIII,



XVIII

which is bound to a suitable carrier, for example an acid cleavable resin, and wherein

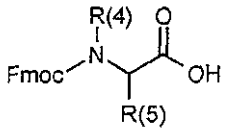
R(26) is hydrogen, -CH_2-R(17), 1-naphthylmethyl, -$(CH_2)_3$-NR(28)-C(=N-R(27))-NH-R(28)



R(27) is R(28), cyano, hydroxy, (C_1-C_6)-alkoxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy which is unsubstituted or substituted in the aryl moiety, or amino;

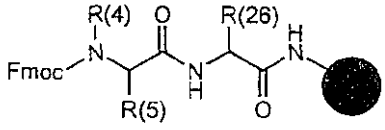
R(28) is hydrogen, (C_1-C_6)-alkyl, or (C_1-C_6)-alkylcarbonyl;
and R(17) is as defined above;

with a compound of the formula XVII



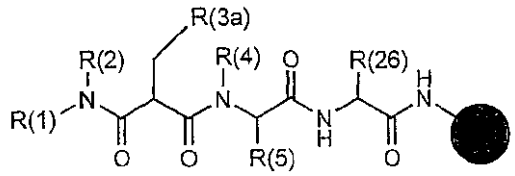
XVII

wherein R(4) and R(5) are as defined above to give a compound of the formula XIX

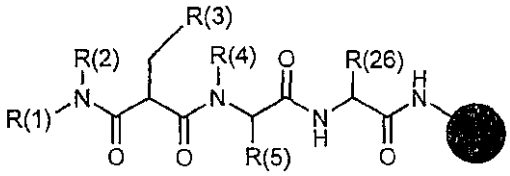


XIX

b) and after deprotecting a compound of the formula XIX with a base coupling the deprotected compound XX to a compound of the formula VII or XIII to give a compound of the formula XXI or XXII;



XXI



XXII

c) optionally converting a compound of the formula XXI to a compound of formula XXII (i.e. transforming the residue R(3a) to a residue R(3) by introducing an amidino group or reduction of a nitro group)

and d) cleaving a compound of the formula XXII off the resin to give a compound of the formula I.

As is demonstrated in the pharmacological tests described below, the compounds of formula I inhibit factor Xa activity. They can therefore advantageously be used as pharmaceuticals, especially when it is desired to reduce factor Xa activity or to produce effects that can be achieved by inhibiting factor Xa activity in a system, such as influencing coagulation or inhibiting blood clotting. Thus, the present invention also relates to the compounds of formula I for use as pharmaceuticals as well as for the production of medicaments, especially of medicaments for treatment or prophylaxis of the conditions and diseases mentioned below and above. Further, the present invention provides a method of specifically inhibiting factor Xa activity by contacting factor Xa with a compound of formula I. More specifically, an effective amount of a compound of the invention inhibits factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex. A preferred embodiment of

the invention comprises such compounds of the formula I which can inhibit factor Xa activity with a $K_i \leq 10$ µM and, preferably, with a $K_i \leq 100$ nM.

As used herein, the term "factor Xa activity" refers to the ability of factor Xa, by itself or in the assembly of subunits known as the prothrombinase complex, to catalyze the conversion of prothrombin to thrombin. When used in reference to factor Xa activity, the term "inhibition" includes both the direct and indirect inhibition of factor Xa activity. Direct inhibition of factor Xa activity can be accomplished, for example, by the binding of a compound of formula I to factor Xa or to prothrombinase so as to prevent the binding of prothrombin to the prothrombinase complex active site. Indirect inhibition of factor Xa activity can be accomplished, for example, by the binding of a compound of the invention to soluble factor Xa so as to prevent its assembly into the prothrombinase complex. As used herein, the term "specific" when used in reference to the inhibition of factor Xa activity means that a compound of formula I can inhibit factor Xa activity without substantially inhibiting the activity of serine proteases such as, for instance, thrombin, trypsin or kallekrein (using the same concentration of the inhibitor). Such proteases are involved in the blood coagulation and fibrinolysis cascade.

Inhibition of factor Xa activity or the production of effects achieved by such an inhibition can take place in vivo, i. e. in an individual. As used herein, the term "individual" means a vertebrate, including a mammal such as, for example a mouse, a rat, a rabbit, a dog, a pig, a monkey, and especially a human, in which factor Xa is involved in the clotting cascade. It can also take place outside the body of an individual, for example, in an extracorporeal circulation or in the treatment of blood samples from an individual, and generally in vitro. In vitro uses of the compounds of formula I are, for example, the use as a biochemical tool in scientific or analytical investigations or the use for in vitro diagnoses. A compound of formula I can advantageously be used as an anticoagulant, which can be contacted with a blood sample to prevent coagulation. For example, an effective amount of a compound of formula I can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample.

As used herein, the term "effective amount" when used in this connection means an amount of a compound of formula I that inhibits factor Xa activity to the desired extent. The skilled artisan would recognize that an effective amount of a compound of the invention can be determined using the methods disclosed herein or otherwise known in the art.

In view of the disclosed utility of the compounds of formula I, the skilled artisan also would recognize that an agent such as heparin can be replaced with a compound of the invention. Such a use of a compound of formula I can result, for example, in a cost saving as compared to other anticoagulants.

In a further embodiment, the present invention provides a method of inhibiting factor Xa in a patient in need thereof, comprising administering to said patient an effective factor Xa inhibitory amount of a compound of formula I. As used herein, the term "patient" refers especially to a warm-blooded animal including a mammal and particularly a human. A patient is in need of treatment to inhibit factor Xa when the patient is suffering from a disease state that can be beneficially influenced by inhibiting factor Xa activity or that is expected by the clinician to be beneficially influenced by inhibiting factor Xa acitivity.

The identification of those patients who are in need of treatment to inhibit factor Xa is well within the ability and knowledge of one skilled in the art. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those patients who are in need of such a treatment.

Since a compound of formula I can inhibit factor Xa activity, such a compound can be used for reducing or inhibiting blood clotting in an individual. Thus, the present invention further provides a method of reducing or inhibiting the formation of blood clots in an individual, especially in a patient in need thereof, by administering a therapeutically effective amount of a compound of formula I.

A therapeutically effective amount relating to the production in an individual of an effect like inhibition or reduction of blood clotting, or an effective factor Xa inhibitory amount of a compound of formula I means the amount or the dose of a compound of formula I that has to be administered to an individual in order to achieve or to maintain the desired effect or to inhibit factor Xa activity in the individual to the desired extent. Such an effective amount or dose to be administered has to be adjusted to the individual circumstances in each case. It can be readily determined by the use of conventional techniques using the methods described herein or otherwise known in the art, and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree or the involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the pharmaceutical preparation administered; the dose regimen selected; and the use of concomitant medication. An appropriate dosage can be established using clinical approaches well known in the medical art.

In general, in view of the above factors it is evident that the effective factor Xa inhibitory amount or the therapeutically effective amount of a compound of formula I will vary and can be varied within wide limits. Usually, an effective amount will vary from about 0.01 milligram per kilogram of body weight per day (mg/kg per day) to about 20 mg/kg per day. A daily dose of from about 0.1 mg/kg to about 10 mg/kg is preferred. These data refer to a human of about 75 kg of body weight. In particular when administering relatively large quantities, it can be favorable to subdivide the daily dose into several, for example 2, 3 or 4 subdose administrations.

A compound of formula I can be administered to an individual for the treatment of a variety of clinical conditions, including, for example, the treatment and prophylaxis of cardiovascular disorders or complications associated, for example, with infection or surgery. Examples of cardiovascular disorders include restenosis, for example restenosis following angioplasty, reocclusion prophylaxis, conditions after coronary

bypass operations, arterial, venous and microcirculatory disease states, cardiac infarction, angina pectoris, thromboembolic diseases, thromboses, embolism, adult respiratory distress syndrome, multi-organ failure, stroke or disseminated intravascular coagulation clotting disorder. Examples of related complications associated with surgery include, for example, deep vein and proximal vein thrombosis, which can occur following surgery. Thus, a compound of the invention is useful as a medicament for reducing or inhibiting unwanted coagulation or blood clotting in an individual.

The compounds of formula I, their physiologically acceptable salts and other suitable derivatives thereof can be employed as medicaments or pharmaceuticals in the above-mentioned methods on their own, in mixtures with each other or in the form of pharmaceutical compositions which comprise, as the active ingredient, an effective amount of at least one compound of formula I and/or of a physiologically acceptable salt and/or another suitable derivative thereof in admixture or otherwise in association with one or more pharmaceutically acceptable carrier substances and auxiliary substances.

In effecting treatment of a patient, compounds of formula I on their own or pharmaceutical compositions comprising them can be administered in any form or mode which makes the compounds of formula I bioavailable in effective amounts, including oral and parenteral routes. For example, they can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures; rectally, for example in the form of suppositories; parenterally, for example intravenously, intramuscularly, transdermally, intranasally, or subcutaneously; in the form of injection solutions or infusion solutions, microcapsules, implants or rods; percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays. Oral administration is generally preferred but depending on the specific case other modes of administration can also be favourable, for example in an acute stage of a disease intravenous administration by means of injection or infusion. One skilled in the art of preparing formulations can readily select the proper form and mode of administration

depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

Pharmaceutical compositions or medicaments comprising a compound of formula I and/or a physiologically acceptable salt and/or another suitable derivative thereof can be made by combining the compounds of formula I and/or their physiologically acceptable salts and/or other suitable derivatives thereof with pharmaceutically acceptable carrier substances and auxiliary substances, the proportion and nature of which are determined by the chosen route of administration and standard pharmaceutical practice. The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The pharmaceutical compositions will, in general, contain an effective amount of a compound of formula I and/or a physiologically acceptable salt and/or another suitable derivative thereof together with a suitable amount of a carrier so as to comprise the proper dosage for administration to an individual. The pharmaceutical compositions may be adapted for oral or parenteral use and may be administered to the patient in the form, for example, of tablets, capsules, suppositories, solutions, suspensions, ointments, tinctures, nasal sprays, aerosol mixtures, implants, rods, microcapsules or the like. Thus, together with the claimed compounds the present invention provides useful pharmaceutical compositions or medicaments for inhibiting factor Xa activity and blood clotting in an individual.

The present invention further encompasses a process for the preparation of pharmaceutical compositions or medicaments which comprise at least one compound of formula I and/or a physiologically acceptable salt and/or another suitable derivative thereof, as well as it encompasses the use of the compounds of formula I and/or physiologically acceptable salts and/or other suitable derivatives thereof for the preparation of medicaments, especially of medicaments for the treatment or prophylaxis of the above-mentioned diseases.

Pharmaceutically acceptable carrier and auxiliary substances are referred to as substances or compositions that are non-toxic to an individual or have acceptable

toxicity as determined by the appropriate regulatory agency. The carrier substance or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. As used herein, the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers such as liquid carriers, for example phosphate buffered saline, water, an emulsion such as an oil/water or water/oil emulsion, or solid or semi-solid carriers such as, for example, lactose, corn starch, fats, waxes, etc. Suitable pharmaceutical carriers and their formulations are well known in the art and are, for example, described by Martin in Remington's Pharmaceutical Sciences, 15th Ed. (Mack Publishing Co., Easton 1975) which is incorporated herein by reference also with respect to other aspects of the ingredients and the preparation of pharmaceutical compositions.

Examples of auxiliary substances are fillers, disintegrants, binders, glidants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, dyes, flavorants, aromatizing agents, thickeners, diluents, buffering substances, solubilizing agents, agents for achieving a slow-release effect, salts for altering the osmotic pressure, coating agents, antioxidants, etc.

For the purpose of oral administration, the compounds of formula I may be incorporated with excipients or inert diluents or edible carriers and used in the form of, for example, tablets, film tablets, coated tablets, pills, troches, capsules, granules, solutions, suspensions, emulsions, elixirs, syrups, wafers, chewing gums and the like, or they may be enclosed in gelatin capsule. The pharmaceutical compositions for oral administration may be varied depending upon the particular form. Usually they contain at least 1 % of the active ingredient of formula I and may conveniently contain up to about 90 % of the weight of the unit. Preferably the content of the compounds of formula I and/or their physiologically acceptable salts and/or other suitable derivatives is from about 4 % to about 70 % by weight. The amount of the active ingredient present in the compositions is such that a unit dosage form suitable for administration will be obtained.

The tablets, pills, capsules, troches and the like may also contain, for example, one or more of the following carrier and auxiliary substances: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin may be added or flavoring agents, such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, for example sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

For the purpose of parenteral administration, the compounds of formula I and/or physiologically acceptable salts thereof and/or other suitable derivatives thereof may be incorporated into a solution or a suspension. The solutions or suspensions may, for example, also include one or more of the following carrier and auxiliary substances: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminotetraacetic acid; buffers such as acetates, citrates or phosphates; agents for the adjustment of toxicity such as sodium chloride or dextrose. The content of the compounds of formula I in the preparations for parenteral adminstration may be varied. Usually they contain at least 0.1 % by weight of the compound of formula I. Preferably the content of the compound of formula I and/or the physiologically acceptable salts thereof and/or other suitable derivatives thereof is from about 0.1 % to 50 %. The parenteral preparations can be enclosed in ampules, disposable syringes, multiple dose vials made of glass or plastic, or infusion bottles. Suitable excipients for microcapsules, implants and rods are, for example, mixed polymers of glycolic acid and lactic acid.

Materials used in preparing the various pharmaceutical compositions should be pharmaceutically pure and non-toxic in the amounts used.

Besides one or more compounds of formula I and/or one or more physiologically acceptable salts thereof and/or one or more other suitable derivatives thereof as active compounds the pharmaceutical compositions according to present invention may also contain one or more other pharmacologically active compounds.

In another, more general embodiment the present invention provides compositions comprising at least one compound of formula I and/or salt thereof and/or another suitable derivative thereof in admixture or otherwise in association with one or more inert carriers. These compositions are useful, for example, as assay standards, as convenient means of making bulk shipments, or as pharmaceutical compositions. An assayable amount of a compound of formula I is an amount which is readily measurable by standard assay procedures and techniques as are well known and appreciated by those skilled in the art. Assayable amount of a compound of formula I will generally vary from about 0.001 % to about 90 % of the composition by weight. Inert carriers can be any material which does not degrade or otherwise covalently react with a compound of formula I. Examples of suitable inert carriers are water; aqueous buffers, such as, for example, those which are generally useful in High Pressure Liquid Chromatography (HPLC) analysis; organic solvents, such as acetonitrile, ethyl acetate, hexane and the like; and pharmaceutically acceptable carrier and auxiliary substances.

The compounds of formula I can also be used as starting materials or chemical intermediates in the preparation of other compounds, especially in the preparation of other pharmacologically active compounds. Examples for such conversions of compounds of the invention into other compounds of the invention are given below. For this use, besides the compounds of formula I and their physiologically acceptable salts also other salts of the compounds of the formula I can be useful which are not suitable or less suitable for use as pharmaceuticals. Thus, the present invention also

relates to compounds of the formula I and their salts in general as chemical intermediates, especially as intermediates in the preparation of pharmacologically active compounds.

The following tests can serve to investigate the pharmacological activity and to illustrate the utility of the compounds of the present invention as factor Xa inhibitors.

Test 1: In Vitro Inhibition of Selected Purified Coagulation Enzymes and Other Serine Proteases

The ability of a compound of formula I to inhibit factor Xa, thrombin, plasmin, elastase and trypsin may be assessed by determining the concentration of compound of formula I that inhibits enzyme activity by 50 % (IC_{50}). Purified enzymes are used in chromogenic assays. To determine the inhibition constant, the IC_{50} value is corrected for competition with substrate using the formula:

$$K_i = IC_{50} \times (1/\{1 + ((\text{substrate concentration})/\text{substrate Km})\})$$

where Km is the Michaelis-Menten-constant (Y.-C. Chen and W.H. Prusoff, Biochem. Pharmacol. 22: 3099-3018 (1973), which is incorporated herein by reference).

a.Factor Xa Assay

TBS-PEG buffer (50 mM Tris-Cl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN_3) is used for this assay. The IC_{50} is determined by combining in appropriate wells of a Costar half-area microtiter plate 25 µl human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, IN) in TBS-PEG; 40 µl 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin OH) in TBS-PEG.

The assays are performed by pre-incubating the compound of formula I plus enzyme for 10 min, then the assay is initiated by adding substrate to obtain a final volume of 100 µl. The initial velocity of chromogenic substrate hydrolysis is measured by the change in absorbance at 405 nm using a Bio-tek Instruments kinetic plate reader (Ceres UV900HDi) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis is predicted by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the compound of formula I concentration. The enzyme concentration is 0.5 nM and substrate concentration is 140 µM.

b. Thrombin Assay

TBS-PEG buffer is used for this assay. The IC_{50} is determined as above for the Factor Xa assay, except that the substrate is S-2366 (L-PyroGlu-L-Pro-L-Arg-p-nitroanilide; Kabi) and the enzyme is human thrombin (Enzyme Research Laboratories, Inc.; South Bend IN). The enzyme concentration is 175 µM.

c. Plasmin Assay

TBS-PEG buffer is used for this assay. The IC_{50} is determined as described above for the factor Xa assay, except that the substrate is S-2251 ((D)-Val-L-Leu-L-Lys-p-nitroanilide; Kabi) and the enzyme is human plasmin (Kabi). The enzyme concentration is 5 nM and the substrate concentration is 300 µM.

d. Trypsin Assay

TBS-PEG buffer containing 10 mM $CaCl_2$ is used for this assay. The IC_{50} is determined as described above in the factor Xa assay, except that the substrate is BAPNA (Benzoyl-L-Arg-p-nitroanilide; Sigma Chemical Co.; St. Louis MO) and the enzyme is bovine pancreatic trypsin (Type XIII, TPCK treated; Sigma). The enzyme concentration is 50 nM and the substrate concentration is 300 µM.

e. Elastase Assay

Tris-Cl, pH 7.4, 300 mM NaCl, 2 % (v/v) N-methyl-pyrrolidone, 0.01 % (w/v) NaN_3 buffer is used for this assay. The IC_{50} is determined as described above in the factor Xa assay, except that the substrate is succinyl-Ala-Ala-Ala-p-nitroanilide (Calbiochem-Nova Biochem Corp.; San Diego CA) and the enzyme is human neutrophil elastase (Athens Research and Technology, Inc.; Athens GA). The enzyme concentration is 75 nM and the substrate concentration is 600 µM. The control compound is "TENSTOP" (N-alpha-tosyl-Gly-p-amidinophenylalanine methyl ester; American Diagnostica, Inc.; Greenwish CT), which is a reversible factor Xa inhibitor (Stuerzebecher et al., Thromb. Res. 54: 245-252 (1989); Hauptmann et al., Thromb. Haem. 63: 220-223 (1990), each of which is incorporated herein by reference).

Test 2: Assays for Determining Inhibition of Coagulation

The effectiveness of compounds of formula I may be assessed by the in vitro prothrombin time (PT) assay using pooled human donor plasma. An ex vivo assay may also be used in which plasma is collected at various times after intravenous (iv) administration of a compound of formula I to rats or to rabbits or intraduodenal (id) administration to rats and analysis using the PT assay to determine plasma half-life. The PT assay is initiated with a thromboplastin dilution selected to obtain an extended and highly reproducible coagulation endpoint, referred to as the "dilute PT assay" as described below. The effectiveness of various compounds may also be determined using an in vivo rat arteriovenous shunt model of thrombosis.

a. In Vitro Dilute Prothrombin Time Assay

100 µl prewarmed (37 °C) pooled human platelet poor plasma (PPP) is added to a fibrometer cup (Baxter Diagnostics., Inc.; McGaw Park IL). 50 µl of various concentrations of a compound of formula I in TBS-BSA with calcium (50 mM Tris-Cl, 100 mM NaCl, 0.1 % (w/v) bovine serum albumin, 20 mM $CaCl_2$) is added. In control

experiments, TBS-BSA with calcium but without test compound of formula I is added for measurement of uninhibited coagulation time. 150 µl diluted prewarmed rabbit thromboplastin (Baxter) with calcium is added to the fibrometer cup and the fibrometer timer is started. A rabbit thromboplastin dilution curve is obtained prior to treating the compound and is used to choose a thromboplastin dilution that allows approximately 30 sec PT time for uninhibited controls. The experimental concentration giving 50 % inhibition of coagulation (EC_{50}) with test compound is calculated from the dilution curve times.

Alternatively, the dilute prothrombin time assay is conducted using the "research" mode on an Instrumentation Laboratories (IL) ACL3000-plus automated coagulation instrument (IL; Milan, Italy). Thromboplastin is diluted until a clotting time of 30-35 sec. is achieved. This clotting time is taken as 100 % activity. A standard curve for calibration is established by serial 2-fold dilution of the diluted thromboplastin reagent (rabbit brain IL-brand thromboplastin). During the assay, a 50 µl sample (plasma separated by centrifugation) is mixed with 100 µl thromboplastin reagent and nephelometric readings are taken over 169 sec. Coagulation time is determined from the maximal rate of change of light scatter calculated by the instrument. Inhibition is expressed as percent activity as determined by comparison with the calibration curve.

b. Ex Vivo Dilute Prothrombin Time Assay

A test compound of formula I is administered iv either through the tail vein (rat) or ear vein (rabbit) following an approved protocol. 0.5 ml blood samples are removed at timed intervals after administration of a test compound of formula I from a cannulated carotid artery (rat) or auricular artery (rabbit). After centrifugation to obtain PPP, the plasma is immediately stored on ice or frozen.

For dilute prothrombin time determination, the plasma is prewarmed and assayed as described above. Percent inhibition is calculated from a thromboplastin dilution curve, which is run with each series of samples, and used to determine the time at which approximately 50 % of the initial anticoagulant activity remains in the plasma ($T_{1/2}$).

The test compounds of formula I can also be administered to rats using an intraduodenal dosing protocol. Male Sprague-Dawley rats weighing approximately 300 g are anesthetized with a combination of ketamine/xylazine, subcutaneously, following an approved protocol. The right carotid artery is cannulated for blood sampling. A laparotomy is performed and duodenum is cannulated with a ball-tip needle and tied into place to ensure that the suture is distal to the point of insertion. An additional tie is placed proximal to the insertion point to prevent leakage of gastric contents. The effectiveness of the suture in preventing a compound from reaching the site of insertion is tested by pressure testing at the conclusion of each experiment. The point of insertion is approximately 4 cm from the duodenal-gastric junction. Compounds are administered in 1 ml normal saline. A 0.7 ml blood sample is drawn prior to administration of the test compound of formula I and at 15, 30, 60, 90 and 120 min after administration. Plasma is separated by centrifugation and assayed for inhibition of coagulation using the dilute prothrombin time assay.

c. Rat Arteriovenous Shunt Model of Thrombosis

The anti-thrombotic efficacy of various compounds of the invention may be assessed using rat extracorporeal arteriovenous (AV) shunt. The AV shunt circuit consisted of a 20 cm length of polyethylene (PE) 60 tubing inserted into the right carotid artery, a 6 cm length of PE 160 tubing containing a 6.5 cm length of mercerized cotton thread (5 cm exposed to blood flow), and a second length of PE 60 tubing (20 cm) completing the circuit into the left jugular vein. The entire circuit is filled with normal saline prior to insertion.

Test compounds of formula I are administered by continuous infusion into the tail vein using a syringe pump and butterfly catheter (infusion volume 1.02 ml/h). A compound is administered for 30 min, then the shunt is opened and blood allowed to flow for a period of 15 min (total of 45 min infusion). At the end of the 15 min period, the shunt is clamped and the thread is carefully removed and weighed on an analytical balance.

Percent inhibition of thrombus formation is calculated using the thrombus weight obtained from control rats, which are infused with saline.

The following Table 1 shows the factor Xa inhibitory activities (K_i-values) of selected compounds of the formula I (testing the compounds for inhibitory activity was accomplished using the in vitro Factor Xa assay described above (Test 1a).

Table 1 Factor Xa inhibitory activity (K_i-values):

Example	Ki (FXa) [µM]
3	0.1558
5	0.0006
6	0.0010
8	0.0351
10	0.6040
14	0.0218
17	2.29
21	8.37
28	0.047
30	0.153
38	1.1
40	0.0107
45	26.5
54	3.01
56	0.0021
58	0.0575
61	0.957
69	0.285
72	4.3

82	0.0393
89	6.48
92	5.93
94	1.7
97	0.04
104	6.5
129	0.36
136	0.01
144	0.011
154	0.001

Examples

The following examples present typical syntheses of the compounds of formula I. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. The compounds of the examples were characterized by mass spectra (MS) and/or NMR spectra and/or melting point.

When in the final step of the synthesis of a compound an acid such as trifluoroacetic acid or acetic acid was used, for example when trifluoroacetic acid was employed to remove a tert-butyl group or when a compound was purified by chromatography using an eluent which contained such an acid, in some cases, depending on the work-up procedure, for example the details of a freeze-drying process, the compound was obtained partially or completely in the form of a salt of the acid used, for example in the form of the acetic acid salt or trifluoroacetic acid salt or hydrochloric acid salt.

Example 1

General Method for Synthesis of Malonic Acids Derivatives on solid phase

General solid-phase peptide synthesis was used to produce most of the compounds of this invention. Such methods were described, for example, by Steward and Young (Solid

Phase Peptide Synthesis (Freeman and Co., San Francisco, 1969), which is incorporated herein by reference.

Unless indicated otherwise, compounds were synthesized on polystyrene resin cross-linked with 1 % divinylbenzene. An acid sensitive linker (Rink Linker) was coupled to the solid support (Rink, Tetr. Lett. 28:3787 (1987); Sieber, Tetr. Lett. 28:2107 (1987), each of which is incorporated herein by reference). All compounds were synthesized on a semi-automated peptide synthesizer built in house. Boc-and Fmoc-protected L- and D-amino acid derivatives were from various commercial sources like Advanced ChemTech (Louisville, KY 40228-9973, USA); Bachem (King of Prussia, PA 19406, USA) and PerSeptive Biosystems (Framingham, MA 01701, USA).

Synthesis of compounds of the formula I was carried out according to the classical Fmoc methodology (E. Atherton and R.C. Sheppard in „ Solid Phase Peptide Synthesis: A Practical Approach", IRL Press, Oxford, England, 1989) using diisopropyl-carbodiimide and benzotriazol-1-ol as activating reagents. All couplings were done in dimethylformamide or dimethylformamide: dichloromethane (1:1 mixture) at room temperature for 40 min. Completion of coupling was monitored by ninhydrin test as described by Kaiser (Kaiser et al., Anal. Biochem. 34:595 (1970)), which is incorporated herein by reference. A second (double) coupling was performed where coupling in the first instance was incomplete.

After completion of peptide assembly on the resin, the final Fmoc deprotection was performed then followed by normal wash cycles and determination of the amount of Fmoc group released by deprotection at 302 nm. Then the malonic acid derivatives were similarly coupled by diisopropyl-carbodiimide/benzotriazol-1-ol procedure. The finished resin was washed successively with dichloromethane, dimethylformamide and dichloromethane, then dried under vacuum and used in the next step.

Solid-Phase Synthesis of Amidoxime:

The general procedure was by mixing the resin (from the step above) of the nitrile containing substance with 20-40 equivalents of hydroxylamine hydrochloride in presence of 1:1:1 (by volumes) mixture of triethylamine, pyridine and dimethylformamide. The suspension was usually sonnicated for about 30 sec. and shaked at room temperature for 12-24 hours. The completion of conversion of nitrile to amidoxime was monitored by either FT-IR (KBr disk) looking for the disappearance of –CN absorption at 2225 cm^{-1} or

by cleavage of small sample of the resin by trifluoroacetic acid: H_2O (95:5) or reagent K (see below) and determination of the molecular weight by electrospray mass spectroscopy. The finished resin was washed with dimethylformamide, 10 % H_2O in dimethylformamide, ethanol, dichloromethane and dried in vacuum before its use in the next step.

Solid-Phase Synthesis of Amidine:

Several methods were reported for the synthesis of amidine-containing compounds (for review see P.J. Dunn (1995) in "Comprehensive Organic Functional Group Transformations: Amidines and N-Substituted Amidines", Vol. 5, 741-782 (edts. Alan R. Katritzky, Otto Meth-Cohen & Charles W. Rees), Pergamon, N.Y., 1995). None of these methods were compatible with the solid-phase organic synthesis. Here we developed the proper procedure of amidine synthesis via amidoxime precursor by reduction using excess triethylsilane in presence of soluble catalyst (dichlorotetrakis (triphenylphosphine) ruthenium (II), DCRu). It was found that addition of triphenylphosphine in presence of acetic acid facilitated the reduction and enhanced the yield of amidine compounds. In a typical experiment the dried resin was added to the reduction cocktail composed of DCRu, triphenylphosphine, acetic acid, dimethylformamide and triethylsilane in a stoppered reaction vessel (see example 4/5). The reduction usually will take 12-24 hours at room temperature. Additional amount of triethylsilan was used in case of incomplete reduction and the time of reaction was extended by 4-8 additional hours. The finished peptidomimetic resin was washed with dimethylformamide, ethanol, dichloromethane and suspended in reagent K (King et al., Int. J. Pept. Prot. Res. 36:255-266 (1990)) cocktail (5 ml/g peptide resin) for 180 min at room temperature. Then the cleavage mixture was filtered in anhydrous diethyl ether and the solid precipitate was isolated by centrifugation and dried in vacuum over solid pellets of KOH and the solid material was dissolved in a mixture of 1:1 of 0.1 % trifluoroacetic acid in water and acetonitrile and lyophilized.

For purification of the compounds of formula I, a sample of crude lyophilized compound was dissolved in a mixture of 0.1 % aqueous trifluoroacetic acid containing 10 % to 50 % acetonitrile. The compound solution usually filtered through a syringe connected to a 0.45 µm nylon "ACRODISC" 13 (Gelman Sciences; Ann Arbor MI) filter. A proper volume of filtered peptidomimetic solution was injected into a semi-preparative C_{18}

column (Vydac Protein and Peptide C18, 218TP1010; The Separation Group; Hesperia CA). The flow rate of a gradient or isocratic mixture of 0.1 % trifluoroacetic acid buffer and acetonitrile (HPLC grade) as an eluent was maintained using a Beckman "SYSTEM GOLD" HPLC. Elution of the peptidomimetic was monitored by UV detection at 230 nm (Beckman, System Gold, Programmable Solvent Module 126 and Programmable Detector Module 166 controlled by "SYSTEM GOLD" software). After identifying the peak corresponding to each diastereomer using MS, the compounds were collected, lyophilized and biologically tested. MS was performed using a SCIEX API III+ instrument. In addition, NMR was performed using a General Electric instrument (300 MHz) or Bruker Avance DPX 300 (300 MHz). For NMR, samples typically were measured in DMSO-d_6 or $CDCl_3$ (Aldrich).

Typical synthesis of individual compounds is summarized in Scheme 6 and the following examples illustrate the experimental details.

Example 2 and 3

N-[(1-(S)-Carbamoyl-4-guanidino-butylcarbamoyl)-(S)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, more polar diastereomerand
N-[(1-(S)-Carbamoyl-4-guanidino-butylcarbamoyl)-(S)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer

a) N-[(1-(S)-{Carbonyl-(Rink-resin)}-4-(bis-tert-butoxycarbonyl-guanidino)-butylcarbamoyl)-(S)-cyclohexyl-methyl]-2-(R,S)-(4-cyano-benzyl)-N',N'-dimethyl-malonamide

Fmoc-deprotected Rink resin (210 mg, 0.16 mmol) was coupled to 2-(Fmoc-amino)-4-(S)-(N,N'-bis-tert-butoxycarbonyl-guanidino)-butyric acid (326 mg, 0.5 mmol, 2 eq.) using benzotriazol-1-ol and diisopropyl-carbodiimide (2 eq. of each) as outlined in example 1. After Fmoc-deprotection, the resin was coupled with (S)-cyclohexyl-(Fmoc-

amino)-acetic acid (2 eq.) using the same coupling conditions. After Fmoc-deprotection the resin was coupled with 2-(R,S)-(4-cyano-benzyl)-N,N-dimethyl-malonamic acid (45 mg, 0.17 mmol, 1.1 eq.) using diisopropyl-carbodiimide/benzotriazol-1-ol (1.1 eq. each) in dimethylformamide for 4 hours at room temperature. The completion of the reaction was confirmed by ninhydrin test. The resin was washed with dimethylformamide, methanol and dichloromethane and dried in vacuo for 2-3 hours.

b) N-[(1-(S)-Carbamoyl-4-guanidino-butylcarbamoyl)-(S)-cyclohexyl-methyl]-2-(R)-[4-(N-hydroxycarbamimidoyl)-benzyl]-N',N'-dimethyl-malonamide trifluoroacetate and N-[(1-(R)-Carbamoyl-4-guanidino-butylcarbamoyl)-(S)-cyclohexyl-methyl]-2-(S)-[4-(N-hydroxycarbamimidoyl)-benzyl]-N',N'-dimethyl-malonamide trifluoroacetate

The dried resin from step a was transferred into a screw-capped 20-ml vial and mixed with hyroxylamine hydrochloride (350 mg, 5 mmole, 25 eq.). To the reaction vial was added a mixture of triethylamine, pyridine and dimethylformamide (1:1:1, 8 ml), the vial capped, and sonnicated for 30 sec. The reaction was rocked at room temperature over night. The completion of the reaction was checked as mentioned in example 1. The finished resin was split into two portions. One portion was cleaved and processed as outlined in example 1 to give the title compound. Analysis by MS gave M.Wt. 573.4 (cal. 573.3). The second portion of the resin was used in example 4 and 5.

Example 4 and 5

2-(4-Carbamimidoyl-benzyl)-N-[(1-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, diastereomeric mixtureand less polar diastereomer

A solution of dichlorotetrakis (triphenylphosphine)ruthenium (II) (20 mg) and triphenylphosphine (80 mg) in dimethylformamide (1 ml) and glacial acetic acid (135 µl) was heated at 50°C for 10-15 minutes to give a clear brown colored solution. The reaction vial was cooled to room temperature and the second portion of the dried resin (100 mg) from example 2/3b was added followed by triethylsilane (1 ml). The vial was capped under N_2 and shaked at room temperature for 12 hours. Completion of reduction to amidine was monitored by cleavage of small amount of the resin and testing the product with HPLC/ESMS. The finished resin was washed with dimethylformamide, methanol, dichloromethane and processed as outlined in example 1. The lyophilized product (14 mg) was purified by HPLC and the two distereoisomers were separated. The purified product was analyzed by ESMS cal. 560.35; found 560.

Example 6 and 7

2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid allyl ester trifluoroacetic acid salt, less polar diastereomer and
2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid allyl ester trifluoroacetic acid salt, more polar diastereomer

a) N-Benzyl-2-(R,S)-(4-cyano-benzyl)-N-methyl-malonamic acid

A solution of benzyl-methyl-amine (120 ml, 887 mmol), bis-(trimethylsilyl)-acetamide (118 ml, 482 mmol) and anhydrous dichloromethane (1000 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool to room temperature and 4-(R,S)-(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-benzonitrile (25 g, 97 mmol) was added portionwize. The reaction mixture was refluxed for further 3 hours, allowed to cool to room temperature and poured into a cool mixture of 1700 ml 1 n hydrochloric acid and 800 ml ethylacetate, brought to pH 4 with 6 n sodium hydroxid solution, and extracted with ethylacetate and dichloromethane. The combined organic layers were

washed with brine, dried and concentrated in vacuo. The precipitated crystals were sucked off and dried to give 25.0 g (80 %) of the desired product.
mp: 152-153°C (dc).

b) (S)-[2-(Benzyl-methyl-carbamoyl)-3-(R,S)-(4-cyano-phenyl)-propionylamino]-cyclohexyl-acetic acid methyl ester

A solution of N-benzyl-2-(R,S)-(4-cyano-benzyl)-N-methyl-malonamic acid (25.0 g, 78 mmol), (S)-amino-cyclohexyl-acetic acid methyl ester (14.2 g, 83 mmol), diisopropylethylamine (16 ml, 94 mmol), 3-hydroxy-3H-benzo[d][1,2,3]triazin-4-one (3.2 g, 20 mmol), and dimethylformamide (520 ml) was cooled to 10°C. A solution of dicyclohexyl-carbodiimide (18.7 g, 91 mmol) in toluene (30 ml) was added dropwize and the reaction mixture stood over night. The precipitated urea was sucked off, the filtrate was evaporated in vacuo, solved in ethylacetate, washed with saturated sodium hydrogen carbonate solution and brine, dried, and evaporated in vacuo. Crystallization from n-heptane/isopropanol gave 6.3 g (17 %) of the desired product. mp: 119-120°C. The filtrate was evaporated and purified by column chromatography on silica gel with n-heptane/ethyl acetate = 10/1 as eluent. Combined fractions gave 6.1 g (17 %) of the desired product. mp: 120-121°C.

c) {2-(Benzyl-methyl-carbamoyl)-3-(R,S)-[4-(N-hydroxycarbamimidoyl)-phenyl]-propionylamino}-(S)-cyclohexyl-acetic acid methyl ester

A suspension of [2-(benzyl-methyl-carbamoyl)-3-(R,S)-(4-cyano-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid methyl ester (12.0 g, 26 mmol) and hydroxylamine (4.3 g, 130 mmol) in ethanol (150 ml) was heated to reflux for 4 hours. The reaction mixture was cooled to room temperature, evaporated in vacuo, solved in ethanol and poured in ice-water. The precipitate was collected by suction and dried at 60°C in vacuo to give 11.6 g (90 %) of the desired product.
mp: 135-138°C, MS: 509 (M+H).

d) [2-(Benzyl-methyl-carbamoyl)-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid methyl ester

{2-(Benzyl-methyl-carbamoyl)-3-(R,S)-[4-(N-hydroxycarbamimidoyl)-phenyl]-propionylamino}-(S)-cyclohexyl-acetic acid methyl ester (11.0 g, 22 mmol) was hydrogenated in acetic acid with palladium/charcoal to give 9.2 g (77 %) of the desired product which was used without further purification in the next step.
mp: 123-124°C, MS: 493 (M+H)

e) [2-(Benzyl-methyl-carbamoyl)-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid trifluoroacetic acid salt

The above [2-(benzyl-methyl-carbamoyl)-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid methyl ester (9.2 g, 19 mmol) was suspended in acetonitrile (350 ml), water/concentrated hydrochloric acid (1/1, 500 ml) was added and the reaction mixture was stirred at room temperature. After 4 days the reaction mixture was evaporated, water was added and the mixture was lyophilized. The product was purified by column chromatography on silica gel with dichloromethane/methanol/trifluoroacetic acid = 15/1/0.5 to 4/1/0.5. Collected fractions gave 8.2 g (74 %) of the desired product.
MS: 479 (M+H).

f) 2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid allyl ester trifluoroacetic acid salt, less polar diastereomer and
2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid allyl ester trifluoroacetic acid salt, more polar diastereomer

To a solution of [2-(benzyl-methyl-carbamoyl)-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid trifluoroacetic acid salt (2.9 g, 4.9 mmol) in dimethylformamide (350 ml) were added collidin (2.4 g, 19.6 mmol) and HATU (2.1 g,

5.4 mmol) at 0°C. The reaction mixture was stirred at this temperature for 30 minutes, then (S)-2-amino-5-guanidino-pentanoic acid allyl ester (1.2 g, 4.9 mmol) was added. The reaction mixture was allowed to warm up to room temperature and stood for 60 hours. The solvent was evaporated in vacuo and the residue was purified by MPLC on RP_{18} material using water/ethanol/trifluoroacetic acid (9/1/0.1 to 5/5/0.1) as eluent to give 1.0 g (23 %) of the more polar diastereomer and 584 mg (13 %) of the less polar diastereomer. Both fractions showed the correct MS spectrum.The following compounds were prepared using the procedures described above:

Expl.	Name	MS	Method
8	N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
9	N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	solid phase
10	2-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionyl]-1,2,3,4-tetrahydro-isoquinoline-3-(S)-carboxylic acid (1-(S)-carbamoyl-4-guanidino-butyl)-amide trifluoroacetic acid salt	ok	solid phase
11	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
12	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2- phenyl-ethyl]-malonamide trifluoroacetic acid salt	ok	solid phase
13	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
14	N-Benzyl-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-	ok	solid

	butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-malonamide trifluoroacetic acid salt		phase
15	N-[2-(4-Amino-phenyl)-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
16	N-[2-(4-Amino-phenyl)-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
17	N-Allyl-N'-[2-(4-amino-phenyl)-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-malonamide trifluoroacetic acid salt	ok	solid phase
18	N-[2-(4-Amino-phenyl)-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N'-phenyl-malonamide	ok	solid phase
19	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-methyl-butyl]-N,N'-dimethyl-malonamide	ok	solid phase
20	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-methyl-butyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
21	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-methyl-butyl]-N-methyl-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
22	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N,N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
23	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-	ok	solid

	carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N'-methyl-malonamide trifluoroacetic acid salt		phase
24	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N-methyl-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
25	2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (1-(S)-carbamoyl-4-guanidino-butyl)-amide trifluoroacetic acid salt	ok	solid phase
26	2-(S)-[2-Allylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (1-(S)-carbamoyl-4-guanidino-butyl)-amide trifluoroacetic acid salt	ok	solid phase
27	2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-phenylcarbamoyl-propionyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (1-(S)-carbamoyl-4-guanidino-butyl)-amide trifluoroacetic acid salt	ok	solid phase
28	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
29	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-malonamide trifluoroactic acid salt	ok	solid phase
30	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N'-phenyl-malonamide trifluoroactic acid salt	ok	solid phase
31	4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-4-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyric acid trifluoroactic acid salt	ok	solid phase
32	4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-	ok	solid

	dimethylcarbamoyl-propionylamino]-4-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyric acid		phase
33	4-(S)-[2-Allylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-4-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyric acid trifluoroacetic acid salt	ok	solid phase
34	4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-phenylcarbamoyl-propionylamino]-4-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyric acid	ok	solid phase
35	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-2-yl-ethyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
36	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-2-yl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
37	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-2-yl-ethyl]-malonamide trifluoroacetic acid salt	ok	solid phase
38	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-2-yl-ethyl]-N'-phenyl-malonamide trifluoroacetic acid	ok	solid phase
39	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-3-phenyl-propyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
40	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-3-phenyl-propyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
41	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-	ok	solid

	carbamoyl-4-guanidino-butylcarbamoyl)-3-phenyl-propyl]-malonamide trifluoroacetic acid salt		phase
42	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-3-phenyl-propyl]-N'-phenyl-malonamide trifluroacetic acid salt	ok	solid phase
43	N-[4-Amino-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyl]-2-(4-carbamimidoyl-benzyl)-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
44	N-[4-Amino-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyl]-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
45	N-Allyl-N'-[4-amino-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyl]-2-(4-carbamimidoyl-benzyl)-malonamide trifluoroacetic acid salt	ok	solid phase
46	N-[4-Amino-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyl]-2-(4-carbamimidoyl-benzyl)-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
47	3-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-N-(1-(S)-carbamoyl-4-guanidino-butyl)-succinamic acid trifluoroacetic acid salt	ok	solid phase
48	3-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-N-(1-(S)-carbamoyl-4-guanidino-butyl)-succinamic acid trifluoroacetic acid salt	ok	solid phase
49	3-(S)-[2-Allylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-N-(1-(S)-carbamoyl-4-guanidino-butyl)-succinamic acid trifluoroacetic acid salt	ok	solid phase
50	3-(S)-[3-(4-Carbamimidoyl-phenyl)-2-phenylcarbamoyl-propionylamino]-N-(1-(S)-carbamoyl-4-guanidino-butyl)-succinamic acid trifluoroacetic acid salt	ok	solid phase

51	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-hydroxy-ethyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
52	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-hydroxy-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
53	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-hydroxy-ethyl]-malonamide trifluoroacetic acid salt	ok	solid phase
54	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-hydroxy-ethyl]-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
55	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-phenyl-methyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
56	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-phenyl-methyl]- N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
57	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)- phenyl-methyl]-malonamide trifluoroacetic acid salt	ok	solid phase
58	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-phenyl-methyl]- N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
59	N-[2-Benzyloxy-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
60	N-[2-Benzyloxy-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
61	N-Allyl-N'-[2-benzyloxy-1-(S)-(1-(S)-carbamoyl-4-	ok	solid

	guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-malonamide trifluoroacetic acid salt		phase
62	N-[2-Benzyloxy-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
63	[5-(S)-[3-(4-Carbamimidoyl-phenyl)-2-ethylcarbamoyl-propionylamino]-5-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-carbamic acid benzyl ester	ok	solid phase
64	[5-(S)-[3-(4-Carbamimidoyl-phenyl)-2-imethylcarbamoyl-propionylamino]-5-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-carbamic acid benzyl ester	ok	solid phase
65	[5-(S)-[2-Allylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-5-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-carbamic acid benzyl ester	ok	solid phase
66	[5-(S)-[3-(4-Carbamimidoyl-phenyl)-2-phenylcarbamoyl-propionylamino]-5-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-carbamic acid benzyl ester	ok	solid phase
67	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
68	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	solid phase
69	4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-4-[1-(S)-(1-(S)-carbamoyl-2-cyclohexyl-ethylcarbamoyl)-4-guanidino-butylcarbamoyl]-butyric acid trifluoroacetic acid salt	ok	solid phase

70	4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-4-[1-(S)-(1-(S)-carbamoyl-2-cyclohexyl-ethylcarbamoyl)-4-guanidino-butylcarbamoyl]-butyric acid trifluoroacetic acid salt	ok	solid phase
71	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt trifluoroacetic acid salt	ok	solid phase
72	2-(S)-{2-(R)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
73	2-(S)-{2-(R)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
74	2-(S)-{2-(R)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
75	2-(4-Carbamimidoyl-benzyl)-N-{1-(S)-[1-(S)-carbamoyl-2-(4-hydroxy-phenyl)-ethylcarbamoyl]-pentyl}-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
76	2-(3-Carbamimidoyl-benzyl)-N-{1-(S)-[1-(S)-carbamoyl-2-(4-hydroxy-phenyl)-ethylcarbamoyl]-pentyl}-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
77	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
78	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
79	2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-	ok	solid

	phenyl)-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt		phase
80	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid; compound with trifluoro-acetic acid trifluoroacetic acid salt	ok	solid phase
81	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
82	2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
83	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-3-cyclohexyl-propionylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
84	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-3-cyclohexyl-propionylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
85	2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-3-cyclohexyl-propionylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt	ok	solid phase
86	2-(4-Carbamimidoyl-benzyl)-N-[1-(R)-(1-(R)-carbamoyl-4-guanidino-butylcarbamoyl)-2-cyclohexyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
87	2-(3-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase

88	4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-phenylcarbamoyl-propionylamino]-4-[1-(S)-(1-(S)-carbamoyl-2-cyclohexyl-ethylcarbamoyl)-4-guanidino-butylcarbamoyl]-butyric acid trifluoroacetic acid salt	ok	solid phase
89	4-(S)-[2-Allylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-4-[1-(S)-(1-(S)-carbamoyl-2-cyclohexyl-ethylcarbamoyl)-4-guanidino-butylcarbamoyl]-butyric acid trifluoroacetic acid salt	ok	solid phase
90	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(2-carbamimidoyl-1-(S)-carbamoyl-ethylcarbamoyl)-cyclohexyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
91	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(2-carbamimidoyl-1-(S)-carbamoyl-ethylcarbamoyl)-cyclohexyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	solid phase
92	2-(4-Carbamimidoyl-benzyl)-N-{1-(S)-[(3-carbamimidoyl-benzyl)-carbamoylmethyl-carbamoyl]-pentyl}-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
93	2-(4-Carbamimidoyl-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	solid phase
94	3-{2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-diisopropylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-2-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-ethyl}-1- methyl-pyridinium trifluoro-acetate trifluoroacetic acid, more polar diastereomer	ok	solid phase
95	3-{2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-	ok	solid

	diisopropylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-2-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-ethyl}-1- methyl-pyridinium trifluoro-acetate trifluoroacetic acid, less polar diastereomer		phase
96	2-(4-Amino-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
97	2-(4-Amino-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	solid phase
98	2-(4-Carbamimidoyl-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisobutyl-malonamide trifluoroacetic acid salt, more polar diasteromer	ok	solid phase
99	2-(4-Carbamimidoyl-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisobutyl-malonamide trifluoroacetic acid salt, less polar diasteromer	ok	solid phase
100	N-[(S)-(1-(S)-Carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-(4-dimethylamino-naphthalen-2-ylmethyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
101	N-[(S)-(1-(S)-Carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-(4-	ok	solid phase

	dimethylamino-naphthalen-2-ylmethyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, less polar diastereomer		
102	N-[(S)-(1-(S)-Carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
103	N-[(S)-(1-(S)-Carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	solid phase
104	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(carbamoylmethyl-pyridin-4-ylmethyl-carbamoyl)-cyclohexyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
105	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(carbamoylmethyl-pyridin-4-ylmethyl-carbamoyl)-cyclohexyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	class. Synth.
106	N-{(S)-[(4-Amino-butyl)-carbamoylmethyl-carbamoyl]-cyclohexyl-methyl}-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoracetic acid salt, more polar diastereomer	ok	solid phase
107	N-{(S)-[(4-Amino-butyl)-carbamoylmethyl-carbamoyl]-cyclohexyl-methyl}-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoracetic acid salt, less polar diastereomer	ok	class. Synth.
108	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid	ok	class. Synth.

	salt, less polar diastereomer		
109	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	class. Synth.
110	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-1-yl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	class. Synth.
111	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-methyl-butyl]-N,N',N'-trimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
112	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N,N',N'-trimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
113	2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (1-(S)-carbamoyl-4-guanidino-butyl)-amide trifluoroacetic acid salt	ok	solid phase
114	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
115	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2,2-dimethyl-propyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
116	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2,2-dimethyl-propyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
117	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-	ok	solid

	carbamoyl-4-guanidino-butylcarbamoyl)-2,2-dimethyl-propyl]-malonamide trifluoroacetic acid salt		phase
118	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2,2-dimethyl-propyl]-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
119	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
120	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt	ok	solid phase
121	2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
122	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-cyclohexyl-ethyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
123	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-cyclohexyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt	ok	solid phase
124	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-cyclohexyl-ethyl]-malonamide trifluoroacetic acid salt	ok	solid phase
125	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-cyclohexyl-ethyl]-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
126	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N'-methyl-malonamide trifluoroacetic acid salt	ok	solid phase
127	N-Allyl-2-(4-carbamimidoyl-benzyl)-N'-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2- phenyl-	ok	solid phase

	ethyl]-malonamide trifluoroacetic acid salt		
128	2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N'-phenyl-malonamide trifluoroacetic acid salt	ok	solid phase
129	N-Benzyl-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	solid phase
130	N-Benzyl-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	solid phase
131	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid ethyl ester hydrochloric acid salt	ok	class. Synth.
132	(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-cyclohexyl-acetic acid, less polar diastereomer	ok	class. Synth.
133	(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-cyclohexyl-acetic acid, more polar diastereomer	ok	class. Synth.
134	2-{2-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-pentanedioic acid diamide hydrochloric acid salt	ok	class. Synth.
135	2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid ethyl ester trifluoroacetic acid salt	ok	class. Synth.
136	2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-	ok	class. Synth.

	guanidino-pentanoic acid ethyl trifluoroacetic acid salt, less polar diastereomer		
137	2-(4-Carbamimidoyl-benzyl)-N-[(S)-cyclohexyl-(4-guanidino-1-(S)-phenethylcarbamoyl-butylcarbamoyl)-methyl]-N',N'-dimethyl-malonamide hydrochloric acid salt	ok	class. Synth.
138	2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid benzyl ester hydrochloric acid acetic acid salt	ok	class. Synth.
139	N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-{(S)-cyclohexyl-[(naphthalen-1-ylmethyl)-carbamoyl]-methyl}-malonamide trifluoroacetic acid salt	ok	class. Synth.

Example 140 and 141

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, less polar diastereomer and
N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, more polar diastereomer

a) N-Benzyl-2-(R,S)-(4-cyano-benzyl)-malonamic acid

A solution of benzylamine (58.6 g, 534 mmol), bis-(trimethylsilyl)-acetamide (71 ml, 90 mmol) and anhydrous dichloromethane (600 ml) was heated to reflux for 3 hours. The reaction mixture was allowed to cool to room temperature and 4-(R,S)-(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-benzonitrile (15 g, 58 mmol) was added portionwize. The reaction mixture was refluxed for further 3 hours, allowed to cool to room temperature and poured into a cool mixture of 1000 ml 1 n hydrochloric acid and 500

ethylacetate. The combined organic layers were washed with brine, dried and concentrated in vacuo. The precipitated crystals were sucked off and dried to give 11.07 g (62 %) of the desired product.
mp: 152-153°C (dc), MS: 309 (M+H).

b) [2-Benzylcarbamoyl-3-(R,S)-(4-cyano-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid methyl ester

A solution of N-benzyl-2-(R,S)-(4-cyano-benzyl)-malonamic acid (10 g, 32.4 mmol), (S)-amino-cyclohexyl-acetic acid methyl ester (5.94 g, 34.7 mmol), diisopropylethylamine (6.45 ml, 37.9 mmol), 3-hydroxy-3H-benzo[d][1,2,3]triazin-4-one (1.32 g, 8.1 mmol), and dimethylformamide (100 ml) was cooled to 10°C. A solution of dicyclohexyl-carbodiimide (7.83 g, 37.9 mmol) in toluene (10 ml) was added dropwize and the reaction mixture stood over night. The precipitated urea was sucked off, the filtrate was evaporated in vacuo, solved in ethylacetate, washed with saturated sodium bicarbonate-solution and brine, dried, and evaporated in vacuo. Crystallization from n-heptane/isopropanol gave 9.91 g (66 %) of the desired product.
mp: 170-174°C, MS: 462 (M+H).

c) {2-Benzylcarbamoyl-3-(R,S)-[4-(N-hydroxycarbamimidoyl)-phenyl]-propionylamino}-(S)-cyclohexyl-acetic acid methyl ester

A suspension of [2-benzylcarbamoyl-3-(R,S)-(4-cyano-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid methyl ester (9.0 g, 19.5 mmol) and hydroxylamine (3.22 g, 97.5 mmol) in ethanol (180 ml) was heated to reflux for 4 hours. The reaction mixture was cooled to room temperature, evaporated in vacuo, solved in ethanol and poured in ice-water. The precipitate was collected by suction and dried at 50°C in vacuo to give 7.9 g (82 %) of the desired product.
mp: 101-104°C, MS: 495 (M+H).

d) [2-Benzylcarbamoyl-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid methyl ester

{2-Benzylcarbamoyl-3-(R,S)-[4-(N-hydroxycarbamimidoyl)-phenyl]-propionylamino}-(S)-cyclohexyl-acetic acid methyl ester (7.6 g, 15.4 mmol) was hydrogenated in acetic acid with palladium/charcoal to give the desired product which was used without further purification in the next step.
mp: 101-104°C, MS: 479 (M+H).

e) [2-Benzylcarbamoyl-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid hydrochloride

The above [2-benzylcarbamoyl-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid methyl ester was suspended in water/concentrated hydrochloric acid (1/1, 200 ml) and stirred at room temperature. After 8 days acetonitrile (100 ml) was added and stirred for further 2 days. The reaction mixture was filtered and poured in ice-water.
The precipitate was collected by fractionized crystallization:
Fr.1: 3.36 g (52 %, diast. mixture:6.7 % more polar, 78.0 % less polar)
Fr.2: 857 mg (13 %, diast. mixture: 55.3 % more polar, 31.9 % less polar), oil
Fr.3: 461 mg (7 %, diast. mixture: 3.8 % more polar, 93.5 % less polar), mp: 166°C (subl.)
Fr.4: 455 mg (7 %, 96.7 % less polar diastereomer), oil
HPLC: polar diastereomer: 15.62 min, non-polar diastereomer: 16.21 min.
HPLC-conditions: Nucleosil 250/4, 7 µM, 1 ml/min, gradient: 100 % (H_2O + 0.1 % trifluoroacetic acid) to 100 % acetonitrile in 30 min, 100 % acetonitrile 5 min, = 254 nm.
MS of all fractions show: 465 (M+H).
It was tried to purify Fr.1 by flash chromatography on silica gel (dichloromethane/methanol/ glacial acetic acid = 9/1/0.5), but isomerization of the malonic chiral center took place to give the acetic acid salt of the title compound.

f) N-Benzyl-2-(R)-(4-carbamimidoyl-benzyl)-N'-[(1-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt and

N-Benzyl-2-(S)-(4-carbamimidoyl-benzyl)-N'-[(1-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt

A solution of [2-benzylcarbamoyl-3-(R,S)-(4-carbamimidoyl-phenyl)-propionylamino]-(S)-cyclohexyl-acetic acid acetate (103 mg, 0.20 mmol), benzotriazol-1-ol hydrate (32 mg, 0.24 mmol), 2-(S)-amino-5-guanidino-pentanoic acid amide in dimethylformamide (4 ml) was stirred for 30 min and cooled to 0 to –5°C. A solution of 1,3-dicyclohexyl urea (49 mg, 0.24 mmol) was added and the reaction mixture was stirred for 24 hours at 0°C. The solvent was evaporated and the residue was purified by preparative HPLC to give 4.5 mg (3 %) of F1 (more polar diastereomer) and 7.8 mg (5 %) of F2 (less polar diastereomer).

HPLC-conditions: Nucleosil 250/21 mm, 7 µM, 15 ml/min, 68 % H_2O + 0.1 % trifluoroacetic acid, 32 % acetonitrile.

F1: mp.: 150-154°C, MS m/z : 620.5 ($(M+H)^+$, 9 %), 310.9 ($(M+2H)^{2+}$, 100 %).

F2: mp.: 102-106°C, MS m/z : 620.5 ($(M+H)^+$, 5 %), 310.9 ($(M+2H)^{2+}$, 34 %), 150.0 (100 %).

The following compounds were prepared using the procedures described above:

142	2-(4-Carbamimidoyl-benzyl)-N-{(S)-[2-(3-carbamimidoyl-phenyl)-1-carbamoyl-ethylcarbamoyl]-cyclohexyl-methyl}-N',N'-dimethyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	class. Synth.
143	2-(4-Carbamimidoyl-benzyl)-N-{(S)-[2-(3-carbamimidoyl-phenyl)-1-carbamoyl-ethylcarbamoyl]-cyclohexyl-methyl}-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	class. Synth.
144	N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-	ok	class. Synth.

	methyl]-N-methyl-malonamide trifluoroacetic acid salt		
145	2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid hydrochloric acid salt	ok	class. Synth.
146	2-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-3-naphthalen-1-yl-propionic acid ethyl ester trifluoroacetic acid salt, less polar diastereomer	ok	class. Synth.
147	2-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-3-naphthalen-1-yl-propionic acid ethyl ester trifluoroacetic acid salt, more polar diastereomer	ok	class. Synth.
148	2-(S)-{2-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid methyl ester trifluoroacetic acid salt, least polar diastereomer	ok	class. Synth.
149	2-(S)-{2-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid methyl ester trifluoroacetic acid salt, less polar diastereomer	ok	class. Synth.
150	2-(S)-{2-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid methyl ester trifluoroacetic acid salt, more polar diastereomer	ok	class. Synth.
151	2-(S)-{2-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid methyl ester trifluoroacetic acid salt, most polar	ok	class. Synth.

	diastereomer		
152	N-Benzyl-N'-{[1-(S)-(benzyl-methyl-carbamoyl)-4-guanidino-butylcarbamoyl]-cyclohexyl- methyl}-2-(4-carbamimidoyl-benzyl)-N-methyl-malonamide trifluoroacetic acid salt, most polar diastereomer	ok	class. Synth.
153	N-Benzyl-N'-{[1-(S)-(benzyl-methyl-carbamoyl)-4-guanidino-butylcarbamoyl]-cyclohexyl- methyl}-2-(4-carbamimidoyl-benzyl)-N-methyl-malonamide trifluoroacetic acid salt, more polar diastereomer	ok	class. Synth.
154	N-Benzyl-N'-{[1-(S)-(benzyl-methyl-carbamoyl)-4-guanidino-butylcarbamoyl]-cyclohexyl- methyl}-2-(4-carbamimidoyl-benzyl)-N-methyl-malonamide trifluoroacetic acid salt, less polar diastereomer	ok	class. Synth.
155	N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[cyclohexyl-(1-(S)-dimethylcarbamoyl-4-guanidino-butylcarbamoyl)-methyl]-N-methyl-malonamide trifluoroacetic acid salt	ok	class. Synth.
156	(S)-[2-(4-Carbamimidoyl-benzylcarbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-cyclohexyl-acetic acid methyl ester trifluoroacetic acid salt	ok	class. Synth.
157	(S)-[2-(4-Carbamimidoyl-benzylcarbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-cyclohexyl-acetic acid trifluoroacetic acid salt	ok	class. Synth.

Abbreviations used:

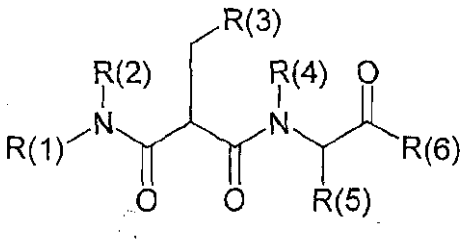
aPTT	activated partial thromboplastin time
ATS	Antistasin
AV	Arteriovenous
BAPNA	benzoyl-L-Arg-p-nitroanilide

Boc	tert butoxycarbonyl
°C	degrees Celsius
cal	Calculated
$CDCl_3$	deutero chloroform
Class. Synth.	classical synthesis
cm	Centimeter
dc	Decomposition
DCCI	Dicyclohexylcarbodiimide
DCRu	Dichlorotetrakis (triphenylphosphine) ruthenium (II)
DIC	disseminated intravascular coagulation
DICI	Diisopropylcarbodiimide
DMSO	Dimethylsulfoxide
DVT	deep vein thrombosis
eq.	Equivalent
ESMS	electro spray mass spectra
expl	Example
FAB	fast atom bombardment
Fmoc	9-fluorenylmethoxycarbonyl
FT-IR	fourier transformed infrared
g	Gram
h	Hour
HATU	N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide
HPLC	high pressure liquid chromatography
HPLC/ESMS	high pressure liquid chromatography/electro spray mass spectra
id	Intraduodenal
iv	Intravenous
kg	Kilogram
Km	Michaelis-Menten-constant
LMWH	low molecular weight haparin
mg	Milligram
MHz	Megahertz

min	Minutes
ml	Milliliter
mM	Millimolar
mmol	Millimol
MS	mass spetra
mp.	melting point
µl	Microliter
µm	Micrometer
µM	Micromolar
nm	Nanometer
nM	Nanomolar
NMR	nuclear magnetic resonance
PE	Polyethylene
PEG	Polyethyleneglycole
PG	protecting group
PPP	platelet poor blood
PT	prothrombin time
sec	Seconds
TAP	tick anticoagulant peptide
TBS-BSA	tris buffered saline bovine serum albumin
TBS-PEG	tris buffered saline polyethylene glycole
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TOTU	O-((cyano-(ethoxycarbonyl)-methylen)amino)-N,N,N',N'-tetra-methyluronium tetrafluoroborate
TPCK	Tosyl phenyl chloromethyl ketone
TRIS-Cl	bis(2-Hydroxyethyl)iminotris(hydroxymethyl)methane 2-bis(2-Hydroxyethyl)amino-2-(hydroxymethyl)-1,3-propanediol, chloride salt
UV	Ultra violett

Patent claims

1. Compounds of the formula I,



(I)

wherein

R(1) is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by R(17);

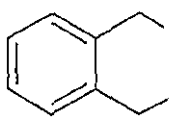
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is (C_6-C_{10})-aryl which is substituted by R(7);

R(4) is hydrogen or (C_1-C_4)-alkyl;

R(5) is (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by a residue R(20), and where alkyl is unsubstituted or substituted by a residue R(21); or

R(4) and R(5) together form a residue of the formula II



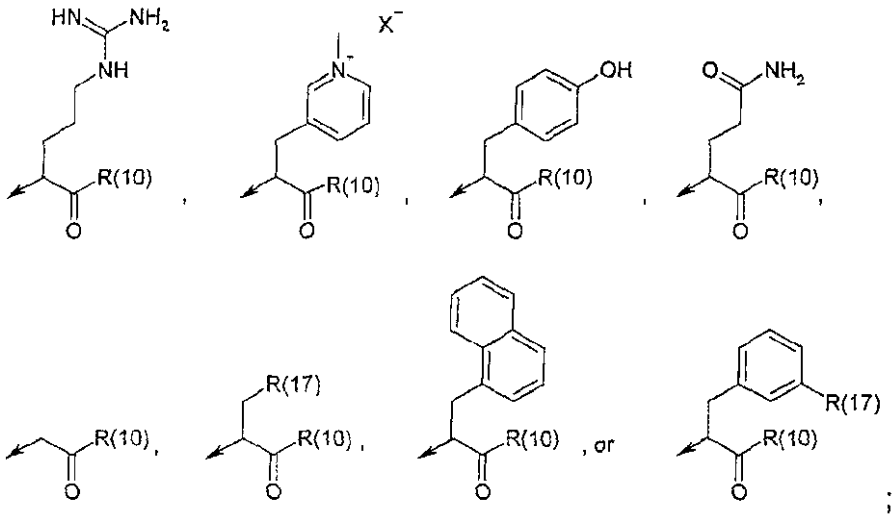
(II) ;

R(6) is NR(8)R(9) or OR(22);

R(7) is R(17) or R(20);

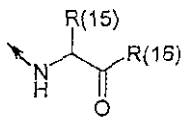
R(8) is hydrogen; (C_1-C_4)-alkyl, where alkyl is unsubstituted or substituted by a residue R(20); heteroaryl-(C_1-C_4)-alkyl; (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl is unsubstituted or substituted by a residue R(17);

R(9) is (C_6-C_{10})-aryl-(C_1-C_4)-alkyl,



;

R(10) is NR(12)R(13), OR(14), or



;

R(12) is hydrogen or (C_1-C_4)-alkyl;

R(13) is hydrogen, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, or (C_1-C_4)-alkyl;

R(14) is hydrogen, (C_1-C_4)-alkyl, (C_2-C_4)-alkenyl or (C_6-C_{10})-aryl-(C_1-C_4)-alkyl;

R(15) is (C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl;

R(16) is R(20);

R(17) is -C(=N-R(18))-N(R(19))$_2$;

R(18) is hydrogen, hydroxy, or an amino protective group;

R(19) is hydrogen, (C_1-C_4)-alkyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl, or an amino protective group;

R(20) is N(R(19))$_2$;

R(21) is hydroxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonylamino, carboxyl, or R(20);

R(22) is hydrogen or (C_1-C_4)-alkyl;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

2. Compounds of the formula I as claimed in claim 1, wherein

R(1) is hydrogen, (C_1-C_4)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

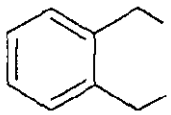
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is phenyl or naphthyl, which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II



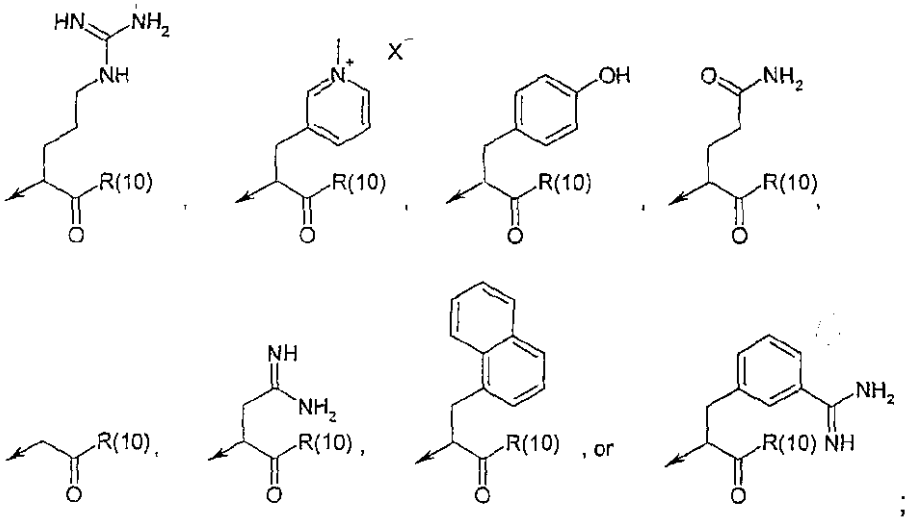
(II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

R(7) is amidino, hydroxyamidino, amino, or dimethylamino;

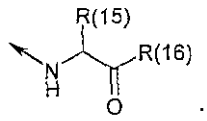
R(8) is hydrogen, pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is naphthylmethyl,



;

R(10) is NR(12)R(13), OR(14) or



;

R(12) is hydrogen or methyl;

R(13) is hydrogen, phenyl-(C_1-C_2)-alkyl, or methyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, benzyl, or allyl;

R(15) is cyclohexylmethyl;

R(16) is amino;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

3. Compounds of the formula I as claimed in claim 1 and/or claim 2, wherein

R(1) is hydrogen, (C_1-C_3)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

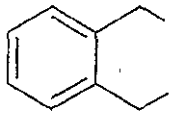
R(2) is hydrogen or (C_1-C_3)-alkyl;

R(3) is phenyl or 2-naphthyl which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, 4-aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II



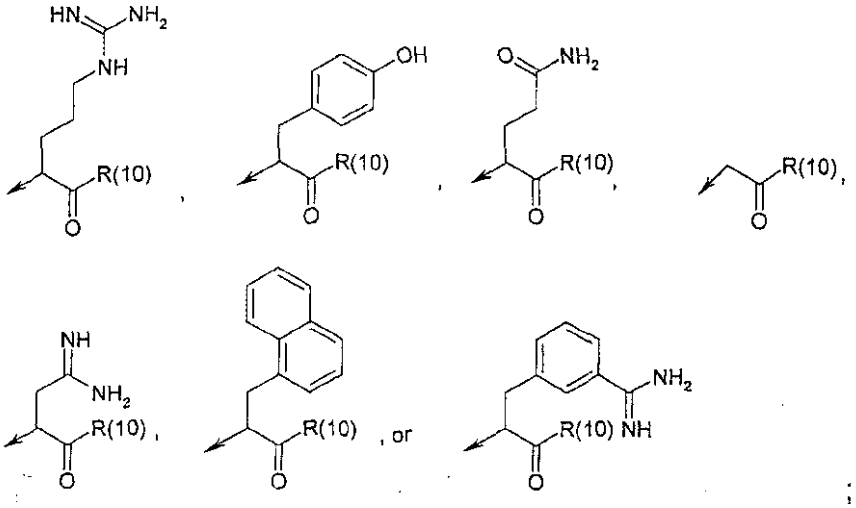
(II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

R(7) is amidino, hydroxyamidino, or dimethylamino;

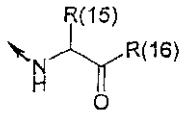
R(8) is hydrogen, pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is naphthylmethyl,



;

R(10) is NR(12)R(13), OR(14), or



;

R(12) is hydrogen or methyl;

R(13) is hydrogen, phenyl-(C_1-C_2)-alkyl, or methyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, benzyl, or allyl;

R(15) is cyclohexylmethyl;

R(16) is amino;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

4. Compounds of the formula I as claimed in one or more of claims 1 to 3, wherein

R(1) is hydrogen, (C_1-C_3)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

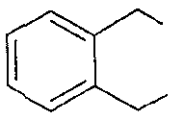
R(2) is hydrogen or (C_1-C_3)-alkyl;

R(3) is phenyl or naphthyl, which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II

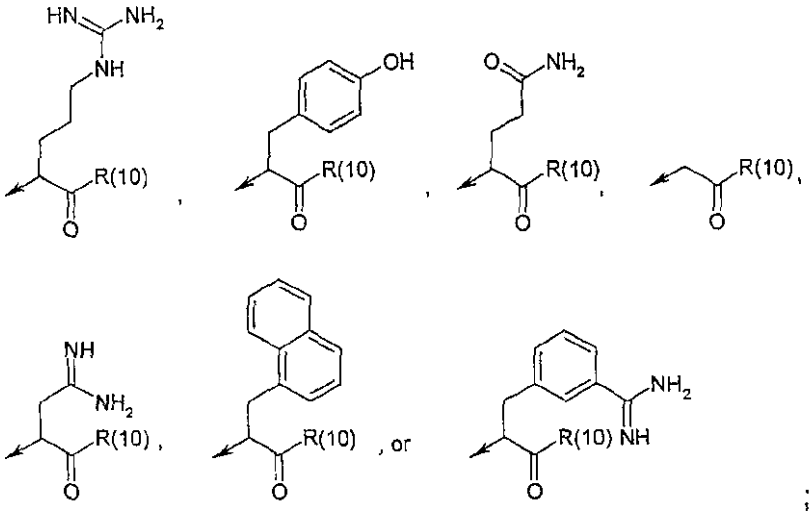
 (II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

R(7) is amidino, hydroxyamidino, or dimethylamino;

R(8) is hydrogen, pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is naphthylmethyl, preferably 1-naphthylmethyl,



;

R(10) is NR(12)R(13), or OR(14);

R(12) is hydrogen or methyl;

R(13) is hydrogen, phenyl-(C_1-C_2)-alkyl, or methyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, benzyl, or allyl;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

5. Compounds of the formula I as claimed in one or more of claims 1 to 4, wherein

R(1) is methyl, allyl, phenyl, or benzyl;

R(2) is hydrogen or methyl;

R(3) is phenyl which is substituted by R(7);

R(4) is hydrogen;

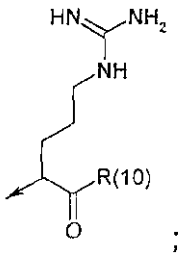
R(5) is butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, benzyloxymethyl, carboxymethyl, or 2-carboxy-ethyl;

R(6) is NR(8)R(9);

R(7) is amidino or hydroxyamidino;

R(8) is hydrogen;

R(9) is



;

R(10) is NR(12)R(13) or OR(14);

R(12) is hydrogen or methyl;

R(13) is hydrogen or phenyl-(C_1-C_2)-alkyl;

R(14) is hydrogen, (C_1-C_2)-alkyl, or allyl;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

6. Compounds of the formula I as claimed in one or more of claims 1 to 5, which are

2-(4-Carbamimidoyl-benzyl)-N-[(1-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid allyl ester trifluoroacetic acid salt, less polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, more polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, less polar diastereomer,

N-Benzyl-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-malonamide trifluoroacetic acid salt,

N-[2-(4-Amino-phenyl)-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N'-methyl-malonamide trifluoroacetic acid salt,

4-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-4-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-butyric acid,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-2-yl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-3-phenyl-propyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

3-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-N-(1-(S)-carbamoyl-4-guanidino-butyl)-succinamic acid trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-phenyl-methyl]-N'-methyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-phenyl-methyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

N-[2-Benzyloxy-1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-ethyl]-2-(4-carbamimidoyl-benzyl)-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-hexanoylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid; compound with trifluoro-acetic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-methylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-3-cyclohexyl-propionylamino}-5-guanidino-pentanoic acid trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-phenyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-naphthalen-1-yl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-pentyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N'-methyl-malonamide trifluoroacetic acid salt,

2-(4-Carbamimidoyl-benzyl)-N-[1-(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-2-cyclohexyl-ethyl]-N',N'-dimethyl-malonamide trifluoroacetic acid salt,

N-Benzyl-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-2-[4-(N-hydroxycarbamimidoyl)-benzyl]-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-dimethylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid ethyl ester hydrochloric acid salt,

2-(S)-{2-(S)-[2-Benzylcarbamoyl-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid ethyl trifluoroacetic acid salt, less polar diastereomer,

2-(4-Carbamimidoyl-benzyl)-N-[(S)-cyclohexyl-(4-guanidino-1-(S)-phenethylcarbamoyl-butylcarbamoyl)-methyl]-N',N'-dimethyl-malonamide hydrochloric acid salt,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, more polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-malonamide trifluoroacetic acid salt, less polar diastereomer,

N-Benzyl-2-(4-carbamimidoyl-benzyl)-N'-[(S)-(1-(S)-carbamoyl-4-guanidino-butylcarbamoyl)-cyclohexyl-methyl]-N-methyl-malonamide trifluoroacetic acid salt,

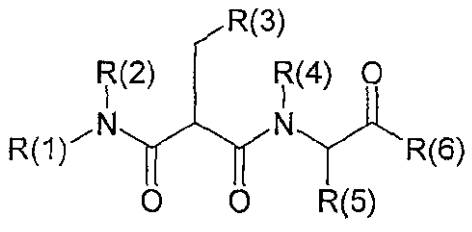
2-(S)-{2-(S)-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid hydrochloric acid salt,

2-(S)-{2-[2-(Benzyl-methyl-carbamoyl)-3-(4-carbamimidoyl-phenyl)-propionylamino]-2-cyclohexyl-acetylamino}-5-guanidino-pentanoic acid methyl ester trifluoroacetic acid salt, least polar diastereomer,

N-Benzyl-N'-{[1-(S)-(benzyl-methyl-carbamoyl)-4-guanidino-butylcarbamoyl]-cyclohexyl-methyl}-2-(4-carbamimidoyl-benzyl)-N-methyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

and/or their physiologically acceptable salts.

7. Compounds of the formula I,



(I)

wherein

R(1) is hydrogen, (C_1-C_6)-alkyl, (C_2-C_6)-alkenyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by R(17);

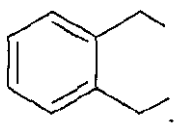
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is (C_6-C_{10})-aryl which is substituted by R(7);

R(4) is hydrogen or (C_1-C_4)-alkyl;

R(5) is (C_1-C_6)-alkyl, (C_3-C_7)-cycloalkyl, (C_3-C_7)-cycloalkyl-(C_1-C_4)-alkyl, (C_6-C_{10})-aryl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl in aryl-alkyl is unsubstituted or substituted by a residue R(20), and where alkyl is unsubstituted or substituted by a residue R(21); or

R(4) and R(5) together form a residue of the formula II



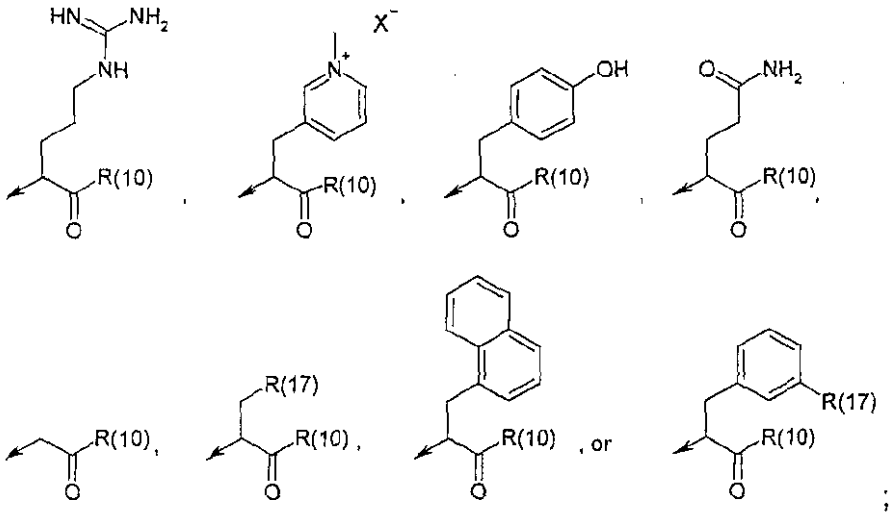
(II) ;

R(6) is NR(8)R(9) or OR(22);

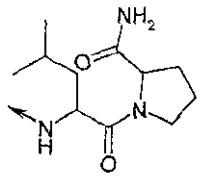
R(7) is R(17) or R(20);

R(8) is hydrogen; (C_1-C_4)-alkyl, where alkyl is unsubstituted or substituted by a residue R(20); heteroaryl-(C_1-C_4)-alkyl; (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, where aryl is unsubstituted or substituted by a residue R(17);

R(9) is



R(10) is



;

R(17) is -C(=N-R(18))-N(R(19))$_2$;

R(18) is hydrogen, hydroxy, or an amino protective group;

R(19) is hydrogen, (C_1-C_4)-alkyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl, or an amino protective group ;

R(20) is N(R(19))$_2$;

R(21) is hydroxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxy, (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonylamino, carboxyl, or R(20);

R(22) is hydrogen or (C_1-C_4)-alkyl;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts;

8. Compounds of the formula I as claimed in claim 7, wherein

R(1) is hydrogen, (C_1-C_4)-alkyl, allyl, phenyl, benzyl, or 4-carbamimidoyl-benzyl;

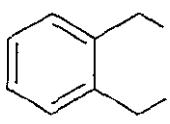
R(2) is hydrogen or (C_1-C_4)-alkyl;

R(3) is phenyl or 2-naphthyl which are substituted by R(7);

R(4) is hydrogen or methyl;

R(5) is n-butyl, sec-butyl, tert-butyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 2-phenyl-ethyl, 1-naphthylmethyl, 2-naphthylmethyl, aminobenzyl, preferably 4-aminobenzyl, hydroxymethyl, benzyloxymethyl, carboxymethyl, 2-carboxy-ethyl, 3-amino-propyl, or 4-(benzyloxycarbonylamino)-butyl; or

R(4) and R(5) together form a residue of the formula II



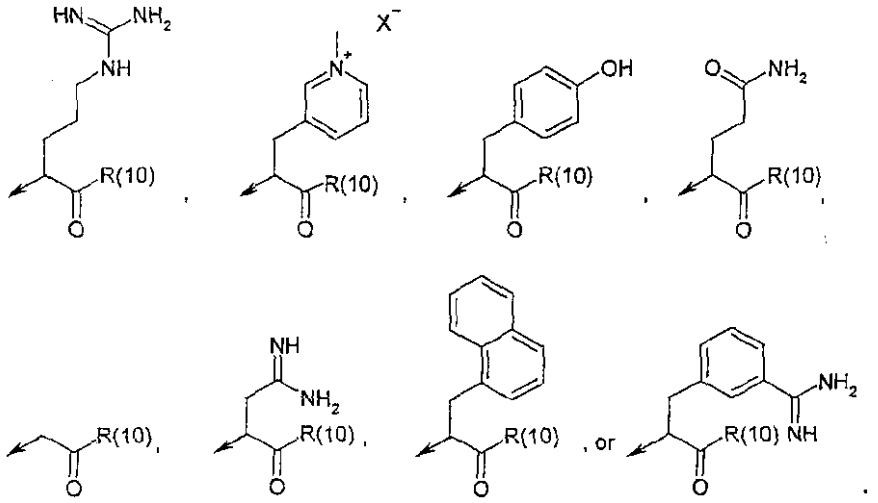
(II) ;

R(6) is NR(8)R(9), OH, or OCH_3;

R(7) is amidino, hydroxyamidino, amino, or dimethylamino;

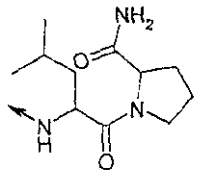
R(8) is hydrogen, pyridylmethyl, preferably 4-pyridylmethyl, 3-carbamimidoylbenzyl, or 4-amino-butyl;

R(9) is



;

R(10) is



;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

9. Compounds of the formula I as claimed in claim 7 and/or claim 8, wherein

R(1) is propyl or butyl;

R(2) is propyl or butyl;

R(3) is phenyl which is substituted by R(7);

R(4) is hydrogen;

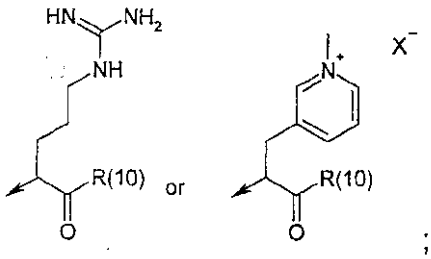
R(5) is cyclohexyl;

R(6) is NR(8)R(9);

R(7) is amidino, or amino;

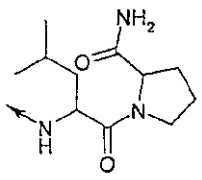
R(8) is hydrogen;

R(9) is



;

R(10) is



;

X^- is a physiologically acceptable anion;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their physiologically acceptable salts.

10. Compounds of the formula I as claimed in one or more of claims 7 to 9, which are 2-(4-Carbamimidoyl-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, less polar diastereomer;

3-{2-(S)-{2-(S)-[3-(4-Carbamimidoyl-phenyl)-2-diisopropylcarbamoyl-propionylamino]-2-cyclohexyl-acetylamino}-2-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-ethyl}-1- methyl-pyridinium trifluoro-acetate trifluoroacetic acid, less polar diastereomer,

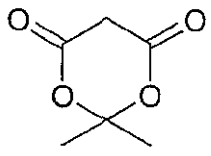
2-(4-Amino-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisopropyl-malonamide trifluoroacetic acid salt, less polar diastereomer,

2-(4-Carbamimidoyl-benzyl)-N-((S)-{1-(S)-[1-(S)-(2-(S)-carbamoyl-pyrrolidine-1-carbonyl)-3-methyl-butylcarbamoyl]-4-guanidino-butylcarbamoyl}-cyclohexyl-methyl)-N',N'-diisobutyl-malonamide trifluoroacetic acid salt, more polar diasteromer, and/or their physiologically acceptable salts.

11. Process for the preparation of a compound of formula I as claimed in one or more of claims 1 to 10, which comprises

i)

a1) alkylating a compound of the formula III



III

with a compound of the formula IV,

$$LG\text{-}CH_2\text{-}R(3a) \quad (IV)$$

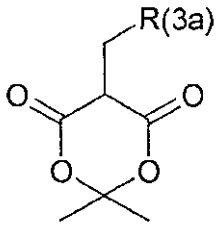
wherein LG is a leaving group and wherein

R(3a) is (C_6-C_{10})-aryl which is substituted by R(23);

R(23) is $N(R(24))_2$, nitro, or cyano;

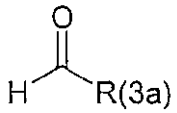
R(24) is (C_1-C_6)-alkyl, (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, (C_1-C_6)-alkylcarbonyl, or (C_1-C_6)-alkoxycarbonyl;

in the presence of a base to give a compound of the formula V,



V

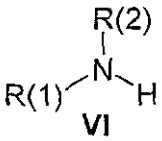
or reacting a compound of the formula III with a compound of the formula IVa,



IVa

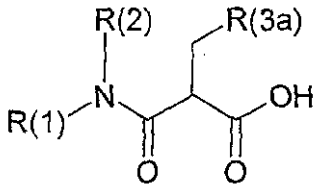
in the presence of a reducing agent to give a compound of the formula V;

b1) reacting a compound of the formula V with a compound of the formula VI,



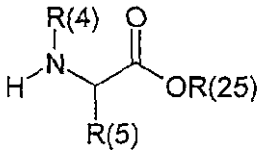
VI

wherein R(1) and R(2) are as claimed in one or more of claims 1 to 10, to give a compound of the formula VII;



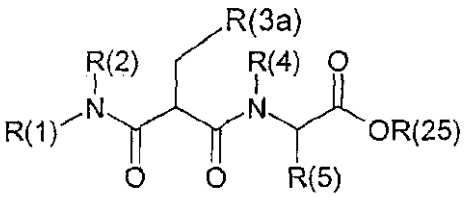
VII

c1) coupling of a compound of the formula VII with a compound of the formula VIII,



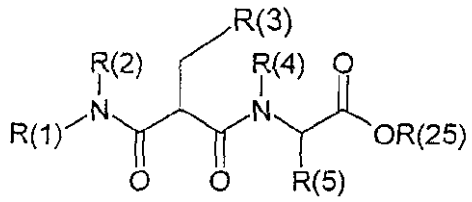
VIII

wherein R(4) and R(5) are as claimed in one or more of claims 1 to 10 and R(25) is an easily cleavable ester to yield a compound of the formula IX,



IX

d1) optionally introducing an amidino group or reduction of a nitro group, by converting a compound of the formula IX into a compound of the formula X,



X

wherein R(3) is as claimed in one or more of claims 1 to 10;

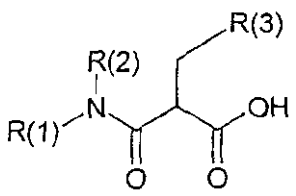
e1) saponification of the ester group R(25) and coupling the resulting compound XI according to step c1) with a compound of the formula XII

HR(6) **(XII)**

wherein R(6) is as claimed in one or more of claims 1 to 10 to give a compound of the formula I; or

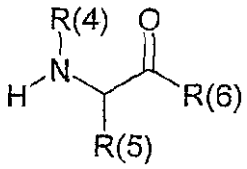
c2) protecting the carboxylfunction in a compound of the formula VII with an easily cleavable protecting group and introducing an amidino group or reduction of a nitro group according to step d1) to give after deprotection of the carboxylfunction a compound of the formula XIII; and

d2) coupling a compound of the formula XIII according to step c1)



XIII

with a compound of formula XVI;

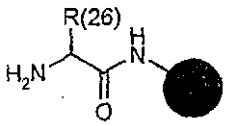


XVI

to give a compound of the formula I; or

ii)

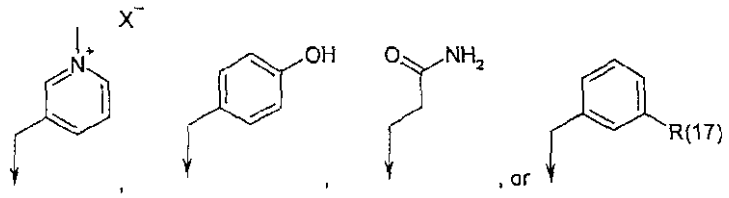
a) coupling a compound of the formula XVIII,



XVIII

which is bound to a suitable carrier, and wherein

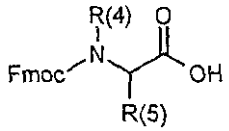
R(26) is hydrogen, $-CH_2-R(17)$, 1-naphthylmethyl, $-(CH_2)_3-NR(28)-C(=N-R(27))-NH-R(28)$



R(27) is R(28), cyano, hydroxy, (C_1-C_6)-alkoxy, (C_6-C_{14})-aryl-(C_1-C_6)-alkoxy which is unsubstituted or substituted in the aryl moiety, or amino;

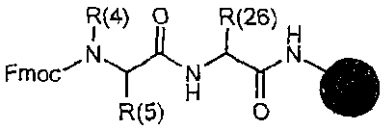
R(28) is hydrogen, (C_1-C_6)-alkyl, or (C_1-C_6)-alkylcarbonyl;
and R(17) is as claimed in one or more of claims 1 to 10;

with a compound of the formula XVII



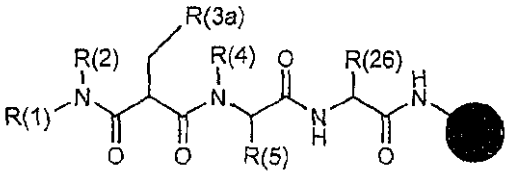
XVII

wherein R(4) and R(5) are as claimed in one or more of claims 1 to 10 to give a compound of the formula XIX

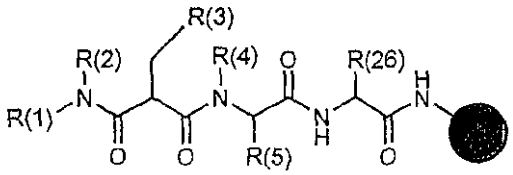


XIX

b) and after deprotecting a compound of the formula XIX with a base coupling the deprotected compound XX to a compound of the formula VII or XIII to give a compound of the formula XXI or XXII;



XXI



XXII

c) optionally converting a compound of the formula XXI to a compound of formula XXII

and d) cleaving a compound of the formula XXII off the resin

to give a compound of the formula I.

12. A pharmaceutical composition, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 10 and/or their physiologically acceptable salts together with a pharmaceutically acceptable carrier and/or auxiliary substances.

13. A compound of the formula I as claimed in one or more of claims 1 to10 and/or its physiologically acceptable salts, for use as a pharmaceutical.

14. A compound of the formula I as claimed in one or more of claims 1 to 10 and/or its physiologically acceptable salts, for use as an inhibitor of factor Xa.

15. A compound of the formula I as claimed in one or more of claims 1 to10 and/or its physiologically acceptable salts, for use as an inhibitor of blood clotting.

16. A compound of the formula I as claimed in one or more of claims 1 to 10 and/or its physiologically acceptable salts, for use in the treatment or prophylaxis of cardiovascular disorders or thromboembolic conditions.

17. A compound of the formula I as claimed in one or more of claims 1 to 10 and/or its physiologically acceptable salts, for use in the treatment or prevention of complications associated with infection or surgery.

18. A compound of the formula I as claimed in one or more of claims 1 to 10 and/or its physiologically acceptable salts, for the use as claimed in claim 16, where cardiovascular disorders are restenosis, restenosis following angioplasty, reocclusion prophylaxis, conditions after coronary bypass operations, arterial, venous and microcirculatory disease states, cardiac infarction, angina pectoris, thromboembolic diseases, thromboses, embolism, adult respiratory distress syndrome, multi-organ failure, stroke or disseminated intravascular coagulation clotting disorder.

19. A compound of the formula I as claimed in one or more of claims 1 to 10 and/or its physiologically acceptable salts, for the use as claimed in claim 17, where complications associated with surgery are deep vein and proximal vein thrombosis, which can occur following surgery.

INTERNATIONAL SEARCH REPORT

Inter Application No
PC[illegible] 01/01928

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D217/14 A61K31/40 A61K31/435 C07D207/08 C07K5/08
A61K38/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 40571 A (HOECHST MARION ROUSSEL DE GMBH) 13 July 2000 (2000-07-13) the whole document	1-19
P,X	EP 1 016 663 A (AVENTIS PHARMA GMBH) 5 July 2000 (2000-07-05) the whole document	1-19
X	WO 95 29189 A (SELECTIDE CORP) 2 November 1995 (1995-11-02) cited in the application * see RN 174132-09-3 * the whole document	1-19
Y	EP 0 075 896 A (WELLCOME FOUND) 6 April 1983 (1983-04-06) the whole document	1-19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 May 2001	06/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 05189 A (PENTAPHARM AG ;STUERZEBECHER JOERG (DE); VIEWEG HELMUT (DE); WIKST) 22 February 1996 (1996-02-22) the whole document	1-19
Y	WO 97 22712 A (HOECHST MARION ROUSSEL INC) 26 June 1997 (1997-06-26) the whole document	1-19
Y	WO 94 18185 A (PENTAPHARM AG ;STUERZEBECHER JOERG (DE); VIEWEG HELMUT (DE); WIKST) 18 August 1994 (1994-08-18) the whole document	1-19
Y	WO 92 08709 A (PENTAPHARM AG) 29 May 1992 (1992-05-29) the whole document	1-19
Y	WO 98 50420 A (AKZO NOBEL NV ;ADANG ANTON EGBERT PETER (NL)) 12 November 1998 (1998-11-12) the whole document	1-19
Y	BRADY S F ET AL: "AMIDE AND ASPIRE-KETO CARBONYL INHIBITORS OF THROMBIN BASED ON ARGININE AND LYSINE: SYNTHESIS, STABILITY AND BIOLOGICAL CHARACTERIZATION" BIOORGANIC & MEDICINAL CHEMISTRY,GB,ELSEVIER SCIENCE LTD, vol. 3, no. 8, 1995, pages 1063-1078, XP000569717 ISSN: 0968-0896 the whole document	1-19
Y	JONES D M ET AL: "THROMBIN INHIBITORS BASED ON KETONE DERIVATIVES OF ARGININE AND LYSINE" JOURNAL OF ENZYME INHIBITION,US,NEW YORK, NY, vol. 9, 1995, pages 43-60, XP000570641 the whole document	1-19
Y	VOIGT,B. ET AL.: "Synthese von N-alpha-(Arylsulfonyl)-4-amidino-phenylalanyl-prolinen und von N-alpha-(Arylsulfonylglycidyl)-4-amidino-phenylalanyl-prolinen und deren Prüfung als Inhibitoren von Serinproteinasen" PHARMAZIE, vol. 43, no. 6, 1988, pages 412-414, XP002107300 BERLIN the whole document	1-19

-/--

INTERNATIONAL SEARCH REPORT

Intern | Application No
PCT, .. 01/01928

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WILEY M R ET AL: "D-Phe-Pro-p-Amidinobenzylamine: a potent and highly selective thrombin inhibitor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 20, 22 October 1996 (1996-10-22), page 2387-2392 XP004135844 the whole document	1-19
Y	STÜRZEBECHER,J. ET AL.: "Structure-Activity Relationships of Inhibitors derived from 3-amidinophenylalanine" J.ENZYME INHIBITION, vol. 9, 1995, pages 87-99, XP002107301 the whole document	1-19

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0040571	A	13-07-2000	EP	1016663 A	05-07-2000
			AU	3043100 A	24-07-2000
EP 1016663	A	05-07-2000	AU	3043100 A	24-07-2000
			WO	0040571 A	13-07-2000
WO 9529189	A	02-11-1995	AU	707653 B	15-07-1999
			AU	2368395 A	16-11-1995
			CA	2186497 A	02-11-1995
			CN	1147261 A	09-04-1997
			CZ	9603140 A	14-05-1997
			EP	0758341 A	19-02-1997
			FI	964317 A	25-10-1996
			HU	76346 A	28-08-1997
			IL	113505 A	31-12-1999
			JP	10503477 T	31-03-1998
			LT	96151 A,B	26-05-1997
			LV	11740 A	20-04-1997
			LV	11740 B	20-12-1997
			NO	964553 A	27-12-1996
			NZ	284977 A	24-09-1998
			PL	317067 A	03-03-1997
			SI	9520044 A	31-10-1997
			SK	136696 A	07-05-1997
			US	5849510 A	15-12-1998
			ZA	9503361 A	12-01-1996
EP 0075896	A	06-04-1983	AT	18201 T	15-03-1986
			AU	8866882 A	31-03-1983
			DE	3269422 D	03-04-1986
			DK	425382 A	26-03-1983
			GB	2108118 A,B	11-05-1983
			JP	58077852 A	11-05-1983
			NZ	201998 A	08-11-1985
			US	4504492 A	12-03-1985
			ZA	8207000 A	30-05-1984
WO 9605189	A	22-02-1996	AU	3107795 A	07-03-1996
WO 9722712	A	26-06-1997	AU	717995 B	06-04-2000
			AU	1125197 A	14-07-1997
			BR	9612059 A	23-02-1999
			CA	2241210 A	26-06-1997
			CZ	9801956 A	13-01-1999
			EP	0868526 A	07-10-1998
			JP	2000501618 T	15-02-2000
			NO	982868 A	19-08-1998
			NZ	324159 A	29-07-1999
			PL	327314 A	07-12-1998
			SK	85598 A	02-12-1998
			TR	9801107 T	21-10-1998
			US	5766932 A	16-06-1998
WO 9418185	A	18-08-1994	AU	5878194 A	29-08-1994
			CA	2133761 A	18-08-1994
			CZ	9402459 A	18-10-1995
			EP	0635008 A	25-01-1995
			HU	68042 A	22-03-1995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9418185 A		JP 7509731 T	26-10-1995
		US 5607937 A	04-03-1997
WO 9208709 A	29-05-1992	AU 8868991 A	11-06-1992
		CA 2073776 A	16-05-1992
		EP 0511347 A	04-11-1992
		JP 5503300 T	03-06-1993
		US 5518735 A	21-05-1996
WO 9850420 A	12-11-1998	AU 729910 B	15-02-2001
		AU 7652098 A	27-11-1998
		BR 9809342 A	04-07-2000
		CN 1254345 T	24-05-2000
		EP 0979240 A	16-02-2000
		HU 0002942 A	29-01-2001
		NO 995316 A	01-11-1999
		PL 336589 A	03-07-2000
		TR 9902692 T	21-07-2000
		ZA 9803629 A	04-11-1998

[19] 中华人民共和国国家知识产权局

IHC021043

[51] Int. Cl⁷
C07D217/14
A61K 31/40 A61K 31/435
C07D207/08 C07K 5/08
A61K 31/06

[12] 发明专利申请公开说明书

[21] 申请号 01805589.3

[43] 公开日 2003 年 3 月 26 日

[11] 公开号 CN 1406226A

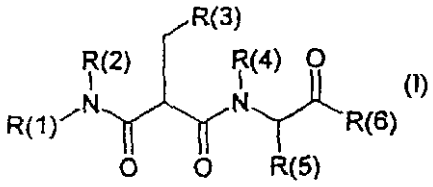
[22] 申请日 2001.2.21 [21] 申请号 01805589.3
[30] 优先权
[32] 2000. 2.26 [33] EP [31] 00104041.9
[86] 国际申请 PCT/EP01/01928 2001.2.21
[87] 国际公布 WO01/62735 英 2001.8.30
[85] 进入国家阶段日期 2002.8.23
[71] 申请人 阿文蒂斯药物德国有限公司
地址 德国法兰克福
[72] 发明人 F·阿尔－欧拜迪 A·沃瑟尔
P·维尔德谷斯
[74] 专利代理机构 中国国际贸易促进委员会专利商标事务所
代理人 李华英

权利要求书 20 页 说明书 75 页

[54] 发明名称 新型丙二酸衍生物，它们的制备方法，它们作为因子 XA 活性的抑制剂的用途和含有它们的药物组合物

[57] 摘要

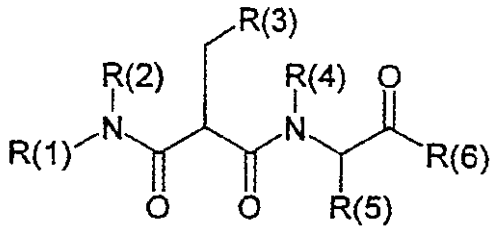
本发明涉及用于血液凝固蛋白质的抑制用的新化合物，更特别地涉及通式(I)的丙二酸衍生物，其中 R(1)，R(2)，R(3)，R(4)，R(5)和 R(6)具有在权利要求中指定的意义。通式(I)的化合物是血液凝固酶因子 Xa 的抑制剂。本发明还涉及制备通式(I)化合物的方法，抑制因子 Xa 活性和抑制血液凝固的方法，通式(I)化合物在能够通过因子 Xa 活性的抑制加以治疗或预防的疾病如血栓栓塞性疾病的治疗和预防中的用途，涉及通式(I)化合物在用于此类疾病的药剂的制备中的使用。本发明进一步涉及含有通式(I)的化合物和一起混合或结合的惰性载体的组合物，尤其是含有通式(I)的化合物和可药用的载体物质和助剂物质的药物组合物。



ISSN1008-4274

知识产权出版社出版

1.通式I的化合物，



(I)

其中

R(1)是氢，(C_1-C_6)-烷基，(C_2-C_6)-链烯基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被R(17)取代；

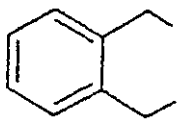
R(2)是氢或(C_1-C_4)-烷基；

R(3)是可被R(7)取代的(C_6-C_{10})-芳基；

R(4)是氢或(C_1-C_4)-烷基；

R(5)是(C_1-C_6)-烷基，(C_3-C_7)-环烷基，(C_3-C_7)-环烷基-(C_1-C_4)-烷基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被残基R(20)取代，和其中烷基是未被取代的或被残基R(21)取代；或

R(4)和R(5)一起形成通式II的残基



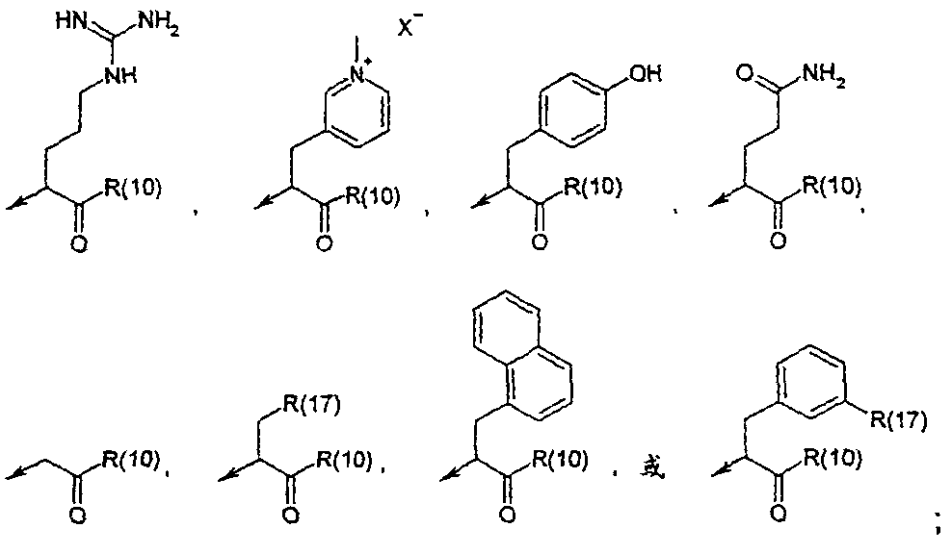
(II)；

R(6)是NR(8)R(9)或OR(22)；

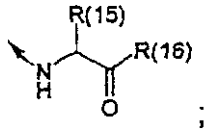
R(7)是R(17)或R(20)；

R(8)是氢；(C_1-C_4)-烷基，其中烷基是未被取代的或被残基R(20)取代；杂芳基-(C_1-C_4)-烷基；(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中芳基是未被取代的或被残基R(17)取代；

R(9)是(C_6-C_{10})-芳基(C_1-C_4)-烷基，



R(10)是NR(12)R(13)，OR(14)，或



R(12)是氢或(C_1-C_4)-烷基；

R(13)是氢，(C_6-C_{10})-芳基(C_1-C_4)-烷基，或(C_1-C_4)-烷基；

R(14)是氢，(C_1-C_4)-烷基，(C_2-C_4)-链烯基或(C_6-C_{10})-芳基(C_1-C_4)-烷基；

R(15)是(C_3-C_7)-环烷基-(C_1-C_4)-烷基；

R(16)是R(20)；

R(17)是$-C(=N-R(18))-N(R(19))_2$；

R(18)是氢，羟基，或氨基保护基；

R(19)是氢，(C_1-C_4)-烷基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基，或氨基保护基；

R(20)是$N(R(19))_2$；

R(21)是羟基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基氨基，羧基，或R(20)；

R(22)是氢或(C_1-C_4)-烷基；

X^-是生理学上可接受的阴离子；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

2.根据权利要求1所要求的通式I的化合物，其中

R(1)是氢，(C_1-C_4)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基-苄基;

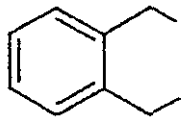
R(2)是氢或(C_1-C_4)-烷基;

R(3)是苯基或萘基，它可被R(7)取代;

R(4)是氢或甲基;

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，羟甲基，苄基氧基甲基，羧甲基，2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



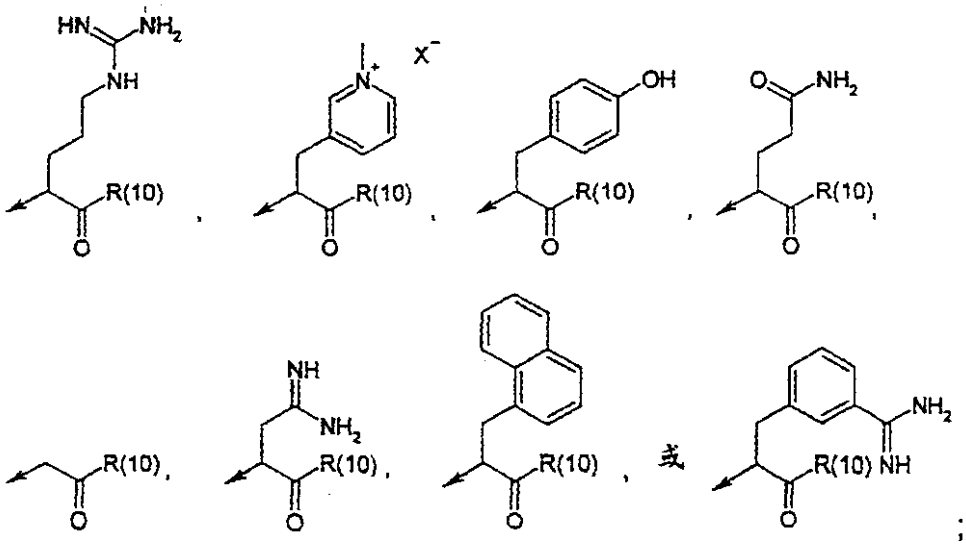
(II);

R(6)是NR(8)R(9)，OH，或OCH_3;

R(7)是脒基，羟基脒基，氨基，或二甲基氨基;

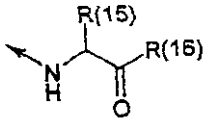
R(8)是氢，吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基;

R(9)是萘基甲基，



;

R(10)是NR(12)R(13)，OR(14)或



；

R(12)是氢或甲基；

R(13)是氢，苯基-(C_1-C_2)-烷基，或甲基；

R(14)是氢，(C_1-C_2)-烷基，苄基或烯丙基；

R(15)是环己基甲基；

R(16)是氨基；

X^-是生理上可接受的阴离子；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

3.根据权利要求1和/或权利要求2的通式I的化合物，其中

R(1)是氢；(C_1-C_3)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基-苄基；

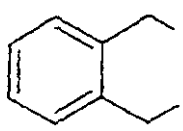
R(2)是氢或(C_1-C_3)-烷基；

R(3)是苯基或2-萘基，它们被R(7)取代；

R(4)是氢或甲基；

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，4-氨基苄基，羟甲基，苄基氧基甲基，羧甲基，2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



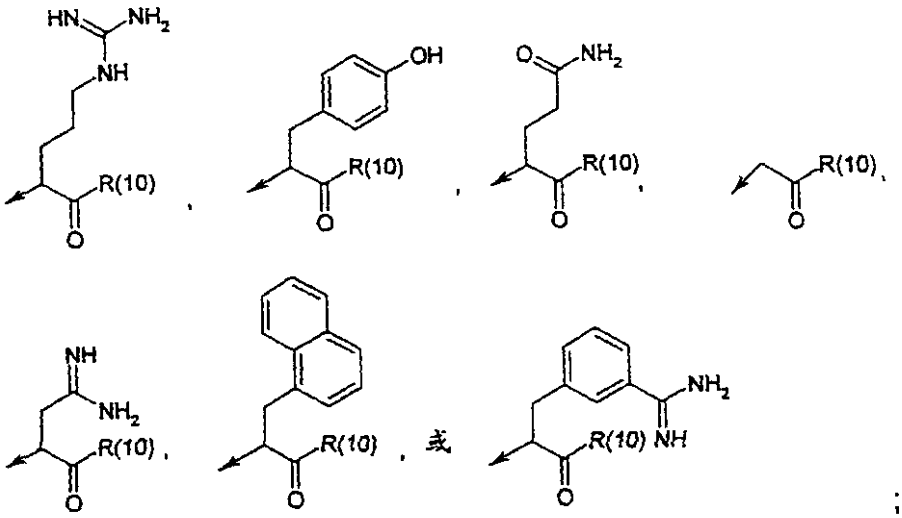
(II)；

R(6)是NR(8)R(9)，OH，或OCH_3；

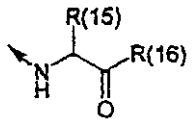
R(7)是脒基，羟基脒基，或二甲基氨基；

R(8)是氢，吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基；

R(9)是萘基甲基，



R(10)是NR(12)R(13)，OR(14)，或



R(12)是氢或甲基；

R(13)是氢，苯基-(C_1-C_2)-烷基，或甲基；

R(14)是氢，(C_1-C_2)-烷基，苄基或烯丙基；

R(15)是环己基甲基；

R(16)是氨基；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

4.根据权利要求1－3中一项或多项所要求的通式I的化合物，其中

R(1)是氢，(C_1-C_3)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基-苄基；

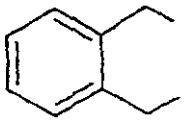
R(2)是氢或(C_1-C_3)-烷基；

R(3)是苯基或萘基，它可被R(7)取代；

R(4)是氢或甲基；

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，羟甲基，苄基氧基甲基，羧甲基，2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



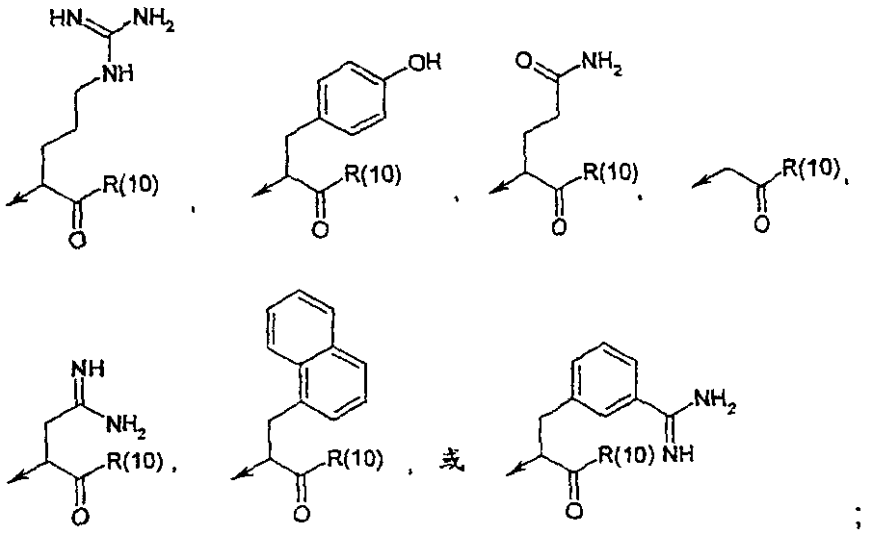
(II)；

R(6)是NR(8)R(9)，OH，或OCH_3；

R(7)是脒基，羟基脒基，或二甲基氨基；

R(8)是氢，吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基；

R(9)是萘基甲基，优选1-萘基甲基，



；

R(10)是NR(12)R(13)，或OR(14)；

R(12)是氢或甲基；

R(13)是氢，苯基-(C_1-C_2)-烷基，或甲基；

R(14)是氢，(C_1-C_2)-烷基，苄基或烯丙基；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

5.根据权利要求1－4中一项或多项的通式I的化合物，其中

R(1)是甲基，烯丙基，苯基，或苄基；

R(2)是氢或甲基；

R(3)是可被R(7)取代的苯基；

R(4)是氢；

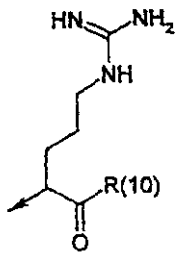
R(5)是丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，苄基氧基甲基，羧甲基，或2-羧基乙基；

R(6)是NR(8)R(9)；

R(7)是脒基或羟基脒基；

R(8)是氢；

R(9)是



；

R(10)是NR(12)R(13)，或OR(14)；

R(12)是氢或甲基；

R(13)是氢或苯基-(C_1-C_2)-烷基；

R(14)是氢，(C_1-C_2)-烷基，或烯丙基；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

6.根据权利要求1－5中一项或多项的通式I的化合物，它们是

2-(4-氨基氨代甲酰基-苄基)-N-[(1-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体，

2-(S)-(2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸烯丙基酯三氟乙酸盐，较少极性的非对映异构体，

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐，更极性的非对映异构体，

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐，较少极性的非对映异构体，

N-苄基-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-丙二酰胺三氟乙酸盐，

N-[2-(4-氨基-苯基)-1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐，

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N'-甲基-丙二酰胺三氟乙酸盐，

4-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-4-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁酸，

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-2-基-乙基)-N',N'-二甲基-丙二酰胺三氟乙酸盐，

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-3-苯基-丙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，

3-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-N-(1-(S)-氨基甲酰基-4-胍基-丁基)-琥珀酰胺酸三氟乙酸盐，

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-N'-甲基-丙二酰胺三氟乙酸盐，

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，

N-[2-苄氧基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,较少极性的非对映异构体,

2-(S)-(2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-己酰基氨基}-5-胍基-戊酸三氟乙酸盐,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸与三氟醋酸三氟乙酸盐和解,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸三氟乙酸盐,

2-(S)-{2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸三氟乙酸盐,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-丙酰基氨基}-5-胍基-戊酸三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,较少极性的非对映异构体,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-1-基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基)-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N'-甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-环己基-乙基]-N',N'-二甲基-丙二酰胺三氟

乙酸盐，

N-苄基-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-丙二酰胺三氟乙酸盐，较少极性的非对映异构体，

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸乙酯盐酸盐，

2-(S)-{2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸乙基三氟乙酸盐，较少极性的非对映异构体，

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-环己基-(4-胍基-1-(S)-苯乙基氨基甲酰基-丁基氨基甲酰基)-甲基]-N',N'-二甲基-丙二酰胺盐酸盐，

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐，更极性的非对映异构体，

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐，较少极性的非对映异构体，

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N-甲基-丙二酰胺三氟乙酸盐，

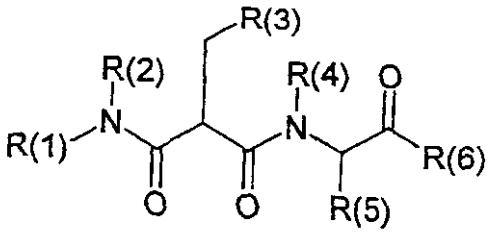
2-(S)-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸盐酸盐，

2-(S)-{2-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸甲酯三氟乙酸盐，最少极性的非对映异构体，

N-苄基-N'-{[1-(S)-(苄基-甲基-氨基甲酰基)-4-胍基-丁基氨基甲酰基]-环己基-甲基}-2-(4-氨基氨代甲酰基-苄基)-N-甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体，

和/或它们的生理上可接受的盐。

7.通式I的化合物，



(I)

其中

R(1)是氢，(C_1-C_6)-烷基，(C_2-C_6)-链烯基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被R(17)取代；

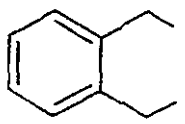
R(2)是氢或(C_1-C_4)-烷基；

R(3)是可被R(7)取代的(C_6-C_{10})-芳基；

R(4)是氢或(C_1-C_4)-烷基；

R(5)是(C_1-C_6)-烷基，(C_3-C_7)-环烷基，(C_3-C_7)-环烷基-(C_1-C_4)-烷基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被残基R(20)取代，和其中烷基是未被取代的或被残基R(21)取代；或

R(4)和R(5)一起形成通式II的残基



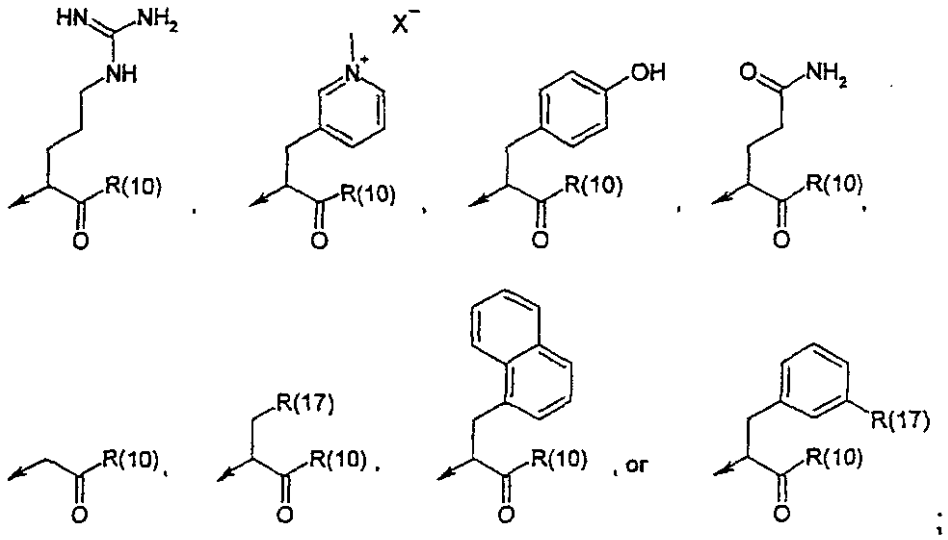
(II)；

R(6)是NR(8)R(9)或OR(22)；

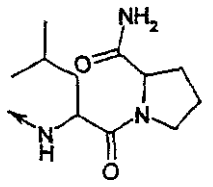
R(7)是R(17)或R(20)；

R(8)是氢；(C_1-C_4)-烷基，其中烷基是未被取代的或被残基R(20)取代；杂芳基-(C_1-C_4)-烷基；(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中芳基是未被取代的或被残基R(17)取代；

R(9)是



R(10)是



R(17)是-C(=N-R(18))-N(R(19))$_2$;

R(18)是氢，羟基，或氨基保护基;

R(19)是氢，(C_1-C_4)-烷基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基，或氨基保护基;

R(20)是N(R(19))$_2$;

R(21)是羟基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基氨基，羧基，或R(20);

R(22)是氢或(C_1-C_4)-烷基;

X^-是生理上可接受的阴离子;

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

8.根据权利要求7所要求的通式I的化合物，其中

R(1)是氢，(C_1-C_4)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基-苄基;

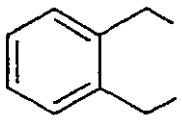
R(2)是氢或(C_1-C_4)-烷基;

R(3)是苯基或2-萘基，它们被R(7)取代;

R(4)是氢或甲基;

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，优选4-氨基苄基，羟甲基，苄基氧基甲基，羧甲基，2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



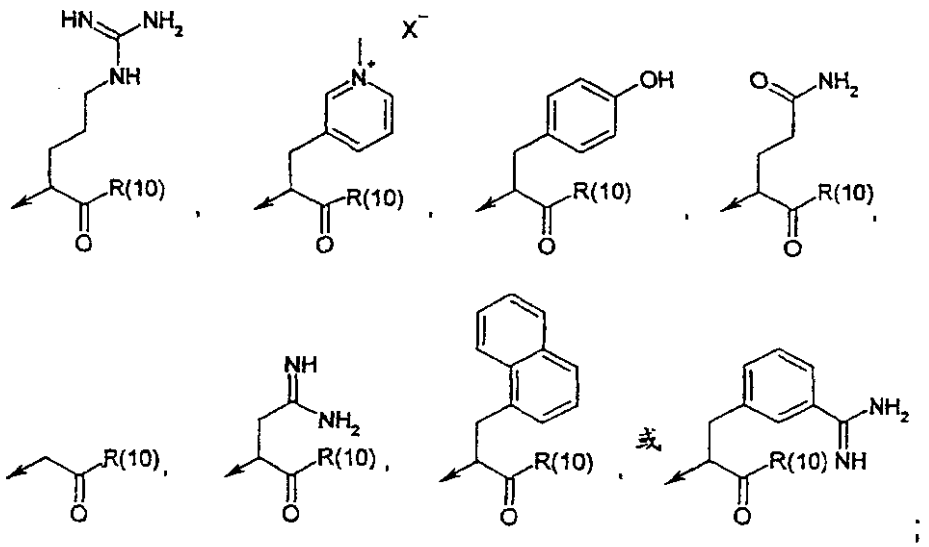
(II)；

R(6)是NR(8)R(9)，OH，或OCH_3;

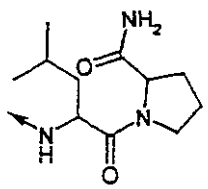
R(7)是脒基，羟基脒基，氨基，或二甲基氨基;

R(8)是氢，吡啶基甲基，优选4-吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基;

R(9)是



R(10)是



;

X^-是生理上可接受的阴离子;

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

9.根据权利要求7和/或权利要求8中所要求的通式I的化合物，其中

R(1)是丙基或丁基;

R(2)是丙基或丁基;

R(3)是被R(7)取代的苯基;

R(4)是氢;

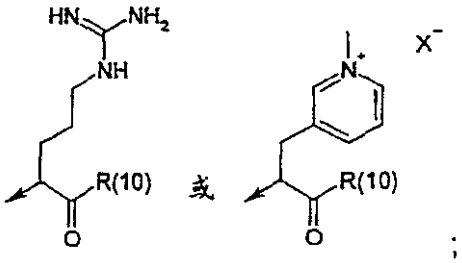
R(5)是环己基;

R(6)是 NR(8)R(9);

R(7)是脒基，或氨基;

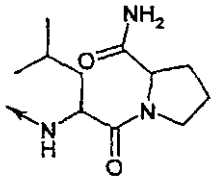
R(8)是氢;

R(9)是



;

R(10)是



;

X^-是生理上可接受的阴离子;

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

10.根据权利要求7－9中一项或多项的通式I的化合物，它们是

2-(4-氨基氨代甲酰基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-胍基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体;

3-{2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二异丙基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-2-[1-(S)-(2-(S)-氨甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-乙基}-1-甲基-吡啶盐三氟-乙酸盐三氟乙酸，较少极性的非对映异构体，

2-(4-氨基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-胍基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体

2-(4-氨基氨代甲酰基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-胍基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丁基-丙二酰胺三氟乙酸盐，更极性的非对映异构体，

和/或它们的生理上可接受的盐。

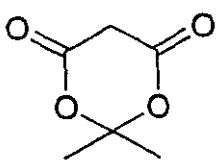
11.根据权利要求1－10中一项或多项所要求的通式I的化合物的制备方法，它包括

i)

a1)用通式IV的化合物

$LG-CH_2-R(3a)$ (IV)

将通式III的化合物在碱存在下加以烷基化



III

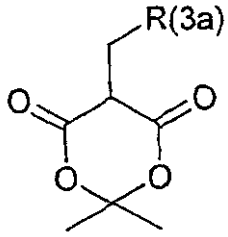
其中LG是离去基团和其中

R(3a)是(C_6-C_{10})-芳基，它可被R(23)取代;

R(23)是$N(R(24))_2$，硝基，或氰基;

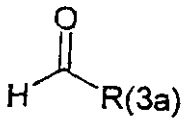
R(24)是(C_1-C_6)-烷基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，(C_1-C_6)-烷基羰基，或(C_1-C_6)-烷氧基羰基;

得到通式V的化合物，



V

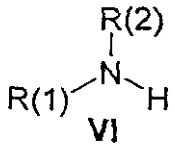
或让通式III的化合物与通式IVa的化合物在还原剂存在下反应，



IVa

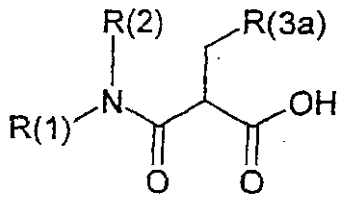
得到通式V的化合物;

b1)让通式V的化合物与通式VI的化合物反应，



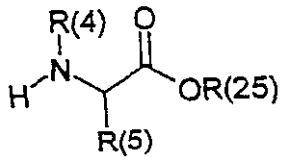
VI

其中R(1)和R(2)是根据权利要求1-10中一项或多项所要求，得到通式VII的化合物;



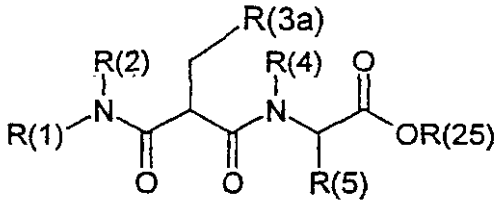
VII

c1)通式VII的化合物与通式VIII的化合物偶合，



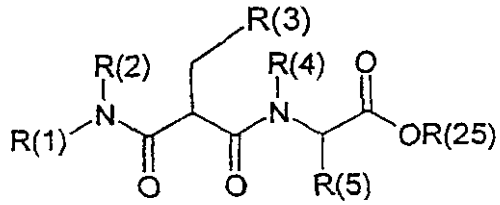
VIII

其中R(4)和R(5)是根据权利要求1－10中一项或多项所要求和R(25)是容易分裂的酯，得到通式IX的化合物，



IX

d1)任选引入脒基或通过将通式IX的化合物转化成通式X的化合物来使硝基还原，



X

其中R(3)是根据权利要求1－10中一项或多项所要求；

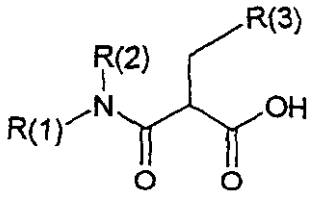
e1)酯基R(25)的皂化和根据步骤c1)的所获得化合物与通式XII的化合物偶合

HR(6)(XII)

其中R(6)是根据权利要求1－10中一项或多项所要求，得到通式I的化合物；或

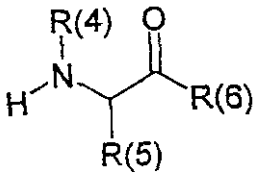
c2)用容易分裂的保护基保护在通式VII化合物中的羧基官能团和引入脒基或根据步骤d1)的硝基的还原使得在羧基官能团的去保护之后得到了通式XIII的化合物；和

d2)让根据步骤c1)的通式XIII的化合物



XIII

与通式XVI的化合物偶合;

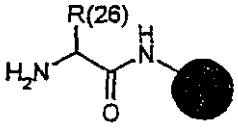


XVI

得到通式I的化合物; 或

ii)

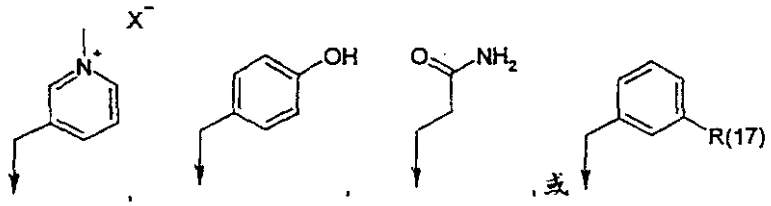
a)让通式XVIII的化合物,



XVIII

它结合于合适的载体上, 和其中

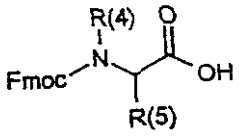
R(26) 是 氢 , $-CH_2-R(17)$, 1- 萘 基 甲 基 , $-(CH_2)_3-NR(28)-C(=N-R(27))-NH-R(28)$



R(27)是R(28), 氰基, 羟基, (C_1-C_6)-烷氧基, (C_6-C_{14})-芳基(C_1-C_6)-烷氧基, 它在芳基结构部分中未被取代或被取代, 或氨基;

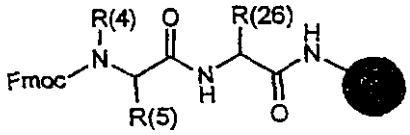
R(28)是氢, (C_1-C_6)-烷基, 或(C_1-C_6)-烷基羰基; 而R(17)是根据权利要求1-10中一项或多项所要求;

与通式XVII的化合物偶合



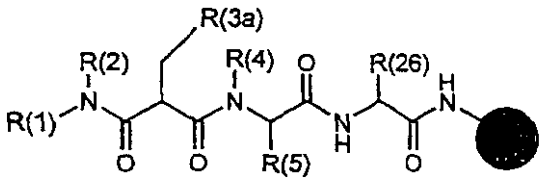
XVII

其中R(4)和R(5)是根据权利要求1－10中一项或多项所要求，得到通式XIX的化合物

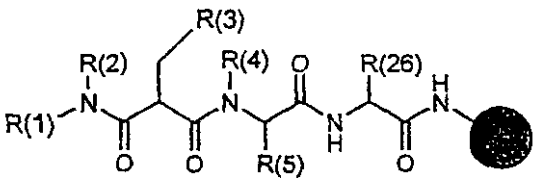


XIX

b)以及在用碱使通式XIX的化合物去保护之后让去保护的化合物XX偶合到通式VII或XIII的化合物上，得到通式XXI或XXII的化合物；



XXI



XXII

c)任选将通式 XXI 的化合物转化成通式 XXII 的化合物，

和d)将通式XXII的化合物从树脂上分裂，得到通式I的化合物。

12. 药物组合物，它包括根据权利要求1－10中一项或多项所要求的通式I的一种或多种化合物和/或它们的生理上可接受的盐与可药用的载体和/或助剂物质。

13. 根据权利要求1－10中一项或多项所要求的通式I的化合物和/或它的生理上可接受的盐，用作药物。

14. 根据权利要求1－10中一项或多项所要求的通式I的化合物和/或它的生理上可接受的盐，用作因子Xa的抑制剂。

15. 根据权利要求1－10中一项或多项所要求的通式I的化合物和/

或它的生理上可接受的盐，用作血液凝固的抑制剂。

16. 根据权利要求1－10中一项或多项所要求的通式I的化合物和/或它的生理上可接受的盐，用于心血管疾病或血栓病症的治疗或预防。

17. 根据权利要求1－10中一项或多项所要求的通式I的化合物和/或它的生理上可接受的盐，用于与感染或外科手术有关的并发症的治疗或预防。

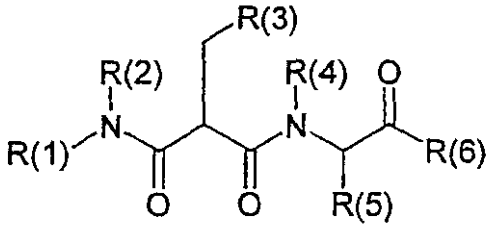
18. 根据权利要求16中所要求的根据根据权利要求1－10中一项或多项所要求的通式I的化合物和/或它的生理上可接受的盐的用途，其中心血管疾病是再狭窄，血管成形术之后的再狭窄，再闭塞预防，冠状动脉旁路手术之后的不良症状，动脉、静脉和微循环疾病，心肌梗塞，心绞痛，血栓栓塞性疾病，形成血栓，栓塞，成人呼吸窘迫综合征，多器官衰竭，中风或弥漫性血管内凝血凝固病症。

19. 根据权利要求 17 所要求的根据权利要求 1－10 中一项或多项所要求的通式 I 的化合物和/或它的生理上可接受的盐的用途，其中与外科手术有关的并发症是在外科手术之后发生的深血管和近侧血管血栓形成。

新型丙二酸衍生物，它们的制备方法，它们作为因子XA活性的抑制剂的用途和含有它们的药物组合物

新型丙二酸衍生物，它们的制备方法，它们的用途和含有它们的药物组合物。

本发明涉及通式I的化合物，



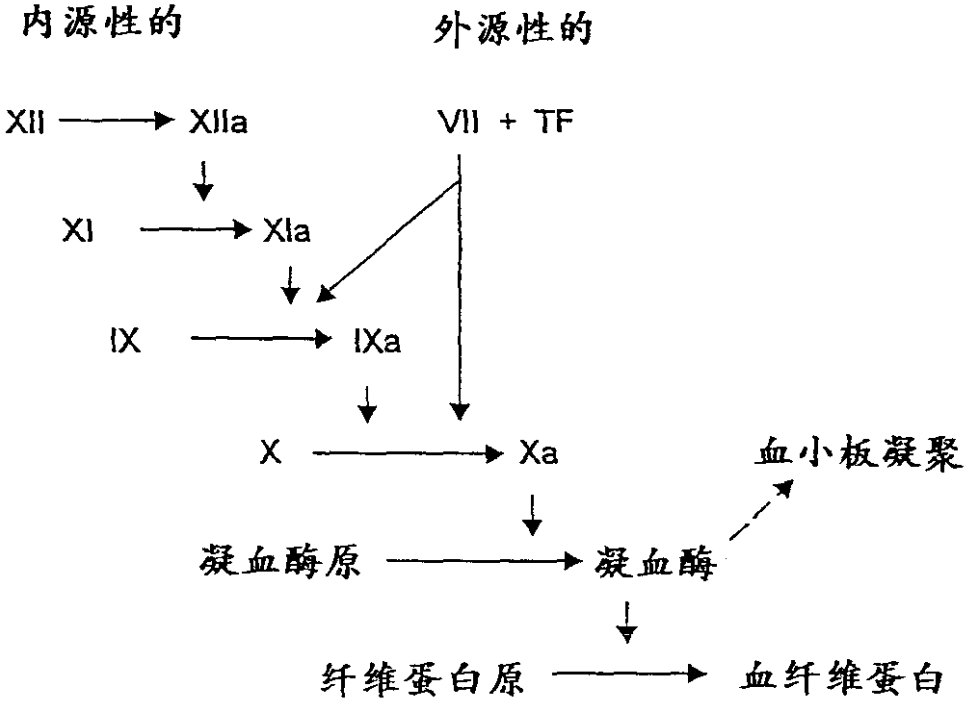
(I)

其中R(1)，R(2)，R(3)，R(4)，R(5)，和R(6)具有下面指定的意义。通式I的化合物是有价值的药理活性化合物。它们显示出强烈的抗血栓形成效果和适合于象血栓栓塞性疾病或再狭窄之类的心血管病症的治疗和预防。它们是血液凝固酶因子Xa的可逆抑制剂，并且一般在存在着所不希望的因子Xa的活性或为了治愈或防止它而需要因子Xa的抑制的情况下来使用。本发明还涉及制备通式I化合物的方法，抑制因子Xa活性和抑制血液凝固的方法，通式I化合物在能够通过因子Xa活性的抑制加以治疗或预防的疾病如血栓栓塞性疾病的治疗和预防中的用途，和涉及通式I化合物在用于此类疾病的药剂的制备中的使用。本发明进一步涉及含有通式I的化合物和一起混合或结合的惰性载体的组合物，尤其是含有通式I的化合物和可药用的载体物质和助剂物质的药物组合物。

形成血凝块的能力是为了生存所不可缺少的。然而，在某些疾病状态下，在循环系统中血凝块的形成达到了所不希望的程度并且本身

是潜在地导致病理性后果的发病的原因。但仍然不希望在此类疾病状态下完全地抑制该凝固系统，因为危急生命的出血也跟着发生。在此类病症的治疗中，在血液凝固系统中需要介入良好的平衡，而且仍然需要显示出合适的药理活性谱以获得这样的结果的物质。

血液凝固是牵涉到逐渐放大系列的酶活化反应的复杂过程，其中血浆酶原顺序地通过有限的蛋白水解来活化。血液凝固级联可以机械地分成内源性的和外源性的途径，它们在凝血因子X的活化时聚合。凝血酶的后续产生通过单个通常的途径来进行(参见反应历程1)。



反应历程1: 血液凝固级联AVE D-2000/A012

给出的证据提示了内源性的途径在血纤维蛋白形成的维持和生长中起重要作用，而外源性的途径是血液凝固的起始阶段中关键的。普遍接受的是，在组织因子(TF)/因子VIIa复合物的形成中自然引发血液凝固。一旦形成，这一复合物通过活化因子IX和X来快速地引发凝固。新产生的活化因子X，即因子Xa，然后与因子Va形成一对一的复合物和与磷脂类形成凝血酶原酶复合物，这利用凝血酶从它的前体凝血酶原的活化而将可溶性纤维蛋白原转化成不溶性血纤维蛋白。随着时间的

推移，因子VIIa/组织因子复合物的活性(外源性的途径)受到Kunitz型蛋白酶抑制剂蛋白质，即TFPI的抑制，后者当与因子Xa配合时能够直接抑制因子VIIa/组织因子的蛋白质分解活性。为了维持在受抑制的外部系统存在下该凝固过程，经过内源性的途径的凝血酶媒介的活性来产生附加的因子Xa。因此，凝血酶起着双重的自催化作用，同时媒介它本身的产生和纤维蛋白原转化成血纤维蛋白。

凝血酶产生的自催化性质是抵抗不受控制的出血的重要防范并确保，一旦存在给定的临界水平的凝血酶原酶，血液凝固将进行到完成，例如一直到出血的结束为止。因此，最希望开发一种试剂，它抑制凝固而不直接抑制凝血酶，但通过抑制在凝固多步级联中的其它步骤，象因子Xa。

在许多临床应用中，非常需要防止血管内血凝块或防血凝治疗。例如，几乎50%的作了总的髋关节置换术的患者将会发展成深静脉血栓形成(DVT)。目前获批准的治疗是固定剂量低分子量肝素(LMWH)和可变剂量肝素。甚至对于这些药物治疗方案，10%－20%的患者会发展DVT和5%－10%会发展出血并发症。

需要更好抗凝血剂的另一临床情况涉及进行经腔的冠状血管成形术的患者和在心肌梗塞或绞痛危急时的患者。由施用肝素和阿斯匹林组成的目前普遍接受的治疗与在24小时的程序中6%到8%的突发性血管闭合比率有关。由于肝素的使用而需要输液治疗的出血并发症的比率也是大约7%。而且，即使延迟的闭合是明显的，在该程序结束之后肝素的施用没有多大价值并且是有害的。

最广泛使用的血凝固抑制剂是肝素和相关的含硫酸的多糖，LMWH和硫酸肝素。这些分子通过促进凝固过程的自然调节剂(抗凝血酶III)结合于凝血酶和结合于因子Xa来发挥它们的抗凝固效果。肝素的抑制活性主要地针对凝血酶，它比因子Xa失活快了大约100倍。虽然与肝素有关，但是硫酸肝素和LMWH是比凝血酶多少更具效力的Xa抑制剂，活体外的差异是中等的(3-30倍)而活体内的效果是无价值的。水蛭素和水蛭肽是已在临床试验中试验的两种附加的为凝血酶特异的抗凝血

剂。然而，抑制凝血酶的这些抗凝血剂也与出血并发症有关。

在猕猴和狗体内的临床研究已揭示因子Xa的特异抑制剂可防止血凝固形成，但不产生对于直接的凝血酶抑制剂所观察到的出血副作用。

已经报道了因子Xa的几种特异性抑制剂。因子Xa的合成的和蛋白质抑制剂已经得到确认，这些包括，例如，安他心("ATS")和壁虱(tick)抗凝血剂肽("TAP")。从水蛭(Haementerin officinalis)分离出的ATS含有119个氨基酸和具有对于因子Xa的Ki为0.05nM。从壁虱(Ornithodoros moubata)分离的TAP含有60个氨基酸和具有对于因子Xa的Ki为大约0.5nM。

重组方法生产的ATS和TAP的效力已经在许多动物模型系统中进行了考察。与其它抗凝血剂相比，两种抑制剂都减少出血时间，并且在深静脉血栓形成的促凝血酶原激酶诱导的、结扎的颈静脉模型中防止血凝固。在这一模型中获得的结果与使用目前所选择的药物肝素所获得的结果有关。

皮下ATS也被发现是在弥漫性血管内凝血(DIC)的促凝血酶原激酶诱导的模型中的有效治疗。在产生活化部分凝血活酶时间(aPTT)的临床上可接受的延长(即低于大约两倍延长)的一种水平上，TAP有效地防止由聚酯("DACRON")移植的外科置换所引起的"高剪切"动脉血栓形成和"减少流动"。相比而言，标准肝素，甚至在引起aPTT的五倍增加的一些剂量下，不会在移植物内防止血栓形成和减少的流动。aPTT是对凝血酶抑制剂特别敏感的凝固临床试验。

ATS和TAP没有在临床上发展。这两种抑制剂的一个主要缺点是，所需要的重复多剂量的施用导致中和抗体的产生，因此限制了它们的有潜力的临床应用。而且，TAP和ATS的剂量使口服变得不可能，进一步限制了能够从这些药剂受益的患者数目。

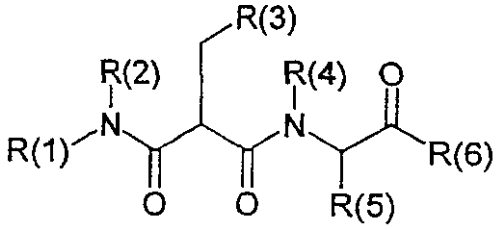
具有有用的性能谱的因子Xa的特异抑制剂能够在医药实践中具有显著的实用价值。尤其，在其中目前所选的药物肝素和相关硫酸多糖显得无效或仅仅轻微有效的情况下因子Xa抑制剂却是有效的。

有效的但不会引起所不希望有的副作用的低分子量、为因子Xa所

特异的血液凝固抑制剂例如描述在WO-A95/29189中。作为低分子量的、因子Xa特异的血液凝固抑制剂的吲哚衍生物已经描述在WO-A-99/33800中。然而，除了是有效的因子Xa特异性的血液凝固抑制剂外，希望该抑制剂还具有附加的药理学性质，例如良好的口服途径生物利用率，在血浆和肝脏中的高稳定性和/或对不希望受抑制的其它丝氨酸蛋白酶如凝血酶的高选择性。因此仍然需要有效的并且也具有以上优点的其它低分子量的因子Xa特异性的血液凝固抑制剂。是合适的因子Xa抑制剂的芳基链烷酰基和丙二酸衍生物已经在欧洲申请No.99100001，99100002，99119537和99119538中提示。

本发明还通过提供通式I的新型化合物来满足以上需要，该化合物显示出因子Xa抑制活性并且是抑制不希望有的血液凝固和血栓形成的理想药剂。

因此，本发明的主题是通式I的化合物，



(I)

其中

R(1)是氢，(C_1-C_6)-烷基，(C_2-C_6)-链烯基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被R(17)取代；

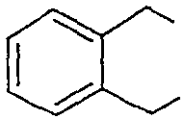
R(2)是氢或(C_1-C_4)-烷基；

R(3)是可被R(7)取代的(C_6-C_{10})-芳基；

R(4)是氢或(C_1-C_4)-烷基；

R(5)是(C_1-C_6)-烷基，(C_3-C_7)-环烷基，(C_3-C_7)-环烷基-(C_1-C_4)-烷基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被残基R(20)取代，和其中烷基是未被取代的或被残基R(21)取代；或

R(4)和R(5)一起形成通式II的残基



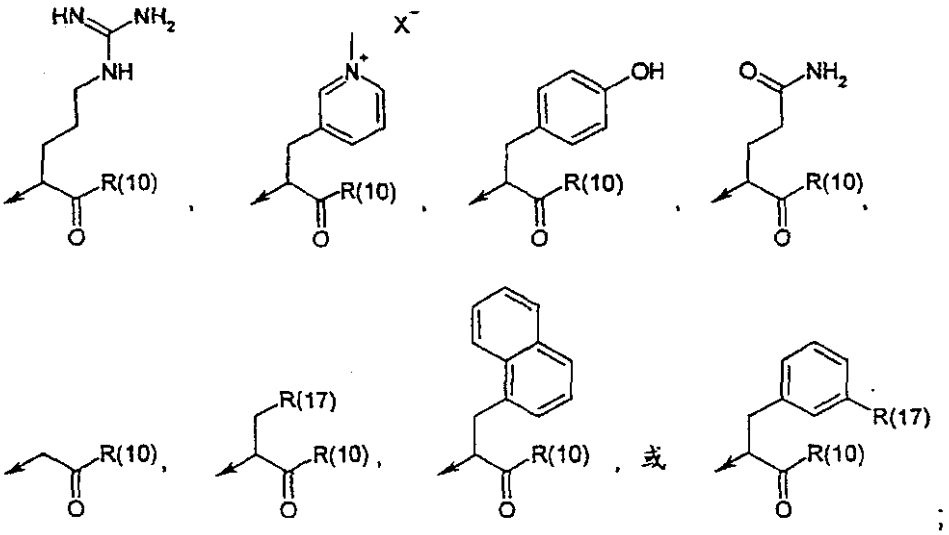
(II)；

R(6)是NR(8)R(9)或OR(22)；

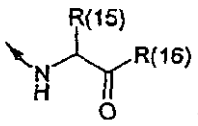
R(7)是R(17)或R(20)；

R(8)是氢；(C_1-C_4)-烷基，其中烷基是未被取代的或被残基R(20)取代；杂芳基-(C_1-C_4)-烷基；(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中芳基是未被取代的或被残基R(17)取代；

R(9)是(C_6-C_{10})-芳基(C_1-C_4)-烷基，



R(10)是NR(12)R(13)，OR(14)，或



；

R(12)是氢或(C_1-C_4)-烷基；

R(13)是氢，(C_6-C_{10})-芳基(C_1-C_4)-烷基，或(C_1-C_4)-烷基；

R(14)是氢，(C_1-C_4)-烷基，(C_2-C_4)-链烯基或(C_6-C_{10})-芳基(C_1-C_4)-

烷基;

R(15)是(C_3-C_7)-环烷基-(C_1-C_4)-烷基;

R(16)是R(20);

R(17)是-C(=N-R(18))-$N(R(19))_2$;

R(18)是氢，羟基，或氨基保护基;

R(19)是氢，(C_1-C_4)-烷基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基，或氨基保护基;

R(20)是$N(R(19))_2$;

R(21)是羟基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基氨基，羧基，或R(20);

R(22)是氢或(C_1-C_4)-烷基;

X^-是生理学上可接受的阴离子;

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

在通式I的化合物中的烷基残基能够是饱和的或不饱和的(因此覆盖了链烯基或炔基残基)和直链或支链的。这在它们携带取代基或作为取代基在其它残基中(例如在烷氧基残基，芳基烷氧基残基，烷氧基羰基残基，环烷基-烷基残基，芳基烷基残基，杂芳基烷基残基，和芳基烷氧基羰基残基中)出现时也适用。饱和的烷基残基的例子是甲基，乙基，正丙基，正丁基，异丙基，异丁基，仲丁基，和叔丁基，正戊基，正己基，异戊基，异己基，新戊基，3-甲基戊基，和叔戊基，不饱和烷基残基的例子是乙烯基，1-丙烯基，2-丙烯基(即烯丙基)，丁烯基，3-甲基-2-丁烯基，戊烯基，己烯基，(链烯基残基)或乙炔基，1-丙炔基，2-丙炔基(即炔丙基)，丁炔基，戊炔基和己炔基(炔基残基)。

在通式I化合物中存在的环烷基残基能够是单-，二-或三环的并且在环中相连。这在它们作为取代基在其它残基中存在时也适用。环烷基残基的例子是环丙基，甲基-环丙基，乙基-环丙基，二甲基-环丙基，丙基环丙基，甲基-乙基-环丙基，丁基-环丙基，甲基-丙基环丙基，

二乙基-环丙基，环丁基，甲基-环丁基，乙基-环丁基，环戊基，甲基-环戊基，乙基-环戊基，二甲基-环戊基，环己基，甲基-环己基，和环庚基，其中乙基，丙基，和丁基，能够是直链或支链的，如上所述。

芳基的例子是苯基或萘基。

在通式I化合物中存在的芳基烷基残基能够由烷基残基组成，它能够含有1－3个芳基结构部分。芳基烷基残基的例子是苯基-甲基，苯基-乙基，苯基-丙基，苯基-丁基，萘基-甲基，萘基-乙基，萘基-丙基，萘基-丁基，二苯甲基，二苯基-乙基，二苯基-丙基，二苯基-丁基，萘基-苯基-甲基，萘基-苯基-丁基，二萘基-丁基，和三苯基-乙基。

杂芳基残基的例子是吡啶基，哒嗪基，嘧啶基，吡嗪基，呋喃基，吡咯基，咪唑基，1H-吡唑基，噻唑基，噁唑基，苯硫基，1H-苯并咪唑基，苯并噻唑基，苯并呋喃基，吲哚基，噻吩并[3,2-c]吡啶基，噻吩并[2,3-c]吡啶基，呋喃并[3,2-c]吡啶基，呋喃并[2,3-c]吡啶基，3H-咪唑并[4,5-c]吡啶基，[1,2,4]噁二唑基，喹啉基，和异喹啉基。该残基能够在每一可能的位置上键接。

吡啶基残基的例子是2-吡啶基，3-吡啶基和4-吡啶基。这也适用于其中氮原子被烷基等取代的吡啶基残基，这一取代导致形成带正电的吡啶鎓基团。这一吡啶鎓基团具有作为平衡离子的X^-。

在单取代的苯基残基中，该取代基能够处于2-位，3-位或4-位上。

萘基残基能够是1-萘基和2-萘基。在取代的萘基残基中，该取代基能够在任何位置上，即在单取代的1-萘基残基中处于2-，3-，4-，5-，6-，7-，或8-位上和在单取代的2-萘基残基中处于1-，3-，4-，5-，6-，7-，或8-位上。

在通式I化合物中的优选的(C_6-C_{10})-芳基(C_1-C_4)-烷基残基是苄基(苯基甲基)。

合适的氨基保护基是本技术领域中那些技术人员所已知的并包括例如通常用于肽合成的那些。在残基R(18)和R(19)中的合适的氨基保护基例如是下列残基:

(C_1-C_6)-烷基，(C_1-C_6)-烷基羰基，(C_1-C_6)-烷氧基羰基，(C_1-C_{18})-

烷基羰氧基-(C_1-C_6)-烷氧基羰基，任选取代的(C_6-C_{14})-芳基羰基，任选取代的(C_6-C_{14})-芳氧基羰基，(C_6-C_{14})-芳基(C_1-C_6)-烷氧基羰基，它们也可以在芳基结构部分中被取代；氰基，硝基，氨基，羟基，(C_1-C_6)-烷氧基，和(C_6-C_{14})-芳基(C_1-C_6)-烷氧基，它在芳基结构部分中未被取代或在芳基结构部分中例如被(C_1-C_4)-烷氧基(优选甲氧基)，氯，或(C_1-C_4)-烷基(优选甲基)取代。

(C_1-C_3)-烷基是指具有1，2或3个碳原子的烷基。

(C_1-C_4)-烷基是指具有1，2，3或4个碳原子的烷基。

(C_1-C_6)-烷基是指具有1，2，3，4，5或6个碳原子的烷基。

(C_2-C_4)-链烯基是指具有2，3或4个碳原子的链烯基。

(C_2-C_6)-链烯基是指具有2，3，4，5或6个碳原子的链烯基。

(C_6-C_{10})-芳基是指具有6，7，8，9或10个碳原子的芳基。

(C_6-C_{14})-芳基是指具有6，7，8，9，10，11，12，13或14个碳原子的芳基。

(C_1-C_4)-烷氧基是指具有1，2，3或4个碳原子的烷氧基。

(C_1-C_6)-烷氧基是指具有1，2，3，4，5或6个碳原子的烷氧基。

(C_1-C_6)-烷氧基羰基是指在烷氧基部分中具有1，2，3，4，5或6个碳原子的烷氧基羰基。

(C_1-C_6)-烷基羰基是指在烷基部分中具有1，2，3，4，5或6个碳原子的烷基羰基。

(C_6-C_{10})-芳基(C_1-C_4)-烷基是指在芳基部分中各自独立地具有6,7,8，9或10个碳原子和在烷基部分中具有1，2，3或4个碳原子的芳基-烷基。

(C_6-C_{14})-芳基(C_1-C_6)-烷氧基是指在芳基部分中各自独立地具有6,7,8,9,10,11,12,13或14个碳原子和在烷氧基部分中具有1，2，3，4，5或6个碳原子的芳基-烷氧基。(C_6-C_{10})-芳基(C_1-C_4)-烷氧基是指在芳基部分中各自独立地具有6，7，8，9或10个碳原子和在烷氧基部分中具有1，2，3或4个碳原子的芳基-烷氧基。

杂芳基-(C_1-C_4)-烷基是指在烷基部分中具有1，2，3或4个碳原子

的杂芳基-烷基。

(C_1-C_{18})-烷基羰氧基-(C_1-C_6)-烷氧基羰基是指在烷基部分中各自独立地具有1，2，3，4，5，6，7，8，9，10，11，12，13，14，15，16，17或18个碳原子和在烷氧基部分中具有1，2，3，4，5或6个碳原子的烷基羰氧基-烷氧基羰基。

(C_6-C_{14})-芳基羰基是指在芳基部分中具有6，7，8，9，10，11，12，13或14个碳原子的芳基羰基。

(C_6-C_{14})-芳氧基羰基是指在芳基部分中具有6，7，8，9，10，11，12，13或14个碳原子的芳氧基羰基。

(C_6-C_{14})-芳基(C_1-C_6)-烷氧基是指在芳基部分中各自独立地具有6，7，8，9，10，11，12，13或14个碳原子和在烷氧基部分中具有1，2，3，4，5或6个碳原子的芳基-烷氧基。

(C_6-C_{14})-芳基-(C_1-C_6)-烷氧基羰基是指在芳基部分中各自独立地具有6，7，8，9，10，11，12，13或14个碳原子和在烷氧基部分中具有1,2,3,4,5或6个碳原子的芳基-烷氧基羰基。(C_6-C_{10})-芳基-(C_1-C_4)-烷氧基羰基是指在芳基部分中各自独立地具有6，7，8，9或10个碳原子和在烷氧基羰基部分中具有1,2,3或4个碳原子的芳基-烷氧基羰基。

(C_3-C_7)-环烷基是指具有3，4，5，6或7个碳原子的环烷基。(C_3-C_7)-环烷基-(C_1-C_4)-烷基是指在环烷基部分中各自独立地具有3，4，5，6或7个碳原子和在烷基部分中具有1，2，3或4个碳原子的环烷基-烷基。

可以理解的是，这些残基能够在通式I化合物中存在一次以上，例如残基R(17)，R(18)，R(19)，R(20)和R(21)彼此独立并且能够相同或不同。

如果存在带正电荷的基团，则在通式I化合物中存在的生理上可接受的阴离子X^-能够是从合适的无机酸或有机羧酸类或磺酸衍生的阴离子。合适的酸是，尤其，可药用的或无毒的盐。此类酸的例子是下面作为酸的例子给出的那些，该酸能够与含有碱性基团的通式I化合物形成生理上可接受的盐。如果通式I的化合物含有阴离子X^-和同时作为在碱性基团上形成的酸加合盐存在，则阴离子X^-能够相同或不同，作为

由成盐引入的阴离子。本发明还覆盖了通式I化合物的盐(或内铵盐)。

通式I化合物的生理上可接受的盐是，尤其，可药用的或无毒的盐。此类盐是从例如含有酸基例如羧酸基团的通式I化合物形成的。此类盐的例子是，例如，含有碱金属或碱土金属(例如钠，钾，镁或钙)的阳离子或未被取代的铵阳离子或有机铵阳离子的盐，有机铵阳离子包括通过质子化作用从生理上可接受的有机胺例如甲胺、乙胺、三乙基胺、乙醇胺、三(2-羟乙基)胺或氨基酸获得的阳离子，或合适的季铵阳离子象，例如，四甲铵。

含有碱性基团例如氨基或脒基的通式I化合物能够与例如无机酸，有机羧酸和有机磺酸形成酸加合盐。此类酸的例子，它的阴离子能够在通式I化合物的生理上可接受的盐中存在，是盐酸，氢溴酸，硫酸，磷酸，乙酸，苯甲酸，草酸，丙二酸，琥珀酸，马来酸，富马酸，苹果酸，酒石酸，柠檬酸，甲磺酸，对甲苯磺酸或萘磺酸。

通式I化合物的生理上可接受的盐能够根据标准程序来制备，例如通过将通式I化合物与所需的碱，例如碱金属氢氧化物或碳酸盐或碳酸氢盐或胺，或与所需的酸在溶剂或稀释剂中混合。通式I化合物的生理上可接受的盐也能够根据标准方法通过阳离子交换或阴离子交换从另一种盐，例如三氟乙酸盐制备。本发明还一般性地覆盖了通式I化合物的盐，它例如在该化合物的化学合成过程中获得并用作供所需生理上可接受的盐的后续制备用的起始原料。本发明进一步覆盖通式I化合物的溶剂化物，例如水合物或乙醇化物。

根据本发明的通式I化合物能够含有旋光碳原子，它们彼此独立地具有R或S构型。它们因此能够以各自对映异构体或各自非对映异构体的形式或以包括外消旋物或非对映的混合物在内的对映异构体混合物形式存在。本发明同时涉及纯的对映异构体和各种对映异构体按所有比率的混合物和涉及纯的非对映异构体和各种非对映异构体按所有比率的混合物。本发明覆盖了通式I的两种立体异构体的混合物以及通式I的两种以上立体异构体的混合物，和在混合物中各种立体异构体的全部比率。

通式I化合物也能够作为E异构体或Z异构体存在。本发明同时涉及纯的E和Z异构体和涉及E/Z异构体按所有比率的混合物。非对映异构体，包括E/Z异构体在内，能够分离成各异构体，例如，通过色谱法。外消旋物能够通过基于手性相的色谱分离法或通过根据标准方法的拆分技术被分离成两种对映异构体。纯的对映异构体另外也能够通过在合成中使用旋光活性起始原料来获得。

根据本发明的通式I的化合物能够进一步含有活泼氢原子，即它们能够以各种互变异构形式存在。本发明还涉及所有这些互变异构体。

本发明还包括通式I化合物的衍生物和改性物，例如前体药物，受保护的形式和其它在生理上可容忍的衍生物包括酯和酰胺，以及通式I化合物的活性代谢物。此类酯和酰胺是，例如，(C_1-C_4)-烷基酯类，未被取代的酰胺或(C_1-C_8)-烷基酰胺。本发明尤其涉及通式I化合物的前体药物和受保护的形式，它们能够在生理条件下转化成通式I的化合物。通式I化合物的合适前体药物，即按所需方式改进了性能(例如相对于溶解性、生物利用率或作用持续时间)的通式I化合物的化学改性衍生物，是本技术领域中那些技术人员所已知的。与前体药物相关的更详细的信息能够在标准文献中见到，象例如DesignofProdrugs，H.Bundgaard(编)，Elsevier，1985；Fleisher等人，AdvancedDrugDeliveryReviews19(1996)115-130；或H.Bundgaard，DrugsoftheFuture16(1991)443，它们全部被引入本文供参考。通式I化合物的合适前体药物尤其是羧酸基的酯前体药物和酰胺前体药物，以及可酰化的含氨基团如氨基、脒基和胍基的酰基前体药物和氨基甲酸酯前体药物。在酰基前体药物和氨基甲酸酯前体药物中，在此类基团中的氮原子上的一个或多个(例如一个或两个)氢原子可被酰基或氧基酰基取代。酰基前体药物和氨基甲酸酯前体药物的合适酰基和氧基酰基是，例如，基团R^{p1}-CO-和R^{p2}O-CO-，其中R^{p1}是氢，(C_1-C_{18})-烷基，(C_3-C_7)-环烷基，(C_3-C_7)-环烷基-(C_1-C_4)-烷基-，(C_6-C_{14})-芳基，它是未被取代的或被残基(C_1-C_2)-烷基、(C_1-C_2)烷氧基、氟或氯取代；杂芳基-，(C_6-C_{14})-芳基-(C_1-C_4)-烷基-，其中芳基是未被取代的或被残基

(C_1-C_2)-烷基、(C_1-C_2)-烷氧基、氟或氯取代；或杂芳基-(C_1-C_4)-烷基-和其中R^{p2}具有对于R^{p1}指定的意义，但氢除外。

优选的是通式I的化合物，其中

R(1)是氢，(C_1-C_4)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基(carbamimidoyl)-苄基；

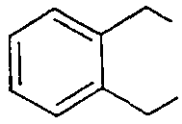
R(2)是氢或(C_1-C_4)-烷基；

R(3)是苯基或萘基，优选2-萘基，它们被R(7)取代；

R(4)是氢或甲基；

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，优选4-氨基苄基，羟甲基，苄基氧基甲基，羧甲基，2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



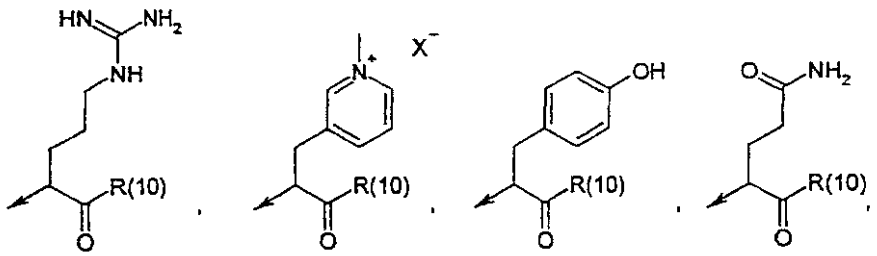
(II)；

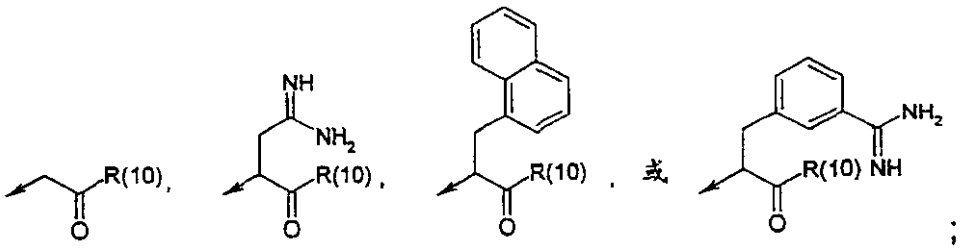
R(6)是NR(8)R(9)，OH，或OCH_3；

R(7)是脒基，羟基脒基，氨基，或二甲基氨基；

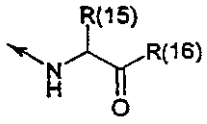
R(8)是氢，吡啶基甲基，优选4-吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基；

R(9)是萘基甲基，优选1-萘基甲基，





R(10)是NR(12)R(13)，OR(14)或



R(12)是氢或甲基；

R(13)是氢，苯基-(C_1-C_2)-烷基，或甲基；

R(14)是氢，(C_1-C_2)-烷基，苄基或烯丙基；

R(15)是环己基甲基；

R(16)是氨基；

X^-是生理学上可接受的阴离子；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

优选的也是通式I的化合物，其中

R(1)是氢，(C_1-C_3)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基-苄基；

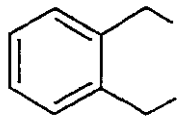
R(2)是氢或(C_1-C_3)-烷基；

R(3)是苯基或2-萘基，它们被R(7)取代；

R(4)是氢或甲基；

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，4-氨基苄基，羟甲基，苄基氧基甲基，羧甲基；2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



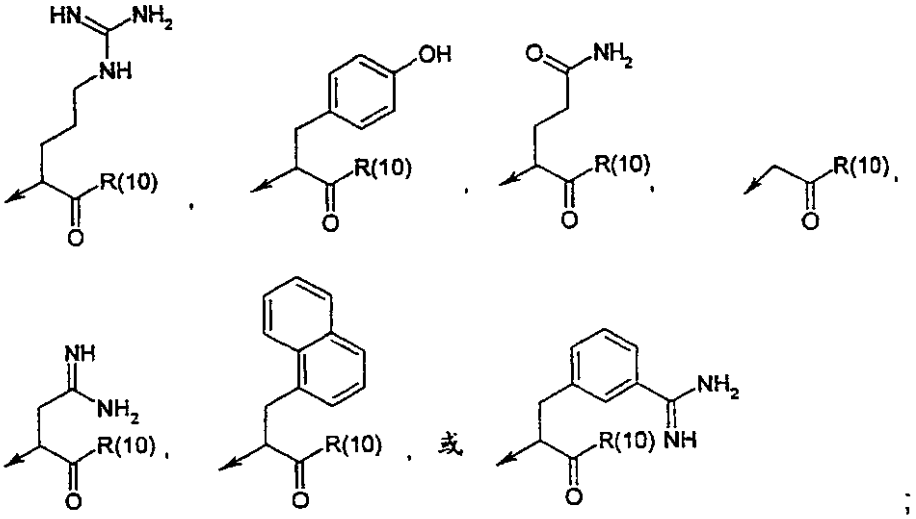
(II)；

R(6)是NR(8)R(9)，OH，或OCH_3；

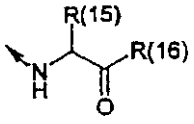
R(7)是脒基，羟基脒基，或二甲基氨基；

R(8)是氢，吡啶基甲基，优选4-吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基；

R(9)是萘基甲基，优选1-萘基甲基，



R(10)是NR(12)R(13)，OR(14)，或



；

R(12)是氢或甲基；

R(13)是氢，苯基-(C_1-C_2)-烷基，或甲基；

R(14)是氢，(C_1-C_2)-烷基，苄基或烯丙基；

R(15)是环己基甲基；

R(16)是氨基；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

特别优选的是通式I的化合物，其中

R(1)是氢，(C_1-C_3)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基-苄基；

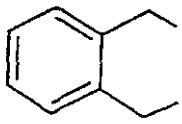
R(2)是氢或(C_1-C_3)-烷基；

R(3)是苯基或萘基，优选2-萘基，它们被R(7)取代；

R(4)是氢或甲基；

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，优选4-氨基苄基，羟甲基，苄基氧基甲基，羧甲基，2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



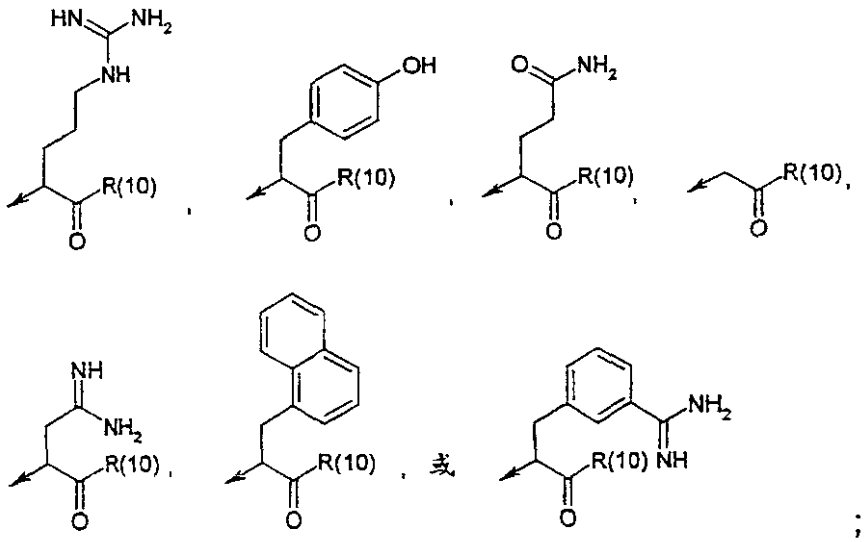
(II)；

R(6)是NR(8)R(9)，OH，或OCH_3；

R(7)是脒基，羟基脒基，或二甲基氨基；

R(8)是氢，吡啶基甲基，优选4-吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基；

R(9)是萘基甲基，优选1-萘基甲基，



；

R(10)是NR(12)R(13)，或OR(14)；

R(12)是氢或甲基；

R(13)是氢，苯基-(C_1-C_2)-烷基，或甲基；

R(14)是氢，(C_1-C_2)-烷基，苄基或烯丙基；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

最特别优选的是通式I的化合物，其中

R(1)是甲基，烯丙基，苯基，或苄基，优选甲基或苄基；

R(2)是氢或甲基；

R(3)是可被R(7)取代的苯基；

R(4)是氢；

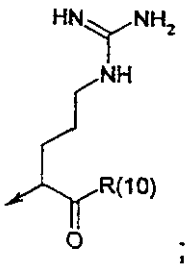
R(5)是丁基，优选正丁基，环己基，环己基甲基，苯基，苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，优选4-氨基苄基，苄基氧基甲基，羧甲基，或2-羧基乙基；

R(6)是NR(8)R(9)；

R(7)是脒基或羟基脒基；

R(8)是氢；

R(9)是



；

R(10)是NR(12)R(13)，或OR(14)；

R(12)是氢或甲基；

R(13)是氢或苯基-(C_1-C_2)-烷基；

R(14)是氢，(C_1-C_2)-烷基，或烯丙基；

包括所有它们的立体异构体形式和它们按任何比率的混合物，以

及它们的生理学上可接受的盐。

可以提及的最特别优选的通式I的化合物是:

2-(4-氨基氨代甲酰基-苄基)-N-[(1-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,较少极性的非对映异构体,

2-(S)-(2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸烯丙基酯三氟乙酸盐,较少极性的非对映异构体,

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐,更极性的非对映异构体,

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐,较少极性的非对映异构体,

N-苄基-N'-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-丙二酰胺三氟乙酸盐,

N-[2-(4-氨基-苯基)-1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N'-甲基-丙二酰胺三氟乙酸盐,

4-(S)-[3-(4-氨基氨代甲酰基-苄基)-2-二甲基氨基甲酰基-丙酰基氨基]-4-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-丁酸,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-2-基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍

基-丁基氨基甲酰基)-3-苯基-丙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,

3-(S)-[3-(4-氨基氨代甲酰基-苄基)-2-二甲基氨基甲酰基-丙酰基氨基]-N-(1-(S)-氨甲酰基-4-胍基-丁基)-琥珀酰胺酸三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-N'-甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,

N-[2-苄氧基-1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲基-丙二酰胺三氟乙酸盐, 较少极性的非对映异构体,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-己酰基氨基}-5-胍基-戊酸三氟乙酸盐,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基-5-胍基-戊酸; 与三氟乙酸形成三氟乙酸盐,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸三氟乙酸盐,

2-(S)-{2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸三氟乙酸盐,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-3-环己基-丙酰基氨基}-5-胍基-戊酸三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐, 较少极性的非对映异构体,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍

基-丁基氨基甲酰基)-2-萘-1-基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N'-甲基-丙二酰胺三氟乙酸盐,

2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-环己基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐,

N-苄基-N'-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-丙二酰胺三氟乙酸盐,较少极性的非对映异构体,

2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸乙酯盐酸盐,

2-(S)-{2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸乙基三氟乙酸盐,较少极性的非对映异构体,

2-(4-氨基氨代甲酰基-苄基)-N-[(S)-环己基-(4-胍基-1-(S)-苯乙基氨基甲酰基-丁基氨基甲酰基)-甲基]-N',N'-二甲基-丙二酰胺盐酸盐,

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐,更极性的非对映异构体,

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐,较少极性的非对映异构体,

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N-甲基-丙二酰胺三氟乙酸盐,

2-(S)-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸盐酸盐，

2-(S)-{2-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸甲酯三氟乙酸盐，最少极性的非对映异构体，

N-苄基-N'-{[1-(S)-(苄基-甲基-氨基甲酰基)-4-胍基-丁基氨基甲酰基]-环己基-甲基}-2-(4-氨基氨代甲酰基-苄基)-N-甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体，

本发明还涉及通式I的化合物，其中

R(1)是氢，(C_1-C_6)-烷基，(C_2-C_6)-链烯基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被R(17)取代；

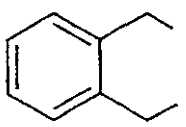
R(2)是氢或(C_1-C_4)-烷基；

R(3)是可被R(7)取代的(C_6-C_{10})-芳基；

R(4)是氢或(C_1-C_4)-烷基；

R(5)是(C_1-C_6)-烷基，(C_3-C_7)-环烷基，(C_3-C_7)-环烷基-(C_1-C_4)-烷基，(C_6-C_{10})-芳基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中在芳基烷基中的芳基是未被取代的或被残基R(20)取代，和其中烷基是未被取代的或被残基R(21)取代；或

R(4)和R(5)一起形成通式II的残基



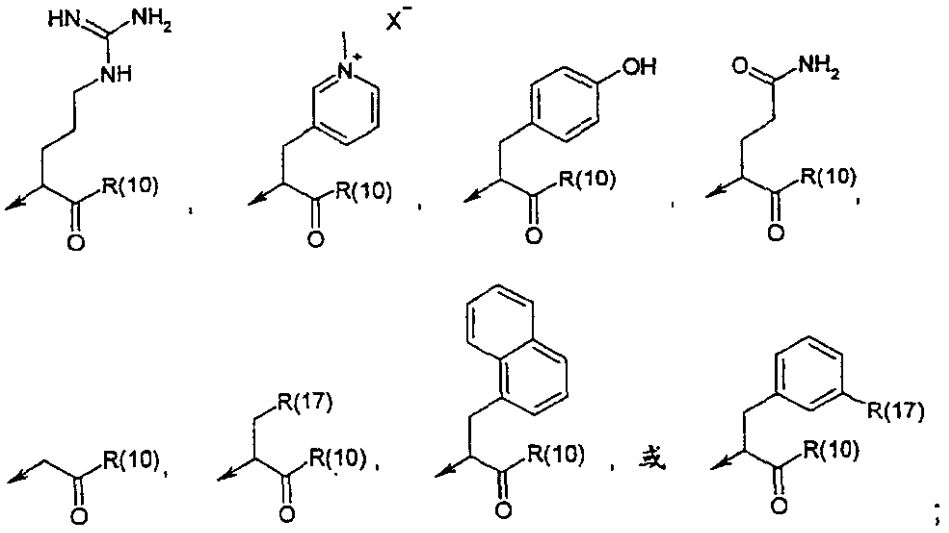
(II)；

R(6)是NR(8)R(9)或OR(22)；

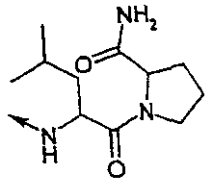
R(7)是R(17)或R(20)；

R(8)是氢；(C_1-C_4)-烷基，其中烷基是未被取代的或被残基R(20)取代；杂芳基-(C_1-C_4)-烷基；(C_6-C_{10})-芳基(C_1-C_4)-烷基，其中芳基是未被取代的或被残基R(17)取代；

R(9)是



R(10)是



R(17)是-C(=N-R(18))-N(R(19))$_2$;

R(18)是氢，羟基，或氨基保护基;

R(19)是氢，(C_1-C_4)-烷基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基，或氨基保护基;

R(20)是N(R(19))$_2$;

R(21)是羟基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基，(C_6-C_{10})-芳基(C_1-C_4)-烷氧基羰基氨基，羧基，或R(20);

R(22)是氢或(C_1-C_4)-烷基;

X^-是生理上可接受的阴离子;

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

本发明还涉及通式I的化合物，其中

R(1)是氢，(C_1-C_4)-烷基，烯丙基，苯基，苄基，或4-氨基氨代甲酰基-苄基;

R(2)是氢或(C_1-C_4)-烷基;

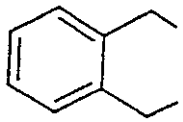
R(3)是苯基或2-萘基，它们被R(7)取代;

R(4)是氢或甲基;

R(5)是正丁基，仲丁基，叔丁基，环己基，环己基甲基，苯基，

苄基，2-苯基-乙基，1-萘基甲基，2-萘基甲基，氨基苄基，优选4-氨基苄基，羟甲基，苄基氧基甲基，羧甲基，2-羧基乙基，3-氨基-丙基，或4-(苄氧基羰基氨基)-丁基；或

R(4)和R(5)一起形成通式II的残基



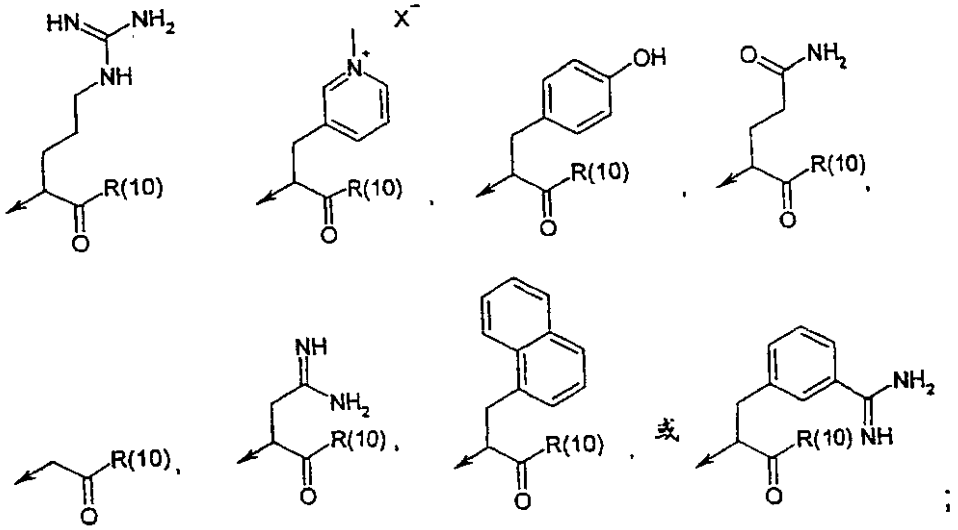
(II)；

R(6)是NR(8)R(9)，OH，或OCH_3；

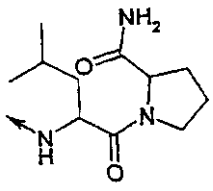
R(7)是脒基，羟基脒基，氨基，或二甲基氨基；

R(8)是氢，吡啶基甲基，优选4-吡啶基甲基，3-氨基氨代甲酰基苄基，或4-氨基-丁基；

R(9)是



R(10)是



；

X^-是生理上可接受的阴离子;

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

优选的是通式I的化合物，其中

R(1)是丙基或丁基；优选丁基;

R(2)是丙基或丁基；优选丁基;

R(3)是可被R(7)取代的苯基;

R(4)是氢;

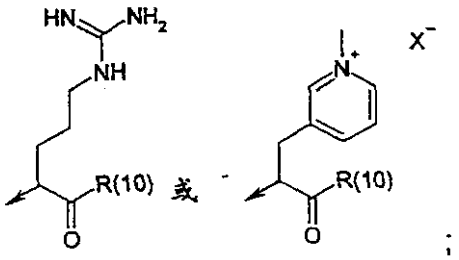
R(5)是环己基;

R(6)是NR(8)R(9);

R(7)是脒基，或氨基;

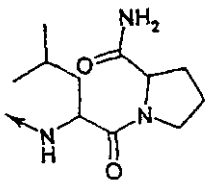
R(8)是氢;

R(9)是



;

R(10)是



;

X^-是生理上可接受的阴离子;

包括所有它们的立体异构体形式和它们按任何比率的混合物，以及它们的生理学上可接受的盐。

可提及的特别优选的化合物是:

2-(4-氨基氨代甲酰基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-胍基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体;

3-(2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二异丙基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-2-[1-(S)-(2-(S)-氨甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-乙基}-1-甲基-吡啶盐三氟-乙酸盐三氟乙酸，较少极性的非对映异构体，

2-(4-氨基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-胍基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体，

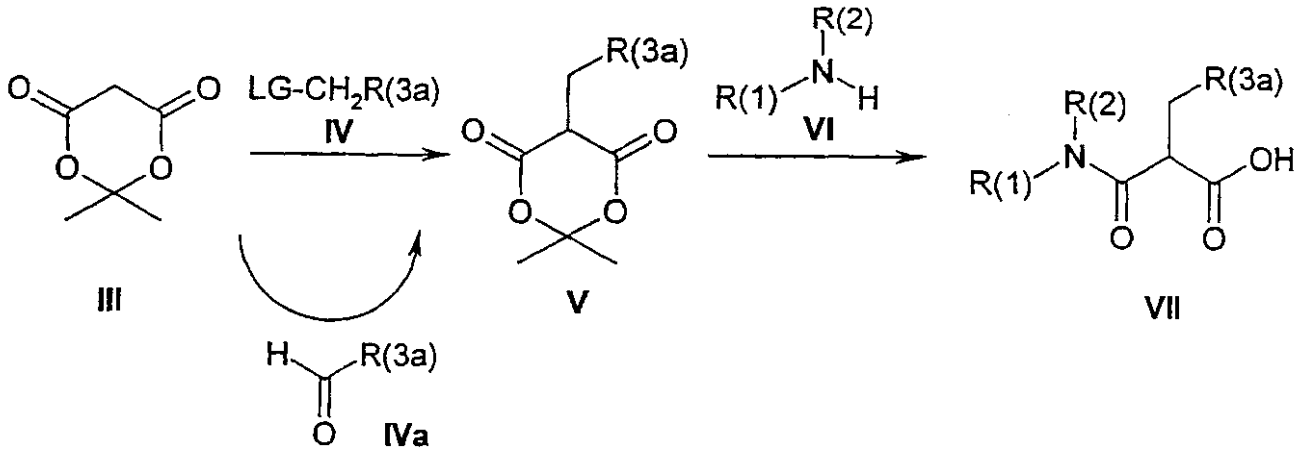
2-(4-氨基氨代甲酰基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-胍基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丁基-丙二酰胺三氟乙酸盐，更极性的非对映异构体，

通式I化合物能够利用本技术领域中普通技术人员公知和了解的程序和技术来制备。在可用于通式I化合物的制备的一般合成程序中使用的起始原料或组成成分是所属技术领域中普通技术人员容易获得的。在很多情况下它们可从市场上买到或已经描述在文献中。另外它们能够与本申请中描述的程序类似地从容易获取的前体化合物来制备。

在通式I化合物的合成中进行的下述反应一般能够根据普通的溶液相化学方法以及根据固相化学方法来进行，这些方法例如在肽合成领域中是众所周知。

通式I的化合物能够通过在反应历程2和3中描述的方法A来制备，其中残基R(1)，R(2)，R(3)，R(4)，R(5)，R(6)如以上所规定。

反应历程2



麦得鲁姆酸(Meldrum acid)III能够通过使用碱例如碳酸钾，氢化钠，或三乙胺和IV来加以烷基化，其中

LG是离去基团象卤素或取代的羟基像甲苯磺酰氧基或甲磺酰氧基;

R(3a)是(C_6-C_{10})-芳基，它可被R(23)取代;

R(23)是N(R(24))$_2$，硝基，或氰基;

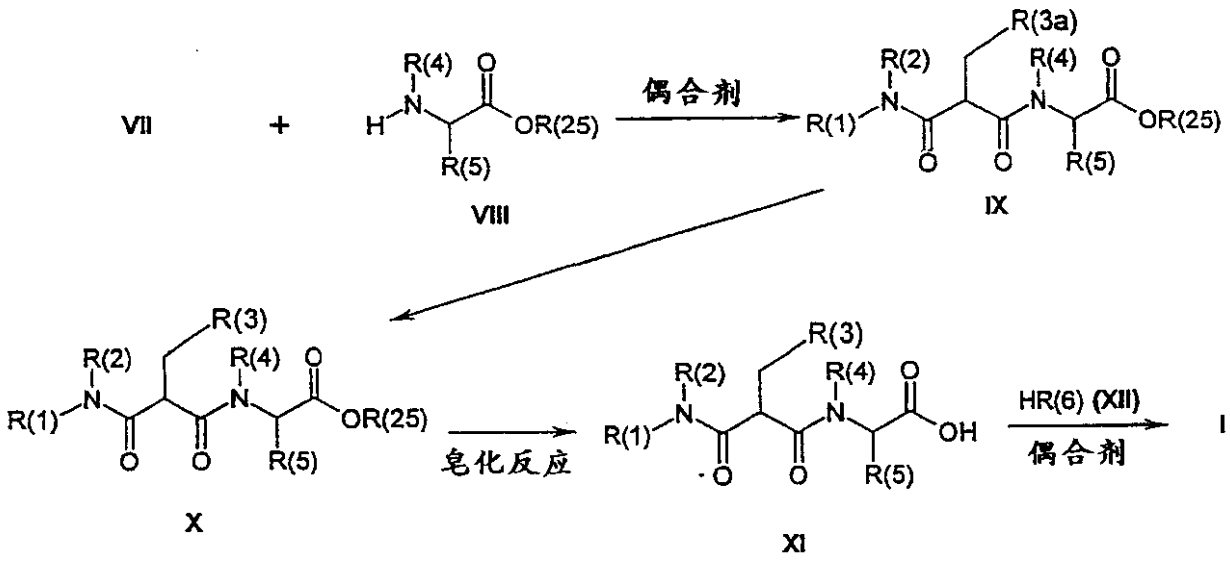
R(24)是(C_1-C_6)-烷基，(C_6-C_{10})-芳基(C_1-C_4)-烷基，(C_1-C_6)-烷基羰基，或(C_1-C_6)-烷氧基羰基;

得到V，或通过麦得鲁姆酸III与醛IVa在还原剂例如氰基硼氢化钠存在下的缩合反应来加以烷基化，

同时，V的开环能够通过，优选在硅烷化剂例如N,O-双(三甲基甲硅烷基)-乙酰胺存在下在有机溶剂中，例如在二氯甲烷中在回流状态下，胺VI的反应来实现，得到丙二酸酰胺VII。

通式II、IV、IVa和VI的化合物是市场上可买到的或能够通过本技术领域中普通技术人员已知的标准方法来制备。

反应历程3



VII与VIII偶合得到IX的过程，其中R(25)是容易裂解的酯(例如(C_1-C_4)-烷基，苄基，或4-甲氧苯甲基)，能够通过在肽合成中使用的普通偶合试剂来进行。此类偶合剂是，例如，碳化二亚胺类象二环己基碳二亚胺(DCCI)或二异丙基碳二亚胺(DICI)，羰基二唑像羰二咪唑和类似的试剂，丙基膦酸酐，O-((氰基-(乙氧基羰基)-亚甲基)氨基)-N,N,N',N'-四甲基尿鎓四氟硼酸盐(TOTU)，N-[(二甲基氨基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基-亚甲基]-N-甲基甲胺鎓(methanaminium)六氟磷酸盐N-氧化物(HATU)，等等。通式VIII的化合物是市场上可买到的或能够通过本技术领域中普通技术人员已知的标准方法来制备。

如果必要，R(3a)到R(3)(IX→X)的转化能够通过引入如下所述的脒基，或通过用例如Raney镍，钯/活性炭或其它催化剂在氢气存在下的氢化反应使硝基还原来进行。

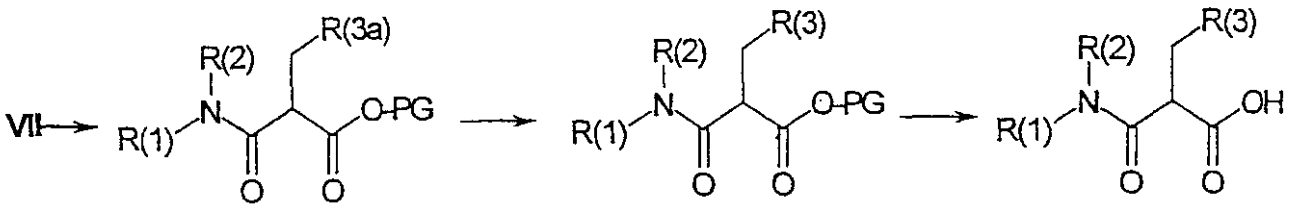
脒类能够从对应的氰基化合物制备，通过在酸性无水介质(例如二噁烷、甲醇或乙醇)中加成醇类例如甲醇或乙醇，和随后进行氨解(例如用在醇类如异丙醇、甲醇或乙醇中的氨进行处理)(G.Wagner,

P.Richter和Ch.Garbe, Pharmazie29(1974), 12-55)。制备脒类的其它方法是硫化氢加成到氰基上，接着让所获得的硫酰胺进行烷基化(例如甲基化)，和随后与氨反应(GDR专利No.235866)，以及羟胺(可用碱从羟铵盐获得)在氰基上的加成，接着酰胺肟转化成脒(例如通过催化氢化)。

通式X的化合物的酯基的皂化得到通式XI的化合物的过程能够通过标准方法来进行。XI与XII的偶合得到通式I的化合物的过程能够用如上所述的偶合剂来进行。通式XII的化合物是市场上可买到的或能够通过本技术领域中普通技术人员已知的标准方法来制备。

通式I的化合物还可以通过在反应历程4和5中描述的方法来获得。

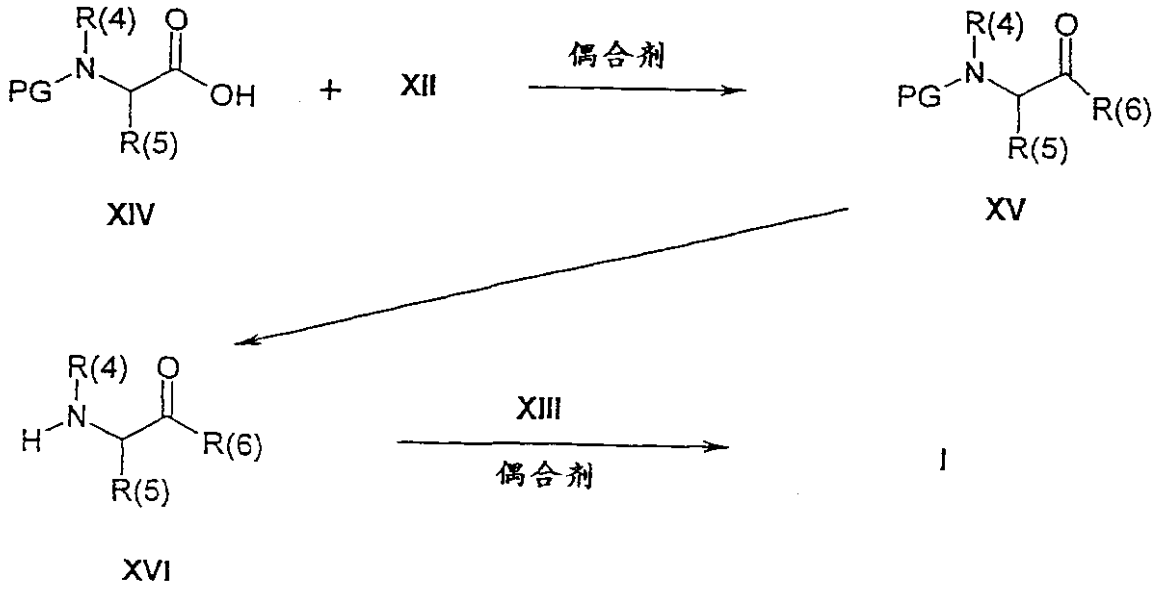
反应历程4



XIII

在通过标准方法用容易分裂的保护基团PG(例如(C_1-C_4)-烷基，苄基，或4-甲氧苯甲基)保护羧基官能团后，在通式VII的化合物中的残基R(3a)能够转变成残基R(3)和按以上所述去保护，得到通式XIII的化合物。

反应历程5



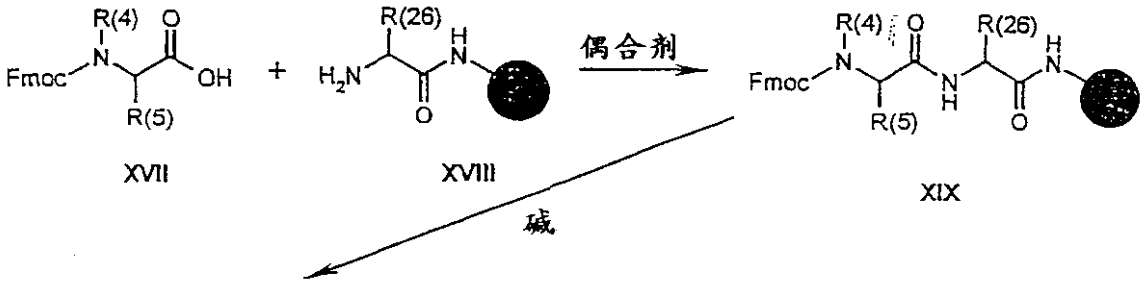
受保护的氨基酸XIV，其中PG是合适的氨基保护基，例如Fmoc、苄氧基羰基(Z)或Boc(优选Fmoc)，能够通过以上所述的标准方法与通式XII的化合物偶合，得到通式XV的化合物。通式XIV的化合物能够通过本技术领域中普通技术人员已知的标准方法来制备。

通式XV的化合物能够通过标准方法，例如通过用于Fmoc-去保护的标准方法(L. A. Carpino等人，J. Org. Chem. 1988，53，6139-44)，来去保护而得到通式XVI的化合物。通式XVI的化合物能够通过标准方法与通式XIII的化合物偶合，得到通式I的化合物。

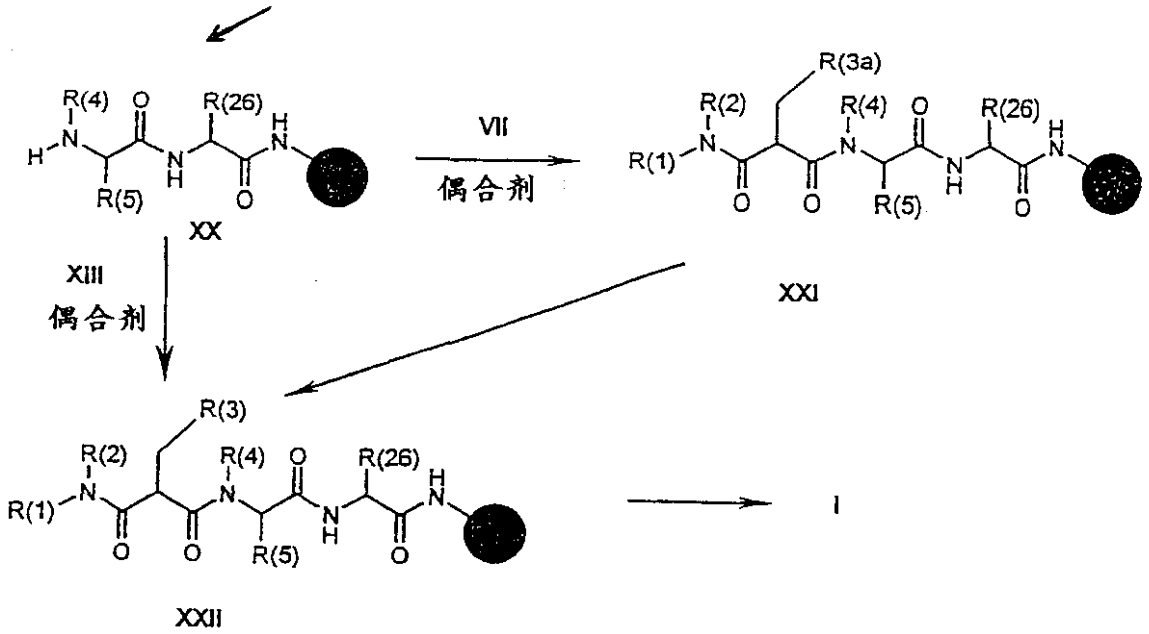
通式I的化合物还可以通过在反应历程6中描述的固相肽合成方法(方法C)来获得。此类方法例如已经由Steward和Young进行了描述(Solid Phase Peptide Synthesis(Freeman and Co.，SanFrancisco，1969)，该文献被引入本文供参考。

在使用固相合成方法时，化合物的化学组成能够进行调节，而与此同时初生的肽连接于树脂上或在肽已经从树脂上分裂之后，获得了例如氨基终端的衍生物。类似的改性也能够针对化合物的羧基来进行，该化合物包括C-终端的羧基，后者例如能够酰胺化。现有技术中的技术人员也能够使用溶液相有机化学方法来合成本发明的化合物。

反应历程 6



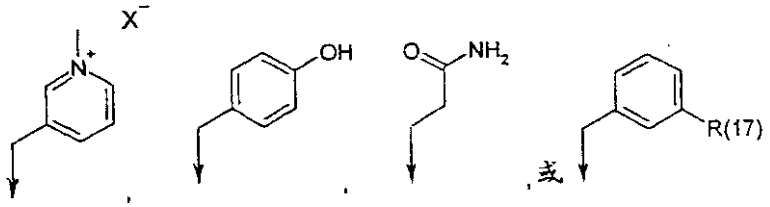
XVII XVIII XIX



键接于酸可分裂的树脂上

使用这一方法(C)(反应历程6)，通式XVIII的化合物，其中氨基酸偶合到合适的载体上，该载体例如是Wang、Trityl或Rink树脂或所属技术领域的专业人员已知的其它酸可分裂的树脂上，和其中

R(26)是氢，$-CH_2-R(17)$，1-萘基甲基，$-(CH_2)_3-NR(28)-C(=N-R(27))-NH-R(28)$，



R(27)是R(28)，氰基，羟基，(C_1-C_6)-烷氧基，(C_6-C_{14})-芳基(C_1-C_6)-烷氧基，它在芳基结构部分中未被取代或被取代，或氨基；

R(28)是氢，(C_1-C_6)-烷基，或(C_1-C_6)-烷基羰基；

能够使用标准技术，与例如Fmoc保护的氨基酸XVII偶合。其它受保护的，例如Boc-保护的氨基酸XVII的使用也是可能的，然而，Fmoc

保护的氨基酸XVII的使用是优选的。

通式XVIII的化合物能够通过本技术领域中普通技术人员已知的标准方法来制备。

所获得的二肽XIX能够使用碱，例如哌啶在二甲基甲酰胺中的浓度20-50%的溶液进行去保护，获得具有伯或仲氨基的通式XX的化合物，它然后能够偶合到通过使用方法A和B所制备的结构嵌段VII或XIII上，得到通式XXI或XXII的化合物。所获得的化合物XXI的残基R(3a)转化成残基R(3)能够如上所述来进行，得到通式XXII的化合物。通式I的化合物能够在酸性条件下例如在不同浓度(取决于所使用的树脂，该浓度是1%到95%的三氟乙酸)的三氟乙酸/水中，通过分裂通式XXII的化合物来获得。

这些合成的化合物能够使用众所周知的方法如反相-高压液相色谱法(RP-HPLC)或其它基于例如化合物的尺寸、电荷或疏水性的分离方法来提纯。类似地，众所周知的方法如氨基酸序列分析或质谱分析方法(MS或HPLCIESMS)能用于表征本发明化合物的结构(参见实施例1)。

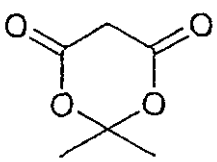
因此，本发明还涉及制备通式I的化合物的方法，它包括

i)

a1)在碱存在下用通式IV的化合物

$LG-CH_2-R(3a)$ (IV)

将通式III的化合物加以烷基化



III

其中LG是离去基团象卤素或取代的羟基像甲苯磺酰氧基或甲磺酰

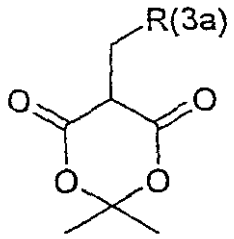
氧基而其中

R(3a)是(C_6-C_{10})-芳基，它可被R(23)取代;

R(23)是N(R(24))$_2$，硝基，或氰基;

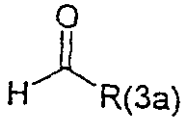
R(24)是(C_1-C_6)-烷基，(C_6-C_{10})-芳基-(C_1-C_4)-烷基，(C_1-C_6)-烷基羰基，或(C_1-C_6)-烷氧基羰基;

得到通式V的化合物，



V

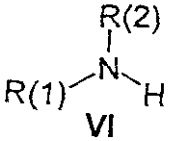
或在还原剂存在下让通式III的化合物与通式IVa的化合物反应，



IVa

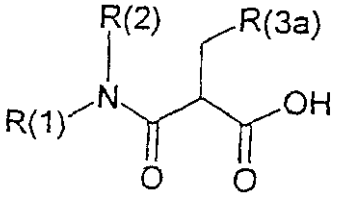
得到通式V的化合物;

b1)让通式V的化合物与通式VI的化合物反应，



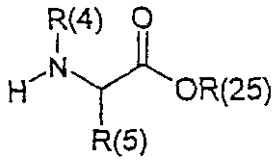
VI

其中R(1)和R(2)如以上所定义，得到通式VII的化合物;



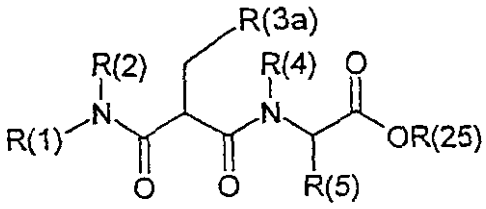
VII

c1)通式 VII 的化合物与通式 VIII 的化合物偶合，



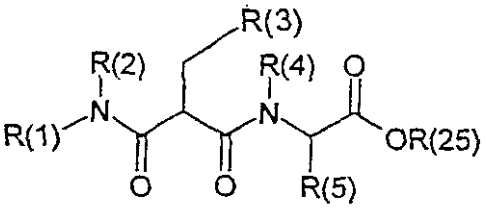
VIII

其中R(4)和R(5)是如以上所定义和R(25)是容易分裂的酯，得到通式IX的化合物，



IX

d1)任选引入脒基或通过将通式IX的化合物转化成通式X的化合物来使硝基还原，



X

其中R(3)如以上所定义；

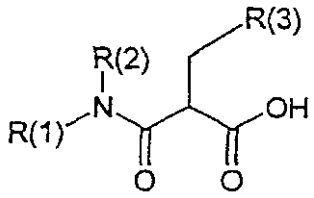
e1)酯基R(25)的皂化和根据步骤c1)的所获得化合物与通式XII的化合物偶合

HR(6) (XII)

其中R(6)如以上所定义，得到通式I的化合物；或

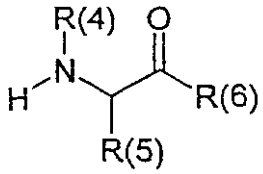
c2)用容易分裂的保护基保护在通式VII化合物中的羧基官能团和引入脒基或根据步骤d1)的硝基的还原使得在羧基官能团的去保护之后得到了通式XIII的化合物；和

d2)让根据步骤c1)的通式XIII的化合物



XIII

与通式XVI的化合物偶合;

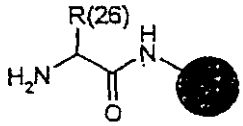


XVI

得到通式I的化合物; 或

ii)

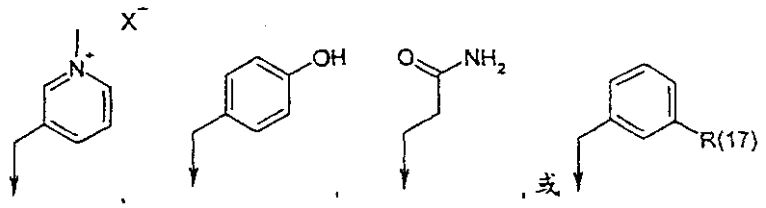
a)让通式XVIII的化合物,



XVIII

它键接于合适的载体例如酸可分裂的树脂上, 和其中

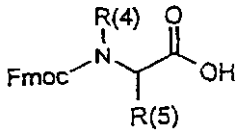
R(26)是氢, $-CH_2-R(17)$, 1-萘基甲基, $-(CH_2)_3-NR(28)-C(=N-R(27))-NH-R(28)$,



R(27)是R(28), 氰基, 羟基, (C_1-C_6)-烷氧基, (C_6-C_{14})-芳基(C_1-C_6)-烷氧基, 它在芳基结构部分中未被取代或被取代, 或氨基;

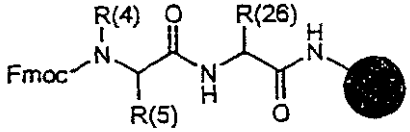
R(28)是氢, (C_1-C_6)-烷基, 或(C_1-C_6)-烷基羰基; 和R(17)是如以上所定义;

与通式XVII的化合物偶合



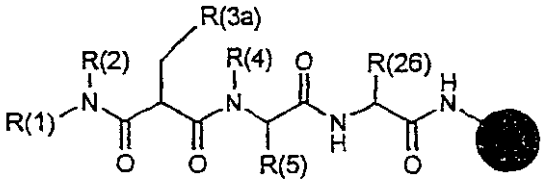
XVII

其中R(4)和R(5)如以上所定义，得到通式XIX的化合物

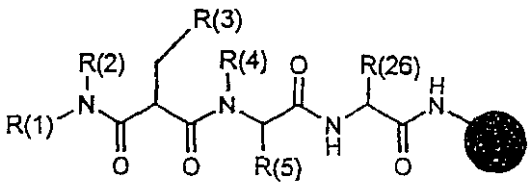


XIX

b)以及在用碱使通式XIX的化合物去保护之后让去保护的化合物XX偶合到通式VII或XIII的化合物上，得到通式XXI或XXII的化合物；



XXI



XXII

c)任选将通式XXI的化合物转变成通式XXII的化合物(即通过引入脒基或通过硝基的还原将残基R(3a)转变成残基R(3))，

和d)将通式XXII的化合物从树脂上分裂，得到通式I的化合物。

正如在下面所述的药理试验中所说明的那样，通式I的化合物抑制因子Xa活性。它们所以能够理想地用作药物，尤其当希望降低因子Xa活性或产生一些效果，这些效果能够通过抑制系统中因子Xa活性来实现，如影响凝固或抑制血液凝固。因此，本发明还涉及用作药物以及用于药剂、尤其用于治疗或预防下面和上面所提及的症状和疾病的药剂的生产中的通式I的化合物。此外，本发明提供通过因子Xa与通式I化合物接触来特定地抑制因子Xa活性的方法。更具体地说，有效量的本发明的化合物或者在凝血酶原酶复合物内或作为可溶性亚单元来直接地抑制因子Xa催化活性，或者通过抑制因子Xa组合成凝血酶原酶复合物来间接地抑制它。本发明的优选实施方案包括以Ki<10μm和优选

以Ki<100nM抑制因子Xa活性的此类通式I的化合物。

这里使用的术语“因子Xa活性”是指因子Xa本身或以公知为凝血酶原酶复合物的亚单元的组合来催化凝血酶原转化成凝血酶的能力。当有关因子Xa活性来使用时，该术语“抑制”同时包括因子Xa活性的直接和间接抑制。因子Xa活性的直接抑制能够通过例如通式I化合物结合于因子Xa或结合于凝血酶原酶，从而防止凝血酶原结合于凝血酶原酶复合物活性部位来实现。因子Xa活性的间接抑制能够通过例如本发明化合物结合于可溶性因子Xa上以防止它组合成凝血酶原酶复合物来实现。当有关因子Xa活性的抑制而使用时的术语“特异(性)”是指通式I的化合物能够抑制因子Xa活性但不会显著抑制丝氨酸蛋白酶类例如凝血酶，胰蛋白酶或舒血管素（kallekrein）的活性(使用相同浓度的抑制剂)。此类蛋白酶类牵涉到血液凝固和纤维蛋白溶解级联。

因子Xa活性的抑制或由该抑制所实现的效果的产生能够在活体内即在个体内发生。这里使用的术语“个体”是指脊椎动物，包括哺乳动物，例如小鼠，大鼠，兔子，狗，猪，猴子，和尤其人，其中因子Xa涉及到凝固级联。它还可以在个体的身体以外发生，例如在体外循环中或在来自个体的血样的处理中，并且通常在活体外。通式I的化合物的活体外使用是，例如，在科学或理论研究中用作生物化学工具或用于活体外诊断。通式I的化合物能够理想地用作抗凝血剂，它能够与血样接触来防止凝固。例如，有效量的通式I的化合物能够与新抽取的血样接触以防止该血样的凝固。

当在本文中使用时，这里使用的术语“有效量”是指抑制因子Xa活性到所需程度的通式I的化合物的量。该熟练的技术人员可以认识到，本发明的化合物的有效量能够使用这里公开的方法或现有技术中已知的方法来确定。

鉴于通式I化合物的所公开用途，熟练的技术人员也会认识到药剂如肝素能够被本发明的化合物取代。通式I化合物的这一使用能够导致，例如，成本节约，与其它抗凝血剂相比。

在其它实施方案中，本发明提供了在需要治疗的患者体内抑制因

子Xa的方法，包括对该患者施用有效的因子Xa抑制量的通式I的化合物。这里使用的术语“患者”尤其谈及温血动物，包括哺乳动物和特别人在内。当患者患有一种疾病时患者需要治疗以抑制因子Xa，该疾病能够通过抑制因子Xa活性来有益地受影响或由临床医生预期通过抑制因子Xa活性来有益地受影响。

需要治疗来抑制因子Xa的那些患者的鉴定是所属技术领域中技术人员的一般能力和知识。通过使用临床试验、身体检查和药物/家族病史，本技术领域中的临床医生能够容易地鉴定需要此类治疗的那些患者。

因为通式I的化合物能够抑制因子Xa活性，此类化合物能够用于减少或抑制个体内的血液凝固。因此，本发明进一步提供了通过施用治疗有效量的通式I化合物来减少或抑制在个体的体内，尤其在需要治疗的患者体内血凝块的形成的一种方法。

与在个体体内象血液凝固的抑制或减少之类的效果的产生有关的通式I化合物的治疗有效量，或通式I化合物的有效的因子Xa抑制量是指为了实现或维持预期效果或抑制个体内的因子Xa活性到所需程度而施用于个体的通式I化合物的量或剂量。在每种情况下需要施用的这一有效量或剂量需要与个体的具体状况相适应作一些调节。它能够通过使用这里所述或在现有技术中已知的方法，或通过观察在类似情况下所获得的结果，由普通技术的使用而容易地确定。在确定有效剂量时，许多因素需要考虑，包括但不限于：患者的种类；它的体格，年龄，和一般健康状况；疾病的程度或复杂情况或严重性；个体患者的响应；所施用的具体化合物；施用的方式；所施用的药物制剂的生物利用率特性；所选择的剂量给药法；和相伴的药物的使用。适当的剂量能够使用医药技术领域中公知的临床方法来确定。

通常，考虑到上述因素，显然通式I化合物的有效的因子Xa抑制量或治疗有效量将会变化而且变化幅度大。通常，有效量将是大约0.01毫克每公斤体重每天(mg/kg/每天)到大约20mg/kg/每天。大约0.1mg/kg到大约10mg/kg的日剂量是优选的。这些数据针对大约75kg

体重的人。尤其当相对大量施用时，有利的是将日剂量分成几个，例如2，3或4个分剂量施用。

通式I的化合物能够施用于个体以治疗各种临床病症，包括例如心血管疾病或与例如感染或外科手术有关的并发症的治疗和预防。心血管病症的例子包括再狭窄，例如在血管成形术之后的再狭窄，再闭塞预防，在冠状动脉旁路手术之后的病症，动脉、静脉和微循环疾病状态，心肌梗塞，心绞痛，血栓栓塞性疾病，形成血栓，栓塞，成人呼吸窘迫综合征，多器官衰竭，中风或弥漫性血管内凝血凝固病症。与外科手术有关的相关并发症的例子包括，例如，在外科手术之后发生的深血管和近侧血管血栓形成。因此，本发明的化合物可用作减少或抑制个体内不希望有的凝固或血液凝固的药剂。

通式I的化合物，它们的生理上可接受的盐及它的其它合适的衍生物能够本身、以彼此的混合物形式或以药物组合物的形式在上述方法中用作药剂或药物，该药物组合物包括作为活性成分的有效量的至少一种通式I化合物和/或它的生理上可接受的盐和/或它的另一种合适衍生物，以及相混合或相结合的一种或多种可药用的载体物质和助剂物质。

在对患者治疗时，通式I的化合物本身或含有它们的药物组合物能够以任何形式或方式施用，该形式或方式可使通式I化合物以有效量被生物利用，并包括口服和非肠道途径。例如，它们能够口服给药，例如以药丸，片剂，涂漆片剂，包衣片剂，粒剂，硬和软明胶胶囊剂，溶液，糖浆剂，乳液，悬浮液或气雾剂混合物的形式；直肠给药，例如以栓剂形式；胃肠外途径，例如静脉内给药，肌内注射，透皮给药，鼻内给药，或皮下给药；以注射溶液或输液溶液，微胶囊，植入物或棒；经皮或局部给药，例如以软膏，溶液或酊剂形式，或以其它方式，例如以气溶胶或鼻内喷雾剂形式。口服通常是优选的，但取决于具体的情况，其它的给药模式也是有用的，例如在疾病的急性期中通过注射或输液的静脉内给药。在制备配制剂的技术领域中的技术人员能够根据需要治疗的疾病状态，疾病的阶段，和其它相关情况来容易地选

择合适的给药形式和模式。

包括通式I的化合物和/或它的生理上可接受的盐和/或另一种合适的衍生物的药物组合物或药剂能够通过将通式I的化合物和/或它的生理上可接受的盐和/或另一种合适的衍生物与可药用的载体物质和助剂物质混合来获得的，它们的组分比例和性质是通过所选择的给药途径和标准药物实践来确定。该药物组合物或药剂按照药物技术中公知的方式来制备。该药物组合物通常含有有效量的通式I的化合物和/或它的生理上可接受的盐和/或另一种合适的衍生物及合适量的载体，以便包括合适的剂量以便为个体给药。该药物组合物可以为口服或胃肠外应用来设计，并能够以例如片剂，胶囊剂，栓剂，溶液，悬浮液，软膏，酊剂，鼻内喷雾剂，气溶胶混合物，植入物，棒条体，微囊剂等的形式施用于患者。因此，与所要求的化合物一起，本发明提供了有用的药物组合物或药剂以便抑制在个体体内的因子Xa活性和血液凝固。

本发明进一步包括含有至少一种通式I的化合物和/或它的生理上可接受的盐和/或另一种合适的衍生物的药物组合物或药剂的制备方法，以及本发明包括通式I化合物和/或它的生理上可接受的盐和/或其它合适的衍生物用于制备药剂，尤其制备供上述疾病的治疗或预防用的药剂的用途。

可药用的载体和助剂物质是指对治疗个体无毒或具有由合适管理机构测定的可接受的毒性的物质或组合物。该载体物质或赋形剂可以是能够用作活性成分的媒介物或介质的固体、半固体或液体材料。这里使用的术语“可药用的载体”包括标准药物载体中的任何一种，如液体载体，例如磷酸盐缓冲盐水，水，乳液如油/水或水/油乳液，或固体或半固体载体，例如，乳糖，玉米淀粉，脂肪，蜡等。合适的药物载体和它们的配方是所属技术领域中众所周知的并且例如由Martin描述在Remington'sPharmaceuticalSciences，第15版(MackPublishingCo.，Easton1975)中，该文献被引入这里供参考，连同有关药物组合物的成分和制备的其它方面一起。

助剂物质的例子是填料，崩解剂，粘结剂，助流剂，润湿剂，稳定剂，乳化剂，防腐剂，增甜剂，染料，香味素，芳化剂，增稠剂，稀释剂，缓冲物质，增溶剂，获得缓释效果的试剂，改变渗透压力的盐类，涂层剂，抗氧化剂，等等。

为了口服目的，通式I的化合物可以与赋形剂或惰性稀释剂或可食用的载体混合并且以片剂，膜片剂，包衣片剂，药丸，锭剂，胶囊，粒剂，溶液，悬浮液，乳液，酏剂，糖浆剂，薄膜，口香糖等，或它们可包封在胶囊内。口服的药物组合物可以根据具体的形式来变化。通常它们含有至少1%的通式I的活性成分和可以方便地含有该单位的至多大约90%的重量。优选，通式I的化合物和/或它们的生理上可接受的盐和/或其它合适的衍生物的含量是大约4%到大约70%(按重量计)。在组合物中存在的活性成分的量应使得可以获得了适合于给药的单位剂型。

该片剂，药丸，胶囊，锭剂等也可含有，例如，下列载体和助剂物质中的一种或多种：粘结剂，如微晶纤维素，黄蓍树胶或凝胶；赋形剂，如淀粉或乳糖，崩解剂比如藻酸，淀粉羟乙酸钠（Primogel），玉米淀粉等；润滑剂，如硬脂酸镁或Sterotex；助流剂，如胶体二氧化硅；和甜味剂，如可以添加蔗糖或糖精或增香剂，如薄荷，水杨酸甲酯或橙调味料。当剂量单位形式是胶囊时，除了上述类似的物质外，它还可以含有液体载体如聚乙二醇或脂肪油。其它剂量单位形式可以含有改变剂量单元的外形的其它各种材料，如包衣。因此，片剂或药丸可以涂有糖，虫胶，或其它肠溶涂敷剂。除了活性成分外，糖浆可以含有例如蔗糖作为甜味剂和某些防腐剂、染料和色料和调味剂。

对于肠胃外投药目的，通式I的化合物和/或它的生理上可接受的盐和/或其它合适的衍生物可以引入到溶液或悬浮液中。溶液或悬浮液例如也可包括一种或多种下列载体和助剂物质：

无菌的稀释剂如注射用水，盐溶液，固定油类，聚乙二醇，甘油，丙二醇或其它合成溶剂；抗菌剂如苄醇或羟苯甲酸甲酯；抗氧化剂如抗坏血酸或亚硫酸氢钠；螯合剂如乙二胺四乙酸；缓冲剂如乙酸盐，

柠檬酸盐或磷酸盐；调节毒性的试剂如氯化钠或葡萄糖。在肠胃外给药的制剂中通式I化合物的含量可以有变化。通常它们含有至少0.1wt%的通式I的化合物。优选，通式I的化合物和/或它们的生理上可接受的盐和/或它们的其它合适的衍生物的含量是大约0.1%到大约50%。该胃肠外的制剂能够包封在安瓿，一次性注射器，由玻璃或塑料制成的多次剂量管形瓶，或输液瓶中。微胶囊剂、植入物和棒条体的合适赋形剂是，例如，乙醇酸和乳酸的混合聚合物。

用于制备各种药物组合物的材料应该是药物纯度和在用量下无毒的。

除了作为活性化合物的通式I的一种或多种化合物和/或它们的生理上可接受的盐和/或它们的其它合适的衍生物，根据本发明的药物组合物也可含有一种或多种其它药理活性的化合物。

在另一个更一般的实施方案中，本发明提供一种组合物，它包括至少一种通式I的化合物和/或它的盐和/或它的另一种合适的衍生物和相混合或结合的一种或多种惰性载体。这些组合物例如可用作试验标准，作为制造散装运输药品(bulk shipments)用的方便方式(means)，或作为药物组合物。可分析量的通式I的化合物是容易由所属领域中那些技术人员公知和领会的标准分析程序和技术测量的一种量。可分析量的通式I的化合物通常是该组合物的大约0.001%到大约90%(重量)。惰性载体能够是不分解通式I的化合物或不与该化合物发生共价键反应的任何材料。合适的惰性载体的例子是水；含水的缓冲液，例如，一般用于高压液相色谱法(HPLC)分析中的那些；有机溶剂，如乙腈，乙酸乙酯，己烷等；和可药用的载体和助剂物质。

通式I的化合物也能够在其它化合物的制备中，尤其在其它药理活性化合物的制备中用作起始原料或化学中间体。下面给出了将本发明的化合物转化成本发明的其它化合物的实施例。为此用途，除了通式I的化合物和它们的生理上可接受的盐外，通式I的化合物的其它盐能够使用，尽管它不适合于或不太适合于用作药物。因此，本发明还涉及作为化学中间体，尤其作为在药理活性化合物的制备中的中间体的通

式I的化合物和它们的盐。

下面的试验能够用于考察药理活性和说明本发明的化合物作为因子Xa抑制剂的用途。

试验1：所选择的纯化凝固酶和其它丝氨酸蛋白酶的活体外抑制作用

通式I的化合物抑制因子Xa、凝血酶、纤维蛋白溶酶、弹性蛋白酶和胰蛋白酶的能力可通过测定抑制酶活性达50%(IC50)的通式I化合物的浓度来进行分析。纯化的酶用于色谱的分析。为了测定抑制常数，使用下式针对与底物的竞争来校正IC50值：

$K_i=IC_{50}\times(1/\{1+((底物浓度)/底物Km)\})$

其中Km是Michaelis-Menten常数(Y.-C.Chen and W.H.Prusoff, Biochem. Pharmacol.22:3099-3018(1973)，引入本文供参考)。

a.因子Xa分析

TBS-PEG缓冲液(50mM Tris-Cl，pH7.8，200mM NaCl，0.05%(w/v)PEG-8000，0.02%(w/v)NaN_3)用于这一分析。通过在Costar半区域微量滴定板的那些合适孔眼中结合了25μl在TBS-PEG中的人因子Xa(Enzyme Research Laboratories, Inc.; South Bend, IN)；40μl的在TBS-PEG中10%(v/v)DMSO(未抑制的对照物)或在TBS-PEG中10%浓度(v/v)DMSO中稀释的各种浓度的待试验化合物；和在TBS-PEG中的底物S-2765(N-苄氧基羰基-D-Arg-Gly-L-Arg-p-硝基酰替苯胺(anilide); kabi Pharmacia, Inc.; Franklin OH)。

通过如下来进行分析：将通式I的化合物+酶一起预培养10分钟，然后通过添加底物获得100μl的最终容积来起始分析。在时间段的线性部分中(通常在添加底物之后的1.5分钟)，在25℃下使用Bio-tekInstruments动力学分析板读数器(kinetic plate reader)(Ceres UV900HDi)，由在405nm下的吸光率变化来测量发色底物水解的初速度。在描绘水解的相对速率(与未抑制的对照物对比)对通式I化合物的浓度的log值的曲线之后，通过线性回归方法预计引起底物水解速率有50%下降的抑制剂浓度。该酶浓度是0.5nM和底物浓度

是140μm。

b.凝血酶分析

TBS-PEG缓冲液用于这一分析中。该IC50与以上对于因子Xa分析同样测定，只是底物是S-2366(L-PyroGlu-L-Pro-L-Arg-p-硝基酰替苯胺; Kabi)和该酶是人凝血酶(Enzyme Research Laboratories, Inc.; South Bend IN)。该酶浓度是175μM。

c.纤维蛋白溶酶（plasmin）试验

TBS-PEG缓冲液用于这一分析中。IC50与以上对于三个因子Xa分析同样方法来测定，只是底物是S-2251((D)-VaI-L-Leu-L-Lys-p-硝基酰替苯胺; Kabi)而该酶是人纤维蛋白溶酶(Kabi)。该酶浓度是5nM而底物浓度是300μM。

d.胰蛋白酶分析

含有10mM $CaCl_2$的TBS-PEG缓冲液用于这一分析中。该IC50与以上在因子Xa分析中所述同样方法测定，只是底物是BAPNA(苯甲酰基-L-Arg-p-硝基酰替苯胺; Sigma Chemical Co.; St.Louis MO)而该酶是牛胰腺的胰蛋白酶(XIII型，TPCK处理; Sigma)。该酶浓度是50nM而底物浓度是300μM。

e.弹性蛋白酶试验

Tris-Cl，pH7.4，300mMNaCl，2%(v/v)N-甲基-吡咯烷酮，0.01%(w/v)NaN_3缓冲液用于这一分析。该IC50是与以上在因子Xa分析中所述同样方法测定,只是底物是琥珀酰基-Ala-Ala-Ala-p-硝基酰替苯胺(Calbiochem-Nova Biochem Corp.; San Diego CA)和该酶是人嗜中性弹性蛋白酶(Athens Researchand Technology, Inc.: AthensGA)。该酶浓度是75nM和底物浓度是600μM。对照化合物是“TENSTOP”(N-α-tosyl-Gly-p-脒基苯基丙氨酸甲酯; American Diagnostica, Inc.; Greenwish CT)，它是可逆的因子Xa抑制剂(Stuerzebecher等人，Thromb.Res.54: 245-252(1989); Hauptmann等人，Thromb.Haem.63: 220-223(1990)，其中每一件被引入本文供参考)。

试验2: 测定凝固的抑制的试验

通式I的化合物的效力可通过使用采集的人捐献者血浆，由活体外前凝血酶时间(PT)分析方法来进行分析。活体外分析也可以使用，其中在通式I化合物静脉(iv)给药于大鼠或给药于兔子或十二指肠内(id)给药于大鼠之后的不同时间收集血浆，然后通过使用PT分析方法测定血浆半衰期来进行分析。用所选择的促凝血酶原激酶稀释启动PT试验以获得延伸的和高度可再现的凝固终点，称作如下所述的“稀释PT试验”。各种化合物的效力也可以使用血栓形成的活体内大鼠动静脉分流模型来测定。

a. 活体外稀释的前凝血酶时间试验

将100μl预热的(37℃)采集的人血小板贫乏血浆(PPP)加入到fibrometer杯(Baxter Diagnostics., Inc.; McGaw ParkIL)中。添加50μl的通式I化合物在TBS-BSA中各种浓度的溶液，它含有钙(5mM Tris-Cl, 100mM NaCl, 0.1%(w/v)牛血清清蛋白, 20mM CaCl2)。在对照实验中，有钙但没有通式I的试验化合物的TBS-BSA被添加，以测量未抑制的凝血时间。将含钙的150ul稀释的预热的兔促凝血酶原激酶(Baxter)加入到fibrometer杯中和启动fibrometer计时器。在处理该化合物之前获得了兔促凝血酶原激酶稀释曲线并用于选择促凝血酶原激酶稀释，以使未抑制的对照物有大约30秒PT时间。从稀释曲线时间计算出用试验化合物获得凝固的50%抑制率时的实验浓度(EC_{50})。

另外地，在Instrumentation Laboratories(IL)ACL3000-加上自动化的凝固仪器(IL; 米兰，意大利)上，使用“研究”模式来进行稀释的前凝血酶时间试验。促凝血酶原激酶被稀释到获得30-35秒的凝固时间为止。这一凝固时间被取作100%活性。通过稀释的促凝血酶原激酶试剂(兔脑IL-商标促凝血酶原激酶)的系列2-倍稀释，建立校正用的标准曲线。在试验期间，50ul样品(离心作用分离出的血浆)与100μl促凝血酶原激酶试剂混合，在169秒过后取浊度读数。从仪器计算的光散射的变化的最大速率来测定凝血时间。抑制率被表达为与校准曲线对比测得的百分活性。

b.活体内稀释的前凝血酶时间试验

按照批准的规程，通过尾部静脉(大鼠)或耳静脉(兔)以iv方式施用通式I的试验化合物。在通式I的试验化合物施用之后，以一定的时间间隔从插套管的颈动脉(大鼠)或耳动脉(兔)中抽取0.5mL血样。在离心处理获得PPP后，该血浆立即在冰上或冷冻贮存。

对于稀释的前凝血酶时间测定，该血浆被预热和如上所述来试验。从促凝血酶原激酶稀释曲线计算百分抑制率，它用每一系列的样品来进行并用于测定在血浆中保持了初始抗凝血剂活性的大约50%时的时间(T1/2)。

通式I的试验化合物也能够通过使用十二指肠内剂量给药规程来施用于大鼠。体重大约300g的雄性Sprague-Dawley大鼠通过按照批准的规程，皮下注射氯胺酮/甲苯噻嗪的结合物来麻醉。右颈动脉被插套管以便于采血。进行剖腹手术和十二指肠用球形尖头针管来安插套管并缝合定位以确保缝线远离该插入点。附加的缝合设置在插入点的附近以防止胃内容物的渗漏。缝线阻止化合物到达插入位置的效力是通过在每一实验的完结时压力试验来测试。插入点是距离十二指肠-胃结合部位大约4厘米。化合物是在1mL生理盐水中施用。在通式I的试验化合物的施用之前和在施用之后的30、60、90和120分钟抽取0.7mL血样。通过离心作用分离血浆并使用稀释的前凝血酶时间试验来测试凝固的抑制。

c.血栓形成的大鼠动静脉分流模型

本发明的各种化合物的抗血栓形成的功效可通过使用大鼠离体的动静脉(AV)分流来进行分析。AV分流回路由插入右颈动脉的20cm长的聚乙烯(PE)60管，含有6.5cm长度的丝光棉纱线(5cm暴露于血流中)的6cm长度PE160管和完成该回路进入左颈静脉的第二长度的PE60管(20cm)组成。在插入之前，该整个回路充满生理盐水。

通过使用注射泵和蝶形导管连续输注到尾部静脉(输注体积1.02ml/h)中来施用通式I的试验化合物。化合物被施用30分钟，然后打开分流支路并让血液流动15分钟的一段时期(总共45分钟输注)。在这一15分钟时期的末尾，分流支路被夹紧，小心地取出纱线并在分析

天平上称重。

使用从输注了盐水的对照大鼠获得的血栓重量，计算血栓形成的百分抑制率。

下面的表1给出了通式I的所选择化合物的因子Xa抑制活性(Ki-值)(测试该化合物的抑制活性是通过使用以上所述的活体外因子Xa试验(试验1a)来完成的)。

表1 因子Xa抑制活性(K_i-值):

实施例	Ki(FXa)[μM]
3	0.1558
5	0.0006
6	0.0010
8	0.0351
10	0.6040
14	0.0218
17	2.29
21	8.37
28	0.047
30	0.153
38	1.1
40	0.0107
45	26.5
54	3.01
56	0.0021
58	0.0575
61	0.957
69	0.285
72	4.3
82	0.0393
89	6.48
92	5.93
94	1.7
97	0.04
104	6.5
129	0.36
136	0.01
144	0.011
154	0.001

实施例

下列实施例给出了通式I的化合物的典型合成方法。这些实施例被理解为仅仅举例而已，不应以任何方式限制本发明的范围。这些实施例的化合物可通过质谱(MS)和/或核磁共振谱和/或熔点来表征。当在化合物合成的最后步骤中使用酸如三氟乙酸或乙酸时，例如当三氟乙酸用于除去叔丁基团或当使用含有此类酸的洗脱剂由色谱法提纯化合物时，在一些情况下，取决于后处理程序，例如取决于冻干过程的多种细节，该化合物部分地或完全以所用酸的盐形式，例如以乙酸盐或三氟乙酸盐或盐酸盐的形式获得。

实施例1

固相合成丙二酸衍生物的一般方法

一般的固相肽合成方法用于生产本发明的大部分的化合物。此类方法例如已经由Steward和Young进行了描述(Solid Phase Peptide Synthesis(Freemanand Co., San Francisco, 1969)，该文献被引入本文供参考。

除非另有说明，否则化合物是在用1%二乙烯基苯交联的聚苯乙烯树脂上合成的。酸敏型的连接剂(Rink Linker)偶合到固体载体上(Rink , Tetr.Lett.28:3787(1987) ; Sieber , Tetr.Lett. 28:2107(1987)，每一件文献被引入供参考)。全部的化合物是在壳体内构建的半自动化的肽合成器上合成的。Boc-和Fmoc-保护的L-和D-氨基酸衍生物是从各种商业来源获得，如Advanced ChemTech(Louisville, KY40228-9973, USA) ; Bachem(King of Prussia, PA19406, USA)和PerSeptive Biosystems(Framingham, MA01701, USA)。

通式I的化合物的合成是通过使用二异丙基碳化二亚胺和苯并三唑-1-醇作为活化试剂，根据传统的Fmoc方法(E.Atherton and R.C.Sheppard in "Solid Phase Peptide Synthesis: A Practical Approach", IRL Press, Oxford, England, 1989)来进行的。全部的偶合是在室温下在二甲基甲酰胺或二甲基甲酰胺:二氯甲烷(1:1混合

物）中进行40分钟。偶合的完成可按照Kaiser(Kaiser等人，Anal.Biochem.34:595(1970))描述的茚三酮试验检测，该文献被引入这里供参考。第二次(双)偶合是在第一种情况下偶合不完全时进行。

在树脂上肽组装完成之后，进行最终的Fmoc去保护，然后进行标准的洗涤周期和进行在302nm下去保护所释放的Fmoc基团的量的测定。然后该丙二酸衍生物由按照二异丙基-碳化二亚胺/苯并三唑-1-醇程序来类似地偶合。完工的树脂依次用二氯甲烷，二甲基甲酰胺和二氯甲烷洗涤，然后在真空下干燥和用于下一步骤中。

酰胺肟的固相合成:

通过在三乙胺、吡啶和二甲基甲酰胺的1:1:1(按体积)混合物存在下，将含腈物质的树脂(来自以上步骤)与20－40当量的盐酸羟胺混合来进行该一般程序。该悬浮液通常(超)声波处理大约30秒和在室温下振荡12-24小时。由FT-IR(KBr圆片)寻找在2225cm-1处-CN吸收的消失或由三氟乙酸:H_2O(95:5)或试剂K(见下面)分裂树脂的小样品和electrospray质谱分析测定分子量，来检测从腈至酰胺肟的转化的完成。该完工的树脂用二甲基甲酰胺，含10%H_2O的二甲基甲酰胺，乙醇，二氯甲烷洗涤，在用于下一步骤之前进行真空干燥。

脒的固相合成:

对于含脒的化合物的合成已报道了多个方法（例如参见P.J.Dunn(1995)在“Comprehensive Organic Functional Group Transformations:Amidines and N-Substituted Amidines”，Vol.5，741-782(edts.Alan R. Katritzky，Otto Meth-Cohen & Charles W.Rees)，Pergamon，N.Y.，1995)。这些方法中任何一种都不与固相有机合成相符。这里我们开发了在可溶性催化剂(二氯四(三苯基膦)钌(II)，DCRu)存在下使用过量三乙基硅烷进行还原，经酰胺肟前体的脒合成的合适程序。已经发现，在乙酸存在下三苯基膦的添加有利于还原和增加脒化合物的产率。在典型的实验中，在塞子塞好的反应容器中将干燥的树脂加入到由DCRu、三苯基膦、乙酸、二甲基甲酰胺和三乙基硅烷组成的还原“鸡尾酒(cocktail)”中。该还原通常在室温下

进行12-24小时。对于不完全还原的情况，可以使用附加量的三乙基硅烷和反应时间延长附加的4-8个小时。该完工的肽模拟(peptidomimetic)树脂用二甲基甲酰胺，乙醇，二氯甲烷洗涤并在室温下悬浮在试剂K(King等人，Int.J.Pept.Prot.Res.36:255-266(1990))鸡尾酒(5ml/g肽树脂)中达180分钟。然后该分裂混合物在无水乙醚中过滤和固体沉淀物通过离心作用来分离并在KOH的固体粒料上真空干燥，然后将固体物质溶于0.1%的三氟乙酸在水中的溶液和乙腈的1:1混合物中，冻干。

对于通式I化合物的提纯，将粗的冻干化合物的样品溶于含有10%-50%乙腈的0.1%三氟乙酸水溶液的混合物中。化合物溶液通常通过连接到0.45μm尼龙"ACRODISC"13(Gelman Sciences; Ann Arbor MI)过滤器的注射器来过滤。将适当体积的过滤的肽模拟(peptidomimetic)的溶液注入半制备性C_{18}柱中(Vydac Protein and Peptide C_{18}，218TP1010; The Separation Group; Hesperia CA)。使用Beckman"SYSTEMGOLD"HPLC，维持作为洗脱液的0.1%三氟乙酸缓冲液和乙腈(HPLC级)的梯度或等浓度混合物的流速。肽模拟物(peptidomimetic)的洗脱通过在230纳米下的UV检测来监控(Beckman，System Gold，Programmable Solvent Module126 and Programmable Detector Module166，由"SYSTEMGOLD"软件控制)。在使用MS鉴别与每种非对映异构体相对应的峰后，收集化合物，冻干和进行生物学试验。MS使用SCIEXAPIIII+仪器进行。另外，通过使用General Electric仪器(300MHz)或Bruker Avance DPX300(300MHz)进行NMR。对于NMR，样品典型地在DMSO-d6或CDCl3(Aldrich)中测量。

各化合物的典型合成方法总结在反应历程6中，下面的实施例说明实验细节。

实施例2和3

N-[(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-(S)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体

N-[(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-(S)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，更极性的非对映异构体

a)N-[(1-(S)-(羰基-(Rink-树脂)}-4-(双-叔丁氧基羰基-胍基)-丁基氨基甲酰基)-(S)-环己基-甲基]-2-(R,S)-(4-氰基-苄基)-N',N'-二甲基-丙二酰胺

按照实施例1中所述，通过使用苯并三唑-1-醇和二异丙基-碳化二亚胺(各自2当量)，将Fmoc-去保护的Rink树脂(210mg，0.16mmol)偶合到2-(Fmoc-氨基)-4-(S)-(N,N'-双-叔丁氧基羰基-胍基)-丁酸(326mg，0.5mmol，2当量)上。在Fmoc去保护之后，使用同样的偶合条件，树脂与(S)-环己基-(Fmoc-氨基)-乙酸(2当量)偶合。在Fmoc去保护之后，在室温下通过使用在二甲基甲酰胺中的二异丙基-碳化二亚胺/苯并三唑-1-醇(各自1.1当量)将树脂与2-(R,S)-(4-氰基-苄基)-N,N-二甲基-丙酰胺酸(45mg，0.17mmol，1.1当量)偶合。反应的完成通过茚三酮试验证实。该树脂用二甲基甲酰胺，甲醇和二氯甲烷洗涤并真空干燥2-3小时。

b)N-[(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-(S)-环己基-甲基]-2-(R)-[4-(N-羟基氨基氨代甲酰基)-苄基]-N',N'-二甲基-丙二酰胺三氟乙酸盐和

N-[(1-(R)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-(S)-环己基-甲基]-2-(S)-[4-(N-羟基氨基氨代甲酰基)-苄基]-N',N'-二甲基-丙二酰胺三氟乙酸盐

来自步骤a的干燥树脂被转移到螺帽封闭的20-ml管形瓶中，与羟胺盐酸盐混合(350mg，5mmol，25当量)。向反应管形瓶中添加三乙胺，吡啶和二甲基甲酰胺(1:1:1，8ml)的混合物，该管形瓶被封闭，超声波处理30秒。该反应在室温下反应一夜。反应的完成按照实施例1中所述来检查。该完工的树脂分成两个部分。一个部分按照实施例1中所述进行分裂和处理，得到标题化合物。MS分析得到M.Wt.573.4(计算值573.3)。第二部分的该树脂用于实施例4和5中。

实施例4和5

2-(4-氨基氨代甲酰基-苄基)-N-[(1-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，非对映的混合物和较少极性的非对映异构体

将二氯四(三苯基膦)钌(II)(20mg)和三苯基膦(80mg)在二甲基甲酰胺(1mL)和冰醋酸(135μl)中的溶液于50℃加热10-15分钟，得到透明的棕色溶液。将反应管形瓶冷却到室温和添加来自实施例2/3b的第二份该干燥树脂(100mg)，随后添加三乙基硅烷(1mL)。该管形瓶在N_2氛围下密封和在室温下振荡12小时。还原成脒的反应的完成是通过少量树脂的分裂和用HPLC/ESMS测试产物来监控。该完工的树脂用二甲基甲酰胺，甲醇，二氯甲烷洗涤，按照在实施例1中所述进行处理。冻干的产物(14mg)通过HPLC提纯，分离出两种非对映异构体。提纯的产物通过ESMS分析，计算值560.35；实测值560。

实施例6和7

2-(S)-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸烯丙基酯三氟乙酸盐，较少极性的非对映异构体和

2-(S)-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸烯丙基酯三氟乙酸盐，更极性的非对映异构体

a)N-苄基-2-(R,S)-(4-氰基-苄基)-N-甲基-丙酰胺酸

苄基-甲基-胺(120mL，887mmol)，双(三甲基甲硅烷基)-乙酰胺(118mL，482mmol)和无水二氯甲烷(1000mL)的溶液被加热回流3小时。反应混合物被冷却到室温，分几份添加4-(R,S)-(2,2-二甲基-4,6-二氧代-[1,3]二噁烷-5-基甲基)-苄腈(25g，97mmol)。反应混合物回流另外3小时，冷却到室温和倾倒在1700mL 1N盐酸和800mL乙酸乙酯的冷却混合物中，用6n氢氧化钠溶液调节至pH4，用乙酸乙酯和二氯甲烷萃取。合并的有机层用盐水洗涤，干燥和真空浓缩。沉淀的晶体被吸取和加以干燥，得到25.0g(80%)所需产物。

mp: 152-153℃(dc)。

b)(S)-[2-(苄基-甲基-氨基甲酰基)-3-(R,S)-(4-氰基-苯基)-丙酰基氨基]-环己基-乙酸甲酯

将N-苄基-2-(R,S)-(4-氰基-苄基)-N-甲基-丙酰胺酸(25.0g, 78mmol), (S)-氨基-环己基-乙酸甲酯(14.2g, 83mmol), 二异丙基乙胺(16mL, 94mmol), 3-羟基-3H-苯并[d][1,2,3]三嗪-4-酮(3.2g, 20mmol), 和二甲基甲酰胺(520mL)的溶液冷却到10℃。滴加双环已基-碳化二亚胺(18.7g, 91mmol)在甲苯(30mL)中的溶液, 反应混合物放置一夜。沉淀的脲被吸取, 该滤液在真空中蒸发, 溶解在乙酸乙酯中, 用饱和的碳酸氢钠溶液和盐水洗涤, 干燥, 和在真空中蒸发。从正庚烷/异丙醇中结晶, 得到6.3g(17%)所需产物。mp: 119-120℃。该滤液进行蒸发, 用正庚烷/乙酸乙酯=10/1作为洗脱液, 在硅胶柱上通过柱色谱法提纯。合并的级分得到6.1g(17%)的所需产物。mp: 120-121℃。

c){2-苄基-甲基-氨基甲酰基}-3-(R,S)-[4-(N-羟基氨基氨代甲酰基)-苯基]-丙酰基氨基}-(S)-环己基-乙酸甲酯

将[2-(苄基-甲基-氨基甲酰基)-3-(R,S)-(4-氰基-苯基)丙酰基氨基]-(S)-环己基-乙酸甲酯(12.0g, 26mmol)和羟胺(4.3g, 130mmol)在乙醇(150mL)中的溶液加热回流4小时。反应混合物被冷却到室温, 在真空中蒸发, 溶解在乙醇中和倾倒在冰-水中。通过吸取来收集沉淀物, 在60℃下真空干燥, 得到11.6g(90%)所需产物。

mp: 135-138℃, MS: 509(M+H)。

d)[2-(苄基-甲基-氨基甲酰基)-3-(R,S)-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸甲酯

{2-(苄基-甲基-氨基甲酰基)-3-(R,S)-[4-羟基氨基氨代甲酰基]-苯基]-丙酰基氨基}-(S)-环己基-乙酸甲酯(11.0g, 22mmol)在乙酸中用钯/活性炭进行氢化, 得到9.2g(77%)的所需产物, 它无需进一步提纯就可用于下一步骤中。

mp: 123-124℃, MS: 493(M+H)。

e)[2-(苄基-甲基-氨基甲酰基)-3-(R,S)-(4-氨基氨代甲酰基-苯

基)-丙酰基氨基]-(S)-环己基-乙酸三氟乙酸盐

将上述[2-(苄基-甲基-氨基甲酰基)-3-(R,S)-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸甲酯(9.2g，19mmol)悬浮于乙腈(350mL)中，添加水/浓盐酸(1/1，500mL)，反应混合物在室温下搅拌。在4天后反应混合物进行蒸发，添加水和混合物被冻干。该产物使用二氯甲烷/甲醇/三氟乙酸=15/1/0.5到4/1/0.5，在硅胶柱上由柱色谱法提纯。所收集的级分得到8.2g(74%)所需产物。

MS: 479(M+H)。

f)2-(S)-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸烯丙基酯三氟乙酸盐，较少极性的非对映异构体和

2-(S)-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸烯丙酯三氟乙酸盐，更极性的非对映异构体

在0℃下向[2-(苄基-甲基-氨基甲酰基)-3-(R,S)-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸三氟乙酸盐(2.9g，4.9mmol)在二甲基甲酰胺(350mL)中的溶液添加三甲基吡啶(2.4g，19.6mmol)和HATU(2.1g，5.4mmol)。反应混合物在这一温度下搅拌30分钟，然后添加(S)-2-氨基-5-胍基-戊酸烯丙酯(1.2g，4.9mmol)。反应混合物升至室温，并静置60小时。溶剂进行真空蒸发和该残留物使用水/乙醇/三氟乙酸(9/1/0.1到5/5/0.1)作为洗脱剂通过在RP18材料上的MPLC来提纯，得到1.0g(23%)的高极性的非对映异构体和584mg(13%)的较少极性的非对映异构体。两级分显示出正确的MS谱。使用以上描述的程序制备下面的化合物:

Expl.	名称	MS	方法
8	N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐，更极性的非	好	固相

	对映异构体		
9	N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基)-丙二酰胺三氟乙酸盐,较少极性的非对映异构体	好	固相
10	2-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基]-1,2,3,4-四氢-异喹啉-3-(S)-羧酸(1-(S)-氨甲酰基-4-胍基-丁基)-酰胺三氟乙酸盐	好	固相
11	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
12	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-丙二酰胺三氟乙酸盐	好	固相
13	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
14	N-苄基-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-丙二酰胺三氟乙酸盐	好	固相
15	N-[2-(4-氨基-苯基)-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
16	N-[2-(4-氨基-苯基)-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
17	N-烯丙基-N'-[2-(4-氨基-苯基)-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-丙二酰胺三氟乙酸盐	好	固相

18	N-[2-(4-氨基-苯基)-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)乙基)-2-(4-氨基氨代甲酰基-苄基)-N'-苯基-丙二酰胺	好	固相
19	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-甲基-丁基]-N,N'-二甲基-丙二酰胺	好	固相
20	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-甲基-丁基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
21	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-甲基-丁基]-N-甲基-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
22	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N,N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
23	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
24	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N-甲基-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
25	2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基]-1,2,3,4-四氢-异喹啉-3-羧酸(1-(S)-氨基甲酰基-4-胍基-丁基)-酰胺三氟乙酸盐	好	固相
26	2-(S)-[2-烯丙基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基]-1,2,3,4-四氢-异喹啉-3-羧酸(1-(S)-氨基甲酰基-4-胍基-丁基)酰胺三氟乙酸盐	好	固相
27	2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-苯氧羰基-丙酰基]-1,2,3,4-四氢-异喹啉-3-羧酸(1-(S)-氨基甲酰	好	固相

	基-4-胍基-丁基)-酰胺三氟乙酸盐		
28	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基)-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
29	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-丙二酰胺三氟乙酸盐	好	固相
30	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
31	4-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-4-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁酸三氟乙酸盐	好	固相
32	4-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-4-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁酸	好	固相
33	4-(S)-[2-烯丙基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-4-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁酸三氟乙酸盐	好	固相
34	4-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-苯氨羰基-丙酰基氨基]-4-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁酸	好	固相
35	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-2-基-乙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
36	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-2-基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
37	N-烯丙基-2-(4-氨基氨代甲酰基-苄	好	固相

	基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-2-基-乙基)-丙二酰胺三氟乙酸盐		
38	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-2-基-乙基]-N'-苯基-丙二酰胺三氟乙酸	好	固相
39	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-3-苯基-丙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
40	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-3-苯基-丙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
41	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-3-苯基-丙基)-丙二酰胺三氟乙酸盐	好	固相
42	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-3-苯基-丙基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
43	N-[4-氨基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁基]-2-(4-氨基氨代甲酰基-苄基)-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
44	N-[4-氨基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁基]-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
45	N-烯丙基-N'-[4-氨基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁基]-2-(4-氨基氨代甲酰基-苄基)-丙二酰胺三氟乙酸盐	好	固相
46	N-[4-氨基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-丁基]-2-(4-氨基氨代甲酰基-苄基)-N'-苯基-丙二酰胺三氟乙酸盐	好	固相

47	3-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-N-(1-(S)-氨基甲酰基-4-胍基-丁基)-琥珀酰胺酸三氟乙酸盐	好	固相
48	3-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-N-(1-(S)-氨基甲酰基-4-胍基-丁基)-琥珀酰胺酸三氟乙酸盐	好	固相
49	3-(S)-[2-烯丙基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-N-(1-(S)-氨基甲酰基-4-胍基-丁基)-琥珀酰胺酸三氟乙酸盐	好	固相
50	3-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-苯氨羰基-丙酰基氨基]-N-(1-(S)-氨基甲酰基-4-胍基-丁基)-琥珀酰胺酸三氟乙酸盐	好	固相
51	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-羟基-乙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
52	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-羟基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
53	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-羟基-乙基]-丙二酰胺三氟乙酸盐	好	固相
54	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-羟基-乙基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
55	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-N'-甲基-丙二酰胺三氟乙酸盐,	好	固相
56	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-N', N'-二	好	固相

	甲基-丙二酰胺三氟乙酸盐		
57	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-丙二酰胺三氟乙酸盐	好	固相
58	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-苯基-甲基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
59	N-[2-苄氧基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
60	N-[2-苄氧基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
61	N-烯丙基-N'-[2-苄氧基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基)-2-(4-氨基氨代甲酰基-苄基)-丙二酰胺三氟乙酸盐	好	固相
62	N-[2-苄氧基-1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-乙基]-2-(4-氨基氨代甲酰基-苄基)-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
63	[5-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-乙基氨基甲酰基-丙酰基氨基]-5-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-氨基甲酸苄基酯	好	固相
64	[5-(S)-(3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-5-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-氨基甲酸苄基酯	好	固相
65	[5-(S)-[2-烯丙基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-5-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-氨基甲酸苄基酯	好	固相
66	[5-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-苯氨羰基-丙	好	固相

	酰基氨基)-5-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基)-氨基甲酸苄基酯		
67	2-(4-氨基氨基甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
68	2-(4-氨基氨基甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	固相
69	4-(S)-[3-(4-氨基氨基甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-4-[1-(S)-(1-(S)-氨基甲酰基-2-环己基-乙基氨基甲酰基)-4-胍基-丁基氨基甲酰基]-丁酸三氟乙酸盐	好	固相
70	4-(S)-[3-(4-氨基氨基甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-4-[1-(S)-(1-(S)-氨基甲酰基-2-环己基-乙基氨基甲酰基)-4-胍基-丁基氨基甲酰基]-丁酸三氟乙酸盐	好	固相
71	2-(4-氨基氨基甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲基-丙二酰胺三氟乙酸盐三氟乙酸盐	好	固相
72	2-(S)-{2-(R)-[3-(4-氨基氨基甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-己酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
73	2-(S)-{2-(R)-[3-(4-氨基氨基甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-己酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
74	2-(S)-{2-(R)-[2-苄基氨基甲酰基-3-(4-氨基氨基甲酰基-苯基)-丙酰基氨基]-己酰基氨基-5-胍基-戊酸三氟乙酸盐	好	固相
75	2-(4-氨基氨基甲酰基-苄基)-N-{1-(S)-[1-(S)-氨基	好	固相

	甲酰基-2-(4-羟基-苯基)-乙基氨基甲酰基]-戊基}-N',N'-二甲基-丙二酰胺三氟乙酸盐		
76	2-(3-氨基氨代甲酰基-苄基)-N-(1-(S)-[1-(S)-氨基甲酰基-2-(4-羟基-苯基)-乙基氨基甲酰基]-戊基-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
77	2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-己酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
78	2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-己酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
79	2-(S)-{2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-己酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
80	2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸; 与三氟乙酸形成三氟乙酸盐	好	固相
81	2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
82	2-(S)-{2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
83	2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-3-环己基-丙酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
84	2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-甲基氨基甲酰基-丙酰基氨基]-3-环己基-丙酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相

85	2-(S)-{2-(S)-(2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-3-环己基-丙酰基氨基}-5-胍基-戊酸三氟乙酸盐	好	固相
86	2-(4-氨基氨代甲酰基-苄基)-N-[1-(R)-(1-(R)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-环己基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
87	2-(3-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
88	4-(S)-[3-(4-氨基氨代甲酰基-苄基)-2-苯氨羰基-丙酰基氨基]-4-[1-(S)-(1-(S)-氨基甲酰基-2-环己基-乙基氨基甲酰基)-4-胍基-丁基氨基甲酰基]-丁酸三氟乙酸盐	好	固相
89	4-(S)-[2-烯丙基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-4-[1-(S)-(1-(S)-氨基甲酰基-2-环己基-乙基氨基甲酰基)-4-胍基-丁基氨基甲酰基]-丁酸三氟乙酸盐	好	固相
90	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(2-氨基氨代甲酰基-1-(S)-氨基甲酰基-乙基氨基甲酰基)-环己基-甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
91	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(2-氨基氨代甲酰基-1-(S)-氨基甲酰基-乙基氨基甲酰基)-环己基-甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	固相
92	2-(4-氨基氨代甲酰基-苄基)-N-(1-(S)-[(3-氨基氨代甲酰基-苄基)-氨基甲酰基甲基-氨基甲酰基]-戊基)-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
93	2-(4-氨基氨代甲酰基-苄	好	固相

	基)-N-((S)-(1-(S)-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-脲基-丁基氨基甲酰基)-环己基-甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体		
94	3-{2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二异丙基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-2-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-乙基}-1-甲基-吡啶鎓三氟-乙酸盐三氟乙酸，更极性的非对映异构体	好	固相
95	3-{2-(S)-{2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二异丙基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-2-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基)-乙基}-1-甲基-吡啶鎓三氟-乙酸盐三氟乙酸，较少极性的非对映异构体	好	固相
96	2-(4-氨基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-脲基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
97	2-(4-氨基-苄基)-N-((S)-(1-(S)-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-脲基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	固相
98	2-(4-氨基氨代甲酰基-苄基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-脲基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丁基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
99	2-(4-氨基氨代甲酰基-苄	好	固相

	基)-N-((S)-{1-(S)-[1-(S)-(2-(S)-氨基甲酰基-吡咯烷-1-羰基)-3-甲基-丁基氨基甲酰基]-4-胍基-丁基氨基甲酰基}-环己基-甲基)-N',N'-二异丁基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体		
100	N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-(4-二甲基氨基-萘-2-基甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
101	N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-(4-二甲基氨基-萘-2-基甲基)-N',N'-二异丙基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	固相
102	N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
103	N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	固相
104	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(氨基甲酰基甲基-吡啶-4-基甲基-氨基甲酰基)-环己基-甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
105	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(氨基甲酰基甲基-吡啶-4-基甲基-氨基甲酰基)-环己基-甲基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	传统合成
106	N-{(S)-[(4-氨基-丁基)-氨基甲酰基甲基-氨基甲酰	好	固相

	基]-环己基-甲基}-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟醋酸盐，更极性的非对映异构体		
107	N-{(S)-[(4-氨基-丁基)-氨基甲酰基甲基-氨基甲酰基]-环己基-甲基}-2-(4-氨基氨代甲酰基-苄基)-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	传统合成
108	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	传统合成
109	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	传统合成
110	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-萘-1-基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	传统合成
111	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-甲基-丁基]-N,N',N'-三甲基-丙二酰胺三氟乙酸盐	好	固相
112	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N,N',N'-三甲基-丙二酰胺三氟乙酸盐	好	固相
113	2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基]-1,2,3,4-四氢-异喹啉-3-羧酸(1-(S)-氨基甲酰基-4-胍基-丁基)-酰胺三氟乙酸盐	好	固相
114	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-戊基]-N',N'-二甲	好	固相

	基-丙二酰胺三氟乙酸盐		
115	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2,2-二甲基-丙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
116	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2,2-二甲基-丙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
117	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2,2-二甲基-丙基]-丙二酰胺三氟乙酸盐	好	固相
118	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2,2-二甲基-丙基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
119	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
120	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐	好	固相
121	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
122	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-环己基-乙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
123	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-环己基-乙基]-N',N'-二甲基-丙二酰胺三氟乙酸盐	好	固相
124	N-烯丙基-2-(4-氨基氨代甲酰基-苄	好	固相

	基)-N'-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-环己基-乙基]-丙二酰胺三氟乙酸盐		
125	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-2-环己基-乙基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
126	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N'-甲基-丙二酰胺三氟乙酸盐	好	固相
127	N-烯丙基-2-(4-氨基氨代甲酰基-苄基)-N'-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-丙二酰胺三氟乙酸盐	好	固相
128	2-(4-氨基氨代甲酰基-苄基)-N-[1-(S)-(1-(S)-氨甲酰基-4-胍基-丁基氨基甲酰基)-2-苯基-乙基]-N'-苯基-丙二酰胺三氟乙酸盐	好	固相
129	N-苄基-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	固相
130	N-苄基-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-2-[4-(N-羟基氨基氨代甲酰基)-苄基]-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	固相
131	2-(S)-(2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基)-5-胍基-戊酸乙酯盐酸盐	好	传统合成
132	(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-环己基-乙酸，较少极性的非对映异构体	好	传统合成
133	(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯	好	传统合成

	基)-丙酰基氨基]-环己基-乙酸,更极性的非对映异构体		
134	2-{2-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-戊二酸肼盐酸盐	好	传统合成
135	2-(S)-{2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸乙酯三氟乙酸盐	好	传统合成
136	2-(S)-(2-(S)-[2-苄基氨基甲酰基-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基)-5-胍基-戊酸乙基三氟乙酸盐，较少极性的非对映异构体	好	传统合成
137	2-(4-氨基氨代甲酰基-苄基)-N-[(S)-环己基-(4-胍基-1-(S)-苯乙基氨基甲酰基-丁基氨基甲酰基)-甲基]-N',N'-二甲基-丙二酰胺盐酸盐	好	传统合成
138	2-(S)-(2-(S)-[3-(4-氨基氨代甲酰基-苯基)-2-二甲基氨基甲酰基-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸苄基酯盐酸乙酸盐	好	传统合成
139	N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-(S)-环己基-[(萘-1-基甲基)-氨基甲酰基]-甲基}-丙二酰胺三氟乙酸盐	好	传统合成

实施例140和141

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐，较少极性的非对映异构体和

N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐，更极性的非对映异构体

a)N-苄基-2-(R,S)-(4-氰基-苄基)-丙酰胺酸

将苄胺(58.6g，534mmol)，双(三甲基甲硅烷基)-乙酰胺(71mL，90mmol)和无水二氯甲烷(600mL)的溶液加热回流3小时。让反应混合物冷却到室温，然后分几份添加4-(R,S)-(2,2-二甲基-4,6-二氧代-[1,3]二噁烷-5-基甲基)-苄腈(15g,58mmol)。反应混合物回流3小时，冷却到室温和倾倒在1000ml1n盐酸和500ml乙酸乙酯的冷却混合物中。合并的有机层用盐水洗涤，干燥和真空浓缩。沉淀的晶体被吸取和加以干燥，得到11.07g(62%)所需产物。

mp:152-153℃(dc)，MS:309(M+H)。

b)[2-苄基氨基甲酰基-3-(R,S)-(4-氰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸甲酯

将N-苄基-2-(R,S)-(4-氰基-苄基)-丙酰胺酸(10g，32.4mmol)，(S)-氨基-环己基-乙酸甲酯(5.94g，34.7mmol)，二异丙基乙胺(6.45mL，37.9mmol)，3-羟基-3H-苯并[d][1,2,3]三嗪-4-酮(1.32g，8.1mmol)，和二甲基甲酰胺(100mL)的溶液冷却到10℃。滴加双环己基-碳化二亚胺(7.83g，37.9mmol)在甲苯(10mL)中的溶液，反应混合物放置一夜。沉淀的脲被吸取，该滤液在真空中蒸发，溶解在乙酸乙酯中，用饱和碳酸氢钠溶液和盐水洗涤，干燥，和真空蒸发。从正庚烷/异丙醇中结晶得到9.91g(66%)的所需产物。

m.p.： 170-174℃，MS:462(M+H)。

c){2-苄基氨基甲酰基-3-(R,S)-[4-(N-羟基氨基氨代甲酰基)-苯基]-丙酰基氨基}-(S)-环己基-乙酸甲酯

将[2-苄基氨基甲酰基-3-(R,S)-(4-氰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸甲酯(9.0g,19.5mmol)和羟胺(3.22g，97.5mmol)在乙醇(180mL)中的悬浮液加热回流4小时。反应混合物被冷却到室温，在真空中蒸发，溶解在乙醇中和倾倒在冰-水中。沉淀物通过吸取来收集，在50℃下真空干燥，得到7.9g(82%)的所需产物。

mp:101-104℃，MS:495(M+H)。

d)[2-苄基氨基甲酰基-3-(R,S)-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸甲酯

{2-苄基氨基甲酰基-3-(R,S)-[4-(N-羟基氨基氨代甲酰基)-苯基]-丙酰基氨基}-(S)-环己基-乙酸甲酯(7.6g, 15.4mmol)在乙酸中用钯/碳加以氢化，得到所需产物，它无需进一步提纯就可在下一步骤中使用。

mp: 101-104℃, MS:479(M+H)。

e)[2-苄基氨基甲酰基-3-(R,S)-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸盐酸盐

将以上[2-苄基氨基甲酰基-3-(R,S)-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸甲酯悬浮于水/浓盐酸(1/1, 200mL)中和在室温下搅拌。在8天后添加乙腈(100mL)，进一步搅拌2天。反应混合物进行过滤和倾倒在冰-水中。

该沉淀物通过分级结晶来收集:

级分1: 3.36g(52%, 非对映异构体混合物: 6.7%高极性, 78.0%低极性)

级分2: 857mg(13%, 非对映异构体混合物: 55.3%高极性, 31.9%低极性), 油

级分3: 461mg(7%, 非对映异构体混合物: 3.8%高极性, 93.5%低极性), mp: 166℃(subl.)

级分4: 455mg(7%, 96.7%低极性非对映异构体), 油

HPLC: 极性非对映异构体: 15.62min, 非极性非对映异构体: 16.21mm。

HPLC-条件: Nucleosil250/4, 7μM, 1ml/min, 梯度: 在30min内100%(H_2O+0.1%三氟乙酸)至100%乙腈，在5min内100%乙腈，=254nm。

全部级分的MS显示: 465(M+H)。

尝试通过在硅胶上的快速色谱法(二氯甲烷/甲醇/冰醋酸=9/1/0.5)来提纯级分1，但丙二酸手性中心发生异构化得到标题化合物的乙酸盐。

f)N-苄基-2-(R)-(4-氨基氨代甲酰基-苄基)-N'-[(1-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐和

N-苄基-2-(S)-(4-氨基氨代甲酰基-苄基)-N'-[(1-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-丙二酰胺三氟乙酸盐

[2-苄基氨基甲酰基-3-(R,S)-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-(S)-环己基-乙酸乙酸盐(103mg, 0.20mmol), 苯并三唑-1-醇水合物(32mg, 0.24mmol), 2-(S)-氨基-5-胍基-戊酸酰胺在二甲基甲酰胺(4mL)中的溶液被搅拌30分钟, 然后冷却到0℃至-5℃。添加1,3-双环己基脲(49mg,0.24mmol)的溶液,反应混合物在0℃下搅拌24小时。蒸发溶剂, 残留物通过制备性HPLC提纯而得到4.5mg(3%)的F1(更极性的非对映异构体)和7.8mg(5%)的F2(较少极性的非对映异构体)。

HPLC-条件: Nucleosil250/21mm, 7uM, 15ml/min, 68%H_2O+0.1%三氟乙酸, 32%乙腈。

F1: mp.: 150-154℃, MSm/z: 620.5((M+H)+, 9%), 310.9($(M+2H)^{2+}$, 100%)。

F2: mp.: 102-106℃, MSm/z: 620.5((M+H)+, 5%), 310.9($(M+2H)^{2+}$, 34%), 150.0(100%)。

使用以上描述的程序制备下面的化合物:

142	2-(4-氨基氨代甲酰基-苄基)-N-{(S)-(2-(3-氨基氨代甲酰基-苯基)-1-氨基甲酰基-乙基氨基甲酰基]-环己基-甲基}-N',N'-二甲基-丙二酰胺三氟乙酸盐, 更极性的非对映异构体	好	传统合成
143	2-(4-氨基氨代甲酰基-苄基)-N-{(S)-[2-(3-氨基氨代甲酰基-苯基)-1-氨基甲酰基-乙基氨基甲酰基]-环己基-甲基}-N',N'-二甲基-丙二酰胺三氟乙酸盐, 较少极性的非对映异构体	好	传统合成
144	N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[(S)-(1-(S)-氨基甲酰基-4-胍基-丁基氨基甲酰基)-环己基-甲基]-N-甲基-丙二酰胺三氟乙酸盐	好	传统合成
145	2-(S)-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨	好	传统合成

	基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸盐酸盐		
146	2-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-3-萘-1-基-丙酸乙酯三氟乙酸盐，较少极性的非对映异构体	好	传统合成
147	2-{2-(S)-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-3-萘-1-基-丙酸乙酯三氟乙酸盐，更极性的非对映异构体	好	传统合成
148	2-(S)-{2-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸甲酯三氟乙酸盐，最少极性的非对映异构体	好	传统合成
149	2-(S)-{2-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸甲酯三氟乙酸盐，较少极性的非对映异构体	好	传统合成
150	2-(S)-{2-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸甲酯三氟乙酸盐，更极性的非对映异构体	好	传统合成
151	2-(S)-{2-[2-(苄基-甲基-氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-2-环己基-乙酰氨基}-5-胍基-戊酸甲酯三氟乙酸盐，最极性的非对映异构体	好	传统合成
152	N-苄基-N'-{[1-(S)-(苄基-甲基-氨基甲酰基)-4-胍基-丁基氨基甲酰基]-环己基-甲基}-2-(4-氨基氨代甲酰基-苄基)-N-甲基-丙二酰胺三氟乙酸盐，最极性的非对	好	传统合成

	映异构体		
153	N-苄基-N'-{[1-(S)-(苄基-甲基-氨基甲酰基)-4-胍基-丁基氨基甲酰基]-环己基-甲基}-2-(4-氨基氨代甲酰基-苄基)-N-甲基-丙二酰胺三氟乙酸盐，更极性的非对映异构体	好	传统合成
154	N-苄基-N'-{[1-(S)-(苄基-甲基-氨基甲酰基)-4-胍基-丁基氨基甲酰基]-环己基甲基}-2-(4-氨基氨代甲酰基-苄基)-N-甲基-丙二酰胺三氟乙酸盐，较少极性的非对映异构体	好	传统合成
155	N-苄基-2-(4-氨基氨代甲酰基-苄基)-N'-[环己基-(1-(S)-二甲基氨基甲酰基-4-胍基-丁基氨基甲酰基)-甲基]-N-甲基-丙二酰胺三氟乙酸盐	好	传统合成
156	(S)-[2-(4-氨基氨代甲酰基-苄基氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-环己基-乙酸甲酯三氟乙酸盐	好	传统合成
157	(S)-[2-(4-氨基氨代甲酰基-苄基氨基甲酰基)-3-(4-氨基氨代甲酰基-苯基)-丙酰基氨基]-环己基-乙酸三氟乙酸盐	好	传统合成

所用的缩写:

aPTT	活化部分凝血活酶时间
ATS	安他心
AV	动静脉途径
BAPNA	苯甲酰基-L-Arg-p-硝基酰替苯胺
Boc	叔丁氧基羰基
℃	摄氏温度
cal	计算值
$CDCl_3$	氘代氯仿
Class. Synth.	传统的合成

cm	厘米
dc	分解
DCCI	二环己基碳二亚胺
DCRu	二氯四(三苯基膦)钌(II)
DIC	弥漫性血管内凝血
DICI	二异丙基碳化二亚胺
DMSO	二甲亚砜
DVT	深静脉血栓形成
eq.	当量
ESMS	电子喷射质谱
expl	实施例
FAB	快速原子轰击
Fmoc	9-芴基甲氧基羰基
FT-IR	傅立叶转换红外线
g	克
h	小时
HATU	N-[(二甲基氨基)-1H-1,2,3-三唑并[4,5-b]吡啶-1-基-亚甲基]-N-甲基甲铵六氟磷酸盐N-氧化物
HPLC	高压液相色谱法
HPLC/ESMS	高压液相色谱法/电子喷射质谱
id	经过十二指肠
iv	静脉内
kg	公斤
Km	Michaelis-Menten-常数
LMWH	低分子量haparin
mg	毫克
MHz	兆赫
min	分钟
ml	毫升

mM	毫摩尔浓度
mmol	毫摩尔
MS	质谱
mp.	熔点
μl	微升
μm	微米
μM	微摩尔浓度
nm	纳米
nM	纳摩尔
NMR	核磁共振
PE	聚乙烯
PEG	聚乙二醇
PG	保护基
PPP	血小板贫血
PT	前凝血酶时间
sec	秒
TAP	壁虱抗凝血肽
TBS-BSA	三羟甲基氨基甲烷缓冲的盐水牛血清清蛋白
TBS-PEG	三羟甲基氨基甲烷缓冲的盐水聚乙二醇
TF	组织因子
TFPI	组织因子途径抑制剂
TOTU	O-((氰基-(乙氧基羰基)-亚甲基)氨基)-N,N,N',N'-四甲基脲镒四氟硼酸盐
TPCK	甲苯磺酰苯基氯甲基酮
TRIS-Cl	双(2-羟乙基)亚氨基三(羟甲基)甲烷2-双(2-羟乙基)氨基-2-(羟甲基)-1,3-丙二醇，氯化物盐
UV	紫外