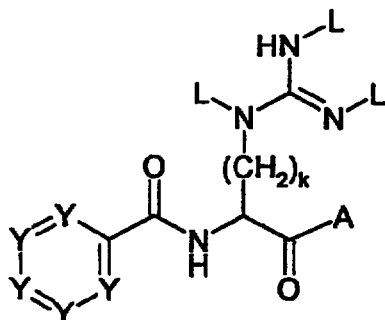


N-GUANIDINOALKYLAMIDES, THEIR PREPARATION, THEIR USE, AND PHARMACEUTICAL PREPARATIONS COMPRISING THEM

5 The present invention relates to compounds of the formula I,



in which A, L, Y and k have the meanings indicated below. The compounds of the
10 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 enzymes factor Xa (FXa) and/or factor VIIa
(FVIIa), and can in general be applied in conditions in which an undesired activity of
15 factor Xa and/or factor VIIa is present or for the cure or prevention of which an
inhibition of factor Xa and/or factor VIIa is intended. The invention furthermore relates
to processes for the preparation of compounds of the formula I, their use, in particular
as active ingredients in pharmaceuticals, and pharmaceutical preparations
comprising them.

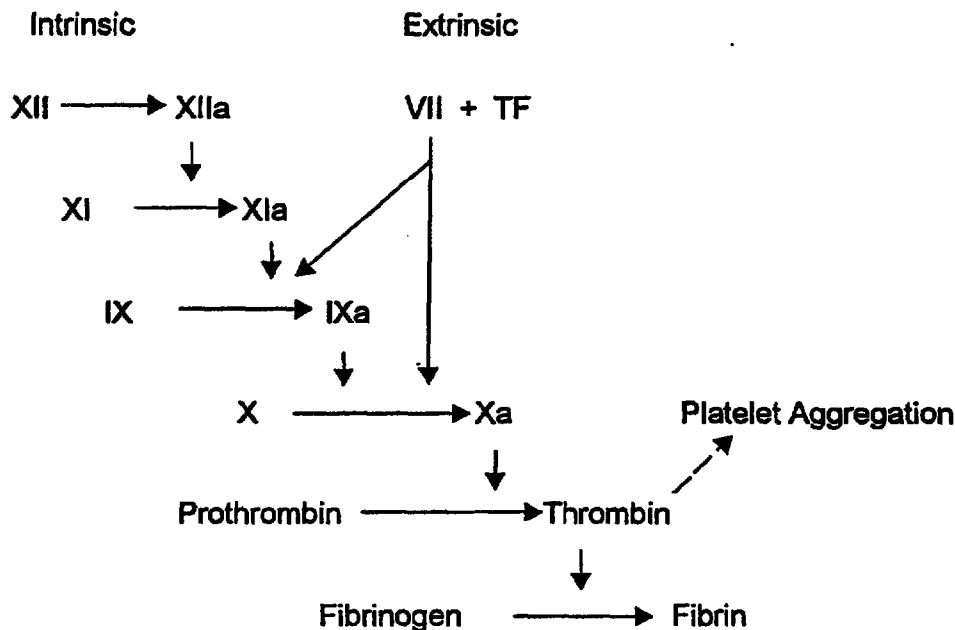
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The ability to form blood clots is vital to survival. The formation of a blood clot or a
thrombus is normally the result of tissue injury which initiates the coagulation
cascade and has the effect of slowing or preventing blood flow in wound healing.
Other factors which are not directly related to tissue injury like atherosclerosis and
25 inflammation may also initiate the coagulation cascade. In general, a relationship
exists between inflammation and the coagulation cascade. Inflammation mediators

regulate the coagulation cascade and coagulation components influence the production and activity of inflammation mediators.

However, in certain disease states the formation of blood clots within the circulatory system reaches an undesired extent and is itself the source of morbidity potentially leading to pathological consequences. It is nevertheless not desirable in such disease states to completely inhibit the blood 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 thrombin proceeds through a single common pathway (see Scheme 1). 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 factor VIIa/tissue factor(TF) 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.



Scheme 1: Blood coagulation cascade

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. 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 and/or factor VIIa activity.

In many clinical applications there is a great need for the prevention of intravascular blood clots or for some anticoagulant treatment. For example, nearly 50 % of patients

who have undergone a total hip replacement develop deep vein thrombosis (DVT). The currently available drugs like heparin and derivatives thereof are not satisfactory in many specific clinical applications. The currently approved therapies include fixed dose low molecular weight heparin (LMWH) and variable dose heparin. Even with
5 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
10 myocardial infarction or suffering from crescendo angina. The present, conventionally accepted therapy which consists of administering heparin and aspirin, is associated with a 6 % to 8 % abrupt vessel closure rate within 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,
15 administration of heparin after termination of the procedures is of little value and can be detrimental.

The widely used blood clotting inhibitors like heparin and related sulfated polysaccharides like LMWH and heparin sulfate exert their anticlotting effects by
20 promoting the binding of a natural regulator of the clotting process, antithrombin 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. Hirudin and hirulog are two additional thrombin specific anticoagulants. However, these anticoagulants which inhibit thrombin are also associated with bleeding
25 complications. Preclinical studies in baboons and dogs have shown that targeting enzymes involved at earlier stages of the coagulation cascade, such as factor Xa or factor VIIa, prevents clot formation without producing the bleeding side effects observed with direct thrombin inhibition.

30 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 K_i for factor Xa of 0.05 nM. TAP, which is isolated from the tick, *Ornithodoros moubata*, contains 60 amino acids and has a K_i for factor Xa of about 0.5 nM.

- 5 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.

10

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

- 15 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.

20

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
25 restricting the number of patients able to benefit from these agents. An inhibitor of factor Xa with a favorable 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, like heparin and related sulfated polysaccharides, are ineffective or only marginally effective.

30

Low molecular weight, factor Xa-specific blood clotting inhibitors that are effective but do 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 disclosed 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 properties, for instance high stability in plasma and
5 liver, high selectivity versus other serine proteases whose inhibition is not intended, such as thrombin, or inhibitory activity against serine proteases whose inhibition is desired, such as factor VIIa. There is an ongoing need for further low molecular weight factor Xa specific blood clotting inhibitors which are effective and have the above advantages as well.

10

Specific inhibition of the factor VIIa/tissue factor catalytic complex using monoclonal antibodies (WO-A-92/06711) or a protein such as chloromethyl ketone inactivated factor VIIa (WO-A-96/12800, WO-A-97/47651) is an extremely effective means of controlling thrombus formation caused by acute arterial injury or the thrombotic

15 complications related to bacterial septicemia. There is also experimental evidence suggesting that inhibition of factor VIIa/tissue factor activity inhibits restenosis following balloon angioplasty. Bleeding studies have been conducted in baboons and indicate that inhibition of the factor VIIa/tissue factor complex has the widest safety window with respect to therapeutic effectiveness and bleeding risk of any

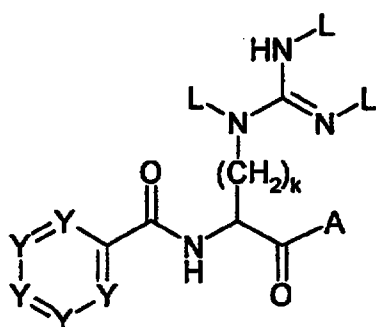
20 anticoagulant approach tested including thrombin, platelet and factor Xa inhibition. Certain inhibitors of factor VIIa have already been described. For example, WO-A-00/15658 (corresponding to EP-A-987274 (application no. 98117506.0)) discloses compounds containing a tripeptide unit which inhibit factor VIIa. However, the property profile of these compounds is still not ideal, and there is an ongoing need for
25 further low molecular weight factor VIIa inhibitory blood clotting inhibitors.

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

30

Thus, the present invention relates to compounds of the formula I,

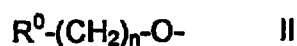
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I

in which

- 5 one or two of the groups Y are carbon atoms carrying a group of the formula II,



- and zero, one, two or three of the groups Y are nitrogen atoms, and the remaining
 10 groups Y are carbon atoms carrying a group R^1 , where the groups Y are independent of each other and can be identical or different;

- L is chosen from hydrogen, (C_1-C_8) -alkylcarbonyl, (C_6-C_{14}) -aryl- (C_1-C_4) -alkylcarbonyl, (C_6-C_{14}) -arylcarbonyl, (C_1-C_8) -alkyloxycarbonyl, (C_6-C_{14}) -aryl- (C_1-C_4) -
 15 alkyloxycarbonyl and (C_6-C_{14}) -aryloxycarbonyl, where the aryl groups present in L are unsubstituted or substituted by one or more identical or different substituents R^{13} , and where the groups L are independent of each other and can be identical or different;

- 20 A is chosen from R^3O- and R^4R^5N- ;

k is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

25

R^0 is chosen from phenyl and monocyclic 6-membered heteroaryl containing one or two nitrogen atoms as ring heteroatoms, where the group R^0 is unsubstituted or substituted by one or more identical or different groups R^2 ;

- 5 R^1 is chosen from hydrogen, halogen, nitro, hydroxy, (C₁-C₈)-alkyloxy-, (C₆-C₁₄)-aryl, (C₁-C₈)-alkyl, hydroxycarbonyl-(C₁-C₈)-alkylureido-, (C₁-C₈)-alkyloxycarbonyl-(C₁-C₈)-alkylureido-, (C₁-C₈)-alkylsulfonyl- and $R^{11}R^{12}N$ -, where the groups R^1 are independent of each other and can be identical or different, and where alkyl and aryl groups present in R^1 are unsubstituted or substituted by one or more identical or
- 10 different substituents R^{13} ,
- or
- two groups R^1 bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to the ring depicted in formula I, where the ring formed by the two groups R^1 is unsubstituted or substituted
- 15 by one or more identical or different substituents R^{13} ;

R^2 is chosen from halogen, nitro, (C₁-C₈)-alkyl, cyano, hydroxy, amino and (C₁-C₈)-alkyloxy-, where alkyl groups present in R^2 are unsubstituted or substituted by one or more identical or different halogen atoms;

20

- R^3 , R^4 and R^5 are chosen from hydrogen, (C₁-C₁₂)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₄)-alkyl-, (C₆-C₁₄)-aryl-, Het- and Het-(C₁-C₄)-alkyl-, where R^4 and R^5 are independent of each other and can be identical or different, and where the groups alkyl, aryl and Het present in R^3 , R^4 and R^5 are unsubstituted or substituted by one or more identical or
- 25 different substituents R^{13} ,

or

- R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 3-membered to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring
- 30 heteroatoms chosen from oxygen, sulfur and nitrogen;

R^{11} and R^{12} which are independent of each other and can be identical or different, are chosen from hydrogen, (C₁-C₈)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₄)-alkyl-, Het-(C₁-C₄)-alkyl-, hydroxycarbonyl-(C₁-C₈)-alkyl-, (C₁-C₈)-alkyloxycarbonyl-(C₁-C₈)-alkyl-, hydroxycarbonyl-(C₁-C₈)-alkylcarbonyl-, (C₁-C₈)-alkyloxycarbonyl-(C₁-C₈)-

5 alkylcarbonyl- and (C₁-C₈)-alkylcarbonyl-, where alkyl and aryl groups present in R^{11} and R^{12} are unsubstituted or substituted by one or more identical or different substituents R^{13} ,

or

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a
10 saturated or unsaturated 5-membered to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen, and in which one or two of the ring carbon atoms can be substituted by oxo to form C=O group(s);

15

R^{13} is chosen from halogen, nitro, cyano, hydroxy, (C₁-C₈)-alkyl, (C₁-C₈)-alkyloxy, trifluoromethyl and amino;

Het is a residue of a saturated, partially unsaturated or aromatic monocyclic or
20 bicyclic, 3-membered to 10-membered heterocyclic ring system containing one, two, three or four identical or different heteroatoms chosen from nitrogen, oxygen and sulfur;

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

In general, the meaning of any group, residue, heteroatom, number etc. which can occur more than once in the compounds of the formula I, is independent of the meaning of this group, residue, heteroatom, number etc. in any other occurrence. All
30 groups, residues, heteroatoms, numbers etc. which can occur more than once in the compounds of the formula I can be identical or different. For example, in case that a

compound of the formula I contains two groups of the formula II they can be identical or different with respect to the number n and/or the group R^0 .

- As used herein, the term alkyl is to be understood in the broadest sense to mean hydrocarbon residues which can be linear, i. e. straight-chain, or branched and which can be acyclic or cyclic residues or comprise any combination of acyclic and cyclic subunits. Further, the term alkyl as used herein expressly includes saturated groups as well as unsaturated groups which latter groups contain one or more, for example one, two or three, double bonds and/or triple bonds, provided that the double bonds are not located within a cyclic alkyl group in such a manner that an aromatic system results. All these statements also apply if an alkyl group occurs as a substituent on another residue, for example in an alkyloxy residue, an alkyloxycarbonyl residue or an arylalkyl residue. Examples of alkyl residues containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, the n -isomers of all these residues, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tert-butyl, tert-pentyl, 2,3,4-trimethylhexyl or isodecyl.
- Unsaturated alkyl residues are, for example, alkenyl residues such as vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl, or alkynyl residues such as ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butyne. Alkyl residues can also be unsaturated when they are substituted.
- Examples of cyclic alkyl residues are cycloalkyl residues containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl which can also be substituted and/or unsaturated. Unsaturated cyclic alkyl groups and unsaturated cycloalkyl groups like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom. The term alkyl as used herein also comprises cycloalkyl-substituted alkyl groups like cyclopropylmethyl-, cyclobutylmethyl-, cyclopentylmethyl-, cyclohexylmethyl-, cycloheptylmethyl-, 1-

cyclopropylethyl-, 1-cyclobutylethyl-, 1-cyclopentylethyl-, 1-cyclohexylethyl-, 2-cyclopropylethyl-, 2-cyclobutylethyl-, 2-cyclopentylethyl-, 2-cyclohexylethyl-, 3-cyclopropylpropyl-, 3-cyclobutylpropyl-, 3-cyclopentylpropyl etc. in which groups the cycloalkyl subgroup as well as acyclic subgroup can be unsaturated and/or
5 substituted.

Of course, a cyclic alkyl group has to contain at least three carbon atoms, and an unsaturated alkyl group has to contain at least two carbon atoms. Thus, a group like (C₁-C₈)-alkyl is to be understood as comprising, among others, saturated acyclic (C₁-C₈)-alkyl, (C₃-C₈)-cycloalkyl, cycloalkyl-alkyl groups like (C₃-C₇)-cycloalkyl-(C₁-C₅)-alkyl- wherein the total number of carbon atoms can range from 4 to 8, and
10 unsaturated (C₂-C₈)-alkyl like (C₂-C₈)-alkenyl or (C₂-C₈)-alkynyl. Similarly, a group like (C₁-C₄)-alkyl is to be understood as comprising, among others, saturated acyclic (C₁-C₄)-alkyl, (C₃-C₄)-cycloalkyl, cyclopropyl-methyl-, and unsaturated (C₂-C₄)-alkyl
15 like (C₂-C₄)-alkenyl or (C₂-C₄)-alkynyl.

Unless stated otherwise, the term alkyl preferably comprises acyclic saturated hydrocarbon residues which can be linear or branched and which more preferably have from one to six carbon atoms. A particular group of saturated acyclic alkyl
20 residues is formed by (C₁-C₄)-alkyl residues like methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

Unless stated otherwise, and irrespective of any specific substituents bonded to alkyl groups which are indicated in the definition of the compounds of the formula I, alkyl
25 groups can in general be unsubstituted or substituted by one or more, for example one, two, three, four or five, identical or different substituents. Any kind of substituents present in substituted alkyl residues can be present in any desired position provided that the substitution does not lead to an unstable molecule. Examples of substituted alkyl residues are alkyl residues in which one or more, for
30 example 1, 2, 3, 4 or 5, hydrogen atoms are replaced with halogen atoms, in particular fluorine atoms.

The term aryl refers to a monocyclic or polycyclic hydrocarbon residue in which at least one carbocyclic ring is present that has a conjugated pi electron system. In a (C₆-C₁₄)-aryl residue from 6 to 14 ring carbon atoms are present. Examples of (C₆-C₁₄)-aryl residues are phenyl, naphthyl, biphenyl, fluorenyl or anthracenyl.

- 5 Examples of (C₆-C₁₀)-aryl residues are phenyl or naphthyl. Unless stated otherwise, and irrespective of any specific substituents bonded to aryl groups which are indicated in the definition of the compounds of the formula I, aryl residues, for example phenyl, naphthyl or fluorenyl, can in general be unsubstituted or substituted by one or more, for example one, two, three or four, identical or different substituents.
- 10 Aryl residues can be bonded via any desired position, and in substituted aryl residues the substituents can be located in any desired position.

Unless stated otherwise, and irrespective of any specific substituents bonded to aryl groups which are indicated in the definition of the compounds of the formula I,

- 15 substituents that can be present in substituted aryl groups are, for example, (C₁-C₈)-alkyl, in particular (C₁-C₄)-alkyl, such as methyl, ethyl or tert-butyl, hydroxy, (C₁-C₈)-alkyloxy, in particular (C₁-C₄)-alkyloxy, such as methoxy, ethoxy or tert-butoxy, methylenedioxy, ethylenedioxy, F, Cl, Br, I, cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxymethyl, formyl, acetyl, amino, mono- or di-(C₁-C₄)-
- 20 alkylamino, ((C₁-C₄)-alkyl)carbonylamino like acetylamino, hydroxycarbonyl, ((C₁-C₄)-alkyloxy)carbonyl, carbamoyl, optionally substituted phenyl, benzyl optionally substituted in the phenyl group, optionally substituted phenoxy or benzyloxy optionally substituted in the phenyl group. A substituted aryl group that can be present in a specific position of the compounds of formula I can independently of
- 25 other aryl groups be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the specific definition of that group. For example, a substituted aryl group may be substituted by one or more identical or different substituents chosen from (C₁-C₄)-alkyl, hydroxy, (C₁-C₄)-alkyloxy, F, Cl, Br, I, cyano, nitro, trifluoromethyl, amino, phenyl, benzyl, phenoxy and benzyloxy. In
- 30 general, preferably not more than two nitro groups are present in the compounds of the formula I.

- In monosubstituted phenyl residues the substituent can be located in the 2-position, the 3-position or the 4-position, with the 3-position and the 4-position being preferred. If a phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In phenyl residues
- 5 carrying three substituents the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position, or 3,4,5-position. Naphthyl residues can be 1-naphthyl and 2-naphthyl. In substituted naphthyl residues the substituents can be located in any positions, for example in monosubstituted 1-naphthyl residues in the 2-, 3-, 4-, 5-, 6-, 7-, or 8-position and in monosubstituted 2-
- 10 naphthyl residues in the 1-, 3-, 4-, 5-, 6-, 7-, or 8-position. Biphenylyl residues can be 2-biphenylyl, 3-biphenylyl and 4-biphenylyl. Fluorenyl residues can be 1-, 2-, 3-, 4- or 9-fluorenyl. In monosubstituted fluorenyl residues bonded via the 9-position the substituent is preferably present in the 1-, 2-, 3- or 4-position.
- 15 The above statements relating to aryl groups correspondingly apply to the aryl subgroup in arylalkyl- groups. Examples of arylalkyl- groups which can also be unsubstituted or substituted in the aryl subgroup as well as in the alkyl subgroup, are benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 1-methyl-3-phenyl-propyl, 1-naphthylmethyl, 2-naphthylmethyl, 1-(1-naphthyl)ethyl, 1-(2-
- 20 naphthyl)ethyl, 2-(1-naphthyl)ethyl, 2-(2-naphthyl)ethyl, or 9-fluorenylmethyl.

- The group Het comprises groups containing 3, 4, 5, 6, 7, 8, 9 or 10 ring atoms in the parent monocyclic or bicyclic heterocyclic ring system. In monocyclic groups Het the heterocyclic ring preferably is a 3-membered, 4-membered, 5-membered, 6-
- 25 membered or 7-membered ring, particularly preferably a 5-membered or 6-membered ring. In bicyclic groups Het preferably two fused rings are present one of which is a 5-membered ring or 6-membered heterocyclic ring and the other of which is a 5-membered or 6-membered heterocyclic or carbocyclic ring, i. e., a bicyclic ring Het preferably contains 8, 9 or 10 ring atoms, particularly preferably 9 or 10 ring
- 30 atoms.

Het comprises saturated heterocyclic ring systems which do not contain any double bonds within the rings, as well as mono-unsaturated and poly-unsaturated heterocyclic ring systems which contain one or more, for example one, two, three, four or five, double bonds within the rings provided that the resulting system is stable.

- 5 Unsaturated rings may be non-aromatic or aromatic, i. e. double bonds within the rings in the group Het may be arranged in such a manner that a conjugated pi electron system results. Aromatic rings in a group Het may be 5-membered or 6-membered rings, i. e. aromatic groups in a group Het contain 5 to 10 ring atoms. Aromatic rings in a group Het thus comprise 5-membered and 6-membered
- 10 monocyclic heterocycles and bicyclic heterocycles composed of two 5-membered rings, one 5-membered ring and one 6-membered ring, or two 6-membered rings. In bicyclic aromatic groups in a group Het one or both rings may contain heteroatoms. Aromatic groups Het may also be referred to by the customary term heteroaryl for which all the definitions and explanations above and below relating to Het
- 15 correspondingly apply.

- Unless stated otherwise, in the groups Het and any other heterocyclic groups preferably 1, 2, 3 or 4 identical or different ring heteroatoms chosen from nitrogen, oxygen and sulfur are present. Particularly preferably in these groups one or two
- 20 identical or different heteroatoms chosen from nitrogen, oxygen and sulfur are present. The ring heteroatoms can be present in any desired number and in any position with respect to each other provided that the resulting heterocyclic system is known in the art and is stable and suitable as a subgroup in a drug substance. Examples of parent structures of heterocycles from which the group Het can be
- 25 derived are aziridine, oxirane, azetidine, pyrrole, furan, thiophene, dioxole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyridine, pyran, thiopyran, pyridazine, pyrimidine, pyrazine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, indole,
- 30 isoindole, benzofuran, benzothiophene, 1,3-benzodioxole, indazole, benzimidazole, benzoxazole, benzothiazole, quinoline, isoquinoline, chromane, isochromane, cinnoline, quinazoline, quinoxaline, phthalazine, pyridoimidazoles, pyridopyridines,

pyridopyrimidines, purine, pteridine etc. as well as ring systems which result from the listed heterocycles by fusion (or condensation) of a carbocyclic ring, for example benzo-fused, cyclopenta-fused, cyclohexa-fused or cyclohepta-fused derivatives of these heterocycles.

5

The fact that many of the before-listed names of heterocycles are the chemical names of unsaturated or aromatic ring systems does not imply that the groups Het could only be derived from the respective unsaturated ring system. The names here only serve to describe the ring system with respect to ring size and the number of the

10 heteroatoms and their relative positions. As explained above, the group Het can be saturated or partially unsaturated or aromatic, and can thus be derived not only from the before-listed heterocycles themselves but also from all their partially or completely hydrogenated analogues and also from their more highly unsaturated analogues if applicable. As examples of completely or partially hydrogenated

15 analogues of the before-listed heterocycles from which the groups Het may be derived the following may be mentioned: pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, piperidine, 1,3-dioxolane, 2-imidazoline, imidazolidine, 4,5-dihydro-1,3-oxazol, 1,3-oxazolidine, 4,5-dihydro-1,3-thiazole, 1,3-thiazolidine, perhydro-1,4-dioxane, piperazine, perhydro-1,4-oxazine (=

20 morpholine), perhydro-1,4-thiazine (= thiomorpholine), perhydroazepine, indoline, isoindoline, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, etc.

The residue Het may be bonded via any ring carbon atom, and in the case of nitrogen heterocycles via any suitable ring nitrogen atom. Thus, for example, a

25 pyrrolyl residue can be 1-pyrrolyl, 2-pyrrolyl or 3-pyrrolyl, a pyrrolidinyl residue can be pyrrolidin-1-yl (= pyrrolidino), pyrrolidin-2-yl or pyrrolidin-3-yl, a pyridinyl residue can be pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, a piperidinyl residue can be piperidin-1-yl (= piperidino), piperidin-2-yl, piperidin-3-yl or piperidin-4-yl. Furyl can be 2-furyl or 3-furyl, thienyl can be 2-thienyl or 3-thienyl, imidazolyl can be imidazol-1-yl, imidazol-2-

30 yl, imidazol-4-yl or imidazol-5-yl, 1,3-oxazolyl can be 1,3-oxazol-2-yl, 1,3-oxazol-4-yl or 1,3-oxazol-5-yl, 1,3-thiazolyl can be 1,3-thiazol-2-yl, 1,3-thiazol-4-yl or 1,3-thiazol-5-yl, pyrimidinyl can be pyrimidin-2-yl, pyrimidin-4-yl (= 6-pyrimidinyl) or 5-pyrimidinyl,

piperazinyl can be piperazin-1-yl (= piperazin-4-yl = piperazino) or piperazin-2-yl. Indolyl can be indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl or indol-7-yl. Similarly benzimidazolyl, benzoxazolyl and benzothiazol residues can be bonded via the 2-position and via any of the positions 4, 5, 6, and 7. Quinolinylnyl can be quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl or quinolin-8-yl, isoquinolinylnyl can be isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl or isoquinolin-8-yl. In addition to being bonded via any of the positions indicated for quinolinylnyl and isoquinolinylnyl, 1,2,3,4-tetrahydroquinolinylnyl and 1,2,3,4-tetrahydroisoquinolinylnyl can also be bonded via the nitrogen atoms in 1-position and 2-position, respectively.

Unless stated otherwise, and irrespective of any specific substituents bonded to groups Het or any other heterocyclic groups which are indicated in the definition of the compounds of the formula I, the group Het can be unsubstituted or substituted on ring carbon atoms with one or more, for example one, two, three, four or five, identical or different substituents like (C₁-C₈)-alkyl, in particular (C₁-C₄)-alkyl, (C₁-C₈)-alkyloxy, in particular (C₁-C₄)-alkyloxy, (C₁-C₄)-alkylthio, halogen, nitro, amino, ((C₁-C₄)-alkyl)carbonylamino like acetylamino, trifluoromethyl, trifluoromethoxy, hydroxy, oxo, hydroxy-(C₁-C₄)-alkyl such as, for example, hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl, methylenedioxy, ethylenedioxy, formyl, acetyl, cyano, methylsulfonyl, hydroxycarbonyl, aminocarbonyl, (C₁-C₄)-alkyloxycarbonyl, optionally substituted phenyl, optionally substituted phenoxy, benzyl optionally substituted in the phenyl group, benzyloxy optionally substituted in the phenyl group, etc. The substituents can be present in any desired position provided that a stable molecule results. Of course an oxo group cannot be present in an aromatic ring. Each suitable ring nitrogen atom in a group Het can independently of each other be unsubstituted, i. e. carry a hydrogen atom, or can be substituted, i. e. carry a substituent like (C₁-C₈)-alkyl, for example (C₁-C₄)-alkyl such as methyl or ethyl, optionally substituted phenyl, phenyl-(C₁-C₄)-alkyl, for example benzyl, optionally substituted in the phenyl group, hydroxy-(C₂-C₄)-alkyl such as, for example 2-hydroxyethyl, acetyl or another acyl group, methylsulfonyl or another sulfonyl group, aminocarbonyl, (C₁-C₄)-alkyloxycarbonyl, etc. In general, in the compounds of the formula I nitrogen heterocycles can also be

- present as N-oxides or as quaternary salts. Ring sulfur atoms can be oxidized to the sulfoxide or to the sulfone. Thus, for example, a tetrahydrothienyl residue may be present as S,S-dioxotetrahydrothienyl residue, or a thiomorpholinyl residue like thiomorpholin-4-yl may be present as 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl. A substituted group Het that can be present in a specific position of the compounds of formula I can independently of other groups Het be substituted by substituents selected from any desired subgroup of the substituents listed before and/or in the definition of that group.
- 10 The above statements relating to the residue Het also correspondingly apply to the Het subgroup in the groups Het-alkyl-. Examples of such groups Het-alkyl- which can also be unsubstituted or substituted in the Het subgroup as well as in the alkyl subgroup, are (pyridin-2-yl)-methyl, (pyridin-3-yl)-methyl, (pyridin-4-yl)-methyl, 2-(pyridin-2-yl)-ethyl, 2-(pyridin-3-yl)-ethyl or 2-(pyridin-4-yl)-ethyl. As far as applicable,
- 15 the above statements relating to the residue Het also apply to the heteroaryl group that can represent the group R^0 , and to a heterocyclic ring that is formed by two groups together with the nitrogen atom to which they are bonded.

- Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or
- 20 bromine, particularly preferably chlorine or bromine.

- Optically active carbon atoms present in the compounds of the formula I can independently of each other have R configuration or S configuration. The compounds of the formula I can be present in the form of pure or substantially pure enantiomers
- 25 or pure or substantially pure diastereomers, or in the form of mixtures of enantiomers and/or diastereomers, for example in the form of racemates. The present invention relates to pure enantiomers and mixtures of enantiomers as well as to pure diastereomers and mixtures of diastereomers. The invention comprises mixtures of two or of more than two stereoisomers of the formula I, and it comprises all ratios of
- 30 the stereoisomers in the mixtures. In case the compounds of the formula I can be present as E isomers or Z isomers (or cis isomers or trans isomers) the invention relates both to pure E isomers and pure Z isomers and to E/Z mixtures in all ratios.

The invention also comprises all tautomeric forms of the compounds of the formula I.

Diastereomers, including E/Z isomers, can be separated into the individual isomers by chromatography, for example. Racemates can be separated into the two
5 enantiomers by customary methods, for example by chromatography on chiral phases or by resolution, for example by crystallization of diastereomeric salts obtained with optically active acids or bases. Stereochemically uniform compounds of the formula I can also be obtained by employing stereochemically uniform starting materials or by using stereoselective reactions.

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The choice of incorporating into a compound of the formula I a building block with R configuration or S configuration, or in the case of an amino acid unit present in a compound of the formula I of incorporating a building block designated as D-amino acid or L-amino acid, can depend, for example, on the desired characteristics of the
15 compound of the formula I. For example, the incorporation of a D-amino acid building block can confer increased stability in vitro or in vivo. The incorporation of a D-amino acid building block also can achieve a desired increase or decrease in the pharmacological activity of the compound. In some cases it can be desirable to allow the compound to remain active for only a short period of time. In such cases, the
20 incorporation of an L-amino acid building block in the compound can allow endogenous peptidases in an individual to digest the compound in vivo, thereby limiting the individual's exposure to the active compound. A similar effect may also be observed in the compounds of the invention by changing the configuration in another building block from S configuration to R configuration or vice versa. By taking into
25 consideration the medical needs a person skilled in the art can determine the desirable characteristics, for example a favorable stereochemistry, of the required compound of the invention.

Physiologically tolerable salts of the compounds of formula I are nontoxic salts that
30 are physiologically acceptable, in particular pharmaceutically utilizable salts. Such salts of compounds of the formula I containing acidic groups, for example a carboxy group COOH, are for example alkali metal salts or alkaline earth metal salts such as

sodium salts, potassium salts, magnesium salts and calcium salts, and also salts with physiologically tolerable quarternary ammonium ions such as tetramethylammonium or tetraethylammonium, and acid addition salts with ammonia and physiologically tolerable organic amines, such as methylamine, dimethylamine, trimethylamine, ethylamine, triethylamine, ethanolamine or tris-(2-hydroxyethyl)amine. Basic groups contained in the compounds of the formula I, for example amino groups or guanidino groups, form acid addition salts, for example with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid, or with organic carboxylic acids and sulfonic acids such as formic acid, acetic acid, oxalic acid, citric acid, lactic acid, malic acid, succinic acid, malonic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, methanesulfonic acid or p-toluenesulfonic acid. Compounds of the formula I which simultaneously contain a basic group and an acidic group, for example a guanidino group and a carboxy group, can also be present as zwitterions (betaines) which are likewise included in the present invention.

Salts of compounds of the formula I can be obtained by customary methods known to those skilled in the art, for example by combining a compound of the formula I with an inorganic or organic acid or base in a solvent or dispersant, or from other salts by cation exchange or anion exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiological tolerability, are not directly suitable for use in pharmaceuticals but are suitable, for example, as intermediates for carrying out further chemical modifications of the compounds of the formula I or as starting materials for the preparation of physiologically tolerable salts. The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols. 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, (C₁-C₄)-alkyl esters, unsubstituted amides or (C₁-C₈)-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.

5 More detailed information relating to prodrugs is found in standard literature like, for example, Design of Prodrugs, H. Bundgaard (ed.), Elsevier, 1985; D. 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
10 prodrugs of carboxylic acid groups, and also acyl prodrugs and carbamate prodrugs of acylatable nitrogen-containing groups such as amino groups 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 a carbamate group. Suitable acyl groups and carbamate groups for acyl
15 prodrugs and carbamate prodrugs are, for example, the groups R^{P1} -CO- and R^{P2} O-CO-, in which R^{P1} is hydrogen, (C₁-C₁₈)-alkyl, (C₃-C₈)-cycloalkyl, (C₃-C₈)-cycloalkyl-(C₁-C₄)-alkyl-, (C₆-C₁₄)-aryl, Het-, (C₆-C₁₄)-aryl-(C₁-C₄)-alkyl- or Het-(C₁-C₄)-alkyl- and in which R^{P2} has the meanings indicated for R^{P1} with the exception of hydrogen.

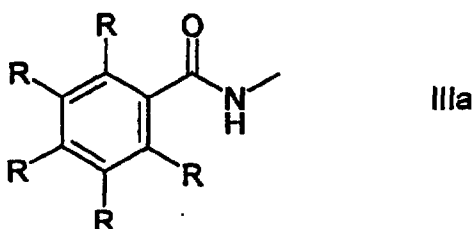
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A specific subgroup of compounds of the present invention is formed by compounds in which A is R^4R^5N -, and another specific subgroup of compounds of the present invention is formed by compounds in which A is R^3O -. Independently thereof, a specific subgroup of compounds of the present invention is formed by compounds in
25 which L is hydrogen, and another specific subgroup is formed by compounds in which one or more of the groups L are acyl groups, for example acyl groups chosen from the acyl groups listed in the above definition of L or chosen from any combination of the listed acyl groups. If an aryl group present in a group L is substituted, it is preferably substituted by one, two, three or four, more preferably by
30 one or two, identical or different substituents. If groups L in the compounds of the formula I are different from hydrogen, preferably only one or two of the groups L are different from hydrogen.

The number k preferably is 2, 3 or 4, more preferably 3. The optically active carbon atom depicted in the formula I which carries the groups $-C(=O)-A$ and $-(CH_2)_k-N(L)-C(=N-L)-NHL$ preferably is present in a uniform configuration or substantially uniform configuration, in particular in S configuration or substantially in S configuration.

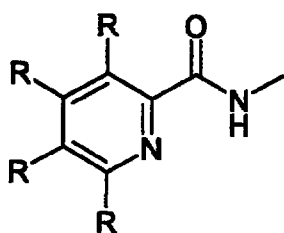
In the aromatic ring system depicted in the formula I which is formed by the five groups Y and the ring carbon atom carrying the amide group, the one or two ring carbon atoms carrying the groups of the formula II and any ring nitrogen atoms can be present in any combination and in any positions provided that the resulting system is stable and suitable as a subgroup in a drug substance. Preferably in the aromatic ring system zero, one or two of the groups Y are nitrogen atoms. Examples of parent structures from which the aromatic ring system can be derived are benzene, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine. Preferably the aromatic ring system is derived from benzene, pyridine or pyrimidine, particularly preferably from benzene.

If zero ring nitrogen atoms are present in the aromatic ring depicted in the formula I, instead of the $CY_5-C(=O)-NH-$ moiety the compounds of the formula I specifically contain a benzamide moiety of the formula IIIa

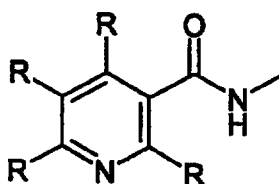


in which one or two of the groups R are identical or different groups of the formula II and the remaining of the groups R are identical or different groups R^1 .

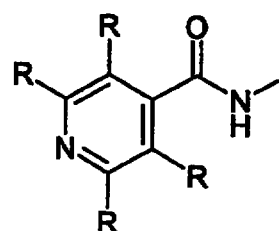
If one ring nitrogen atom is present in the aromatic ring system depicted in the formula I it can be present in a 2-position or a 3-position or in the 4-position with respect to the ring carbon atom carrying the amide group $C(=O)-NH$ depicted in the formula I. I. e., if one ring nitrogen atom is present, instead of the $CY_5-C(=O)-NH$ - moiety the compounds of the formula I specifically contain a pyridine-2-carboxamide moiety of the formula IIIb, a pyridine-3-carboxamide moiety of the formula IIIc or a pyridine-4-carboxamide moiety of the formula IIId,



IIIb



IIIc



IIId

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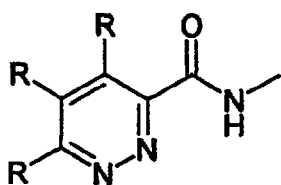
in all of which one or two of the groups R are identical or different groups of the formula II and the remaining of the groups R are identical or different groups R^1 . In case one ring nitrogen atom is present, the $CY_5-C(=O)-NH$ - moiety preferably is a pyridine-2-carboxamide moiety of the formula IIIb or a pyridine-4-carboxamide moiety of the formula IIId.

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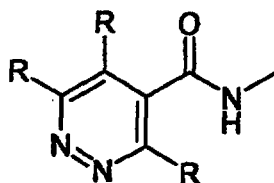
If two ring nitrogen atoms are present in the aromatic ring system depicted in the formula I they can be present in positions 2 and 3, or in positions 2 and 4, or in positions 2 and 5, or in positions 2 and 6, or in positions 3 and 4, or in positions 3 and 5 with respect to the ring carbon atom carrying the amide group $C(=O)-NH$ depicted in the formula I. I. e., if two ring nitrogen atoms are present, instead of the $CY_5-C(=O)-NH$ - moiety the compounds of the formula I specifically contain a pyridazine-3-carboxamide moiety of the formula IIIe, a pyridazine-4-carboxamide moiety of the formula IIIf, a pyrimidine-2-carboxamide moiety of the formula IIIg, a pyrimidine-4-carboxamide moiety of the formula IIIh, a pyrimidine-5-carboxamide moiety of the formula IIIi or a pyrazine-2-carboxamide moiety of the formula IIIj,

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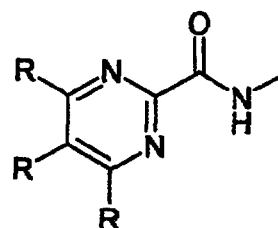
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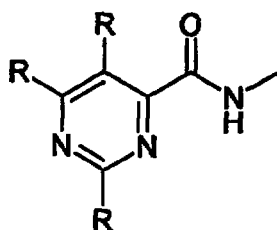
IIIe



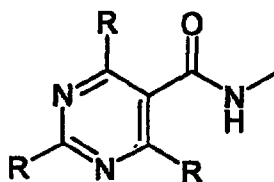
IIIf



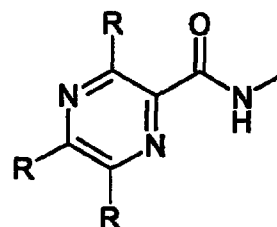
IIIg



IIIh



IIIi



IIIj

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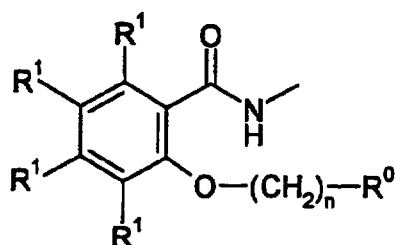
in all of which one or two of the groups R are identical or different groups of the formula II and the remaining of the groups R are identical or different groups R¹. In case two ring nitrogen atoms are present, the CY₅-C(=O)-NH- moiety preferably is a pyrimidinecarboxamide moiety of the formulae IIIg, IIIh or IIIi, in particular a

- 10 pyrimidine-4-carboxamide moiety of the formula IIIh. The preceding explanations correspondingly apply to aromatic ring systems in which three ring nitrogen atoms are present.

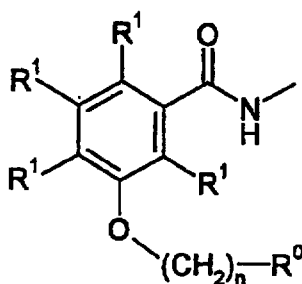
- In general, any one or two of the groups Y in the aromatic ring depicted in the
- 15 formula I which are no nitrogen atoms can be carbon atoms carrying a group of the formula II. Thus, if one group Y is a carbon atom carrying a group of the formula II, the group of the formula II can be present in a 2-position or in a 3-position or in the 4-position with respect to the ring carbon atom carrying the amide group C(=O)-NH depicted in the formula I. Preferably, if only one group Y is a carbon atom carrying a
- 20 group of the formula II, the group of the formula II is present in the 3-position or in the

- 4-position with respect to the carbon atom carrying the amide group $C(=O)-NH$ depicted in the formula I, particularly preferably in the 3-position with respect to said carbon atom. If two groups Y are carbon atoms carrying a group of the formula II, the groups of the formula II can be present in positions 2 and 3, positions 2 and 4, positions 2 and 5, positions 2 and 6, positions 3 and 4 or positions 3 and 5 with respect to the ring carbon atom carrying the amide group $C(=O)-NH$ depicted in the formula I. Preferably, if two groups Y are carbon atoms carrying a group of the formula II, one or both of the groups of the formula II are present in positions 3, 4 and 5 with respect to the carbon atom carrying the amide group $C(=O)-NH$ depicted in the formula I, and particularly preferably the two groups of the formula II are present in positions 3 and 4 or positions 3 and 5 with respect to said carbon atom.

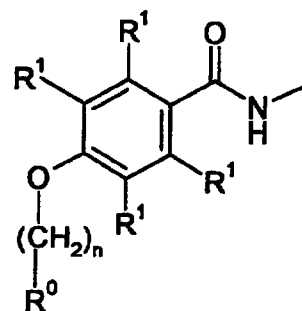
- For example, if the compound of the formula I contains a benzamide moiety of the formula IIIa and only one group Y is a carbon atom carrying a group of the formula II, the compound of the formula I can contain a benzamide moiety of the formula IIIa-1 or a benzamide moiety of the formula IIIa-2 or a benzamide moiety of the formula IIIa-3,



IIIa-1



IIIa-2



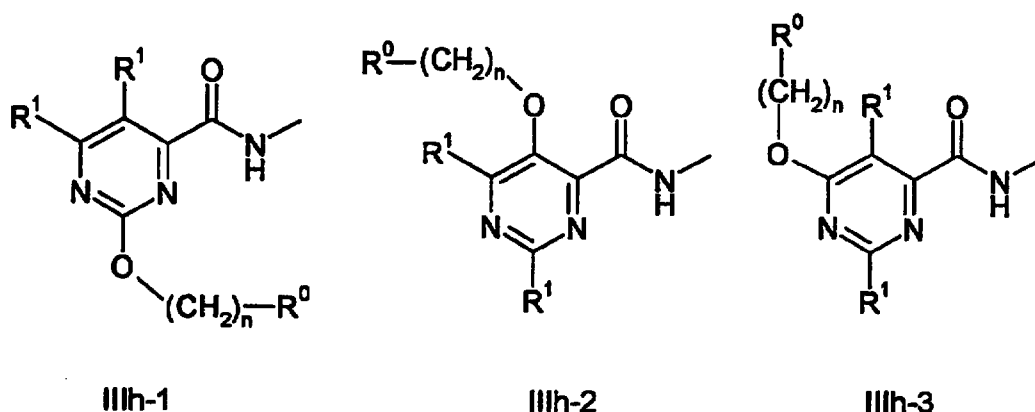
IIIa-3

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in all of which R^0 , R^1 and n are defined as above, and of which the benzamide moieties of the formulae IIIa-2 and IIIa-3 are preferred and that of the formula IIIa-2 is particularly preferred.

Accordingly, if the compound of the formula I contains a pyridinecarboxamide moiety and only one group Y is a carbon atom carrying a group of the formula II, in case of a pyridine-2-carboxamide moiety of the formula IIIb the group of the formula II can be present in the 3-position or the 4-position or the 5-position or the 6-position with respect to the ring nitrogen atom in the 1-position, the 4-position, 5-position and 6-position being preferred and the 4-position and the 6-position being particularly preferred. In case of a pyridine-3-carboxamide moiety of the formula IIIc the group of the formula II can be present in the 2-position or the 4-position or the 5-position or the 6-position with respect to the ring nitrogen atom in the 1-position, the 5-position and 6-position being preferred and the 5-position being particularly preferred. In case of a pyridine-4-carboxamide moiety of the formula IIId the group of the formula II can be present in a 2-position or a 3-position with respect to the ring nitrogen atom in the 1-position, the 2-positions being preferred. Just so in all compounds of the formula I containing a diaza-arenecarboxamide moiety of the formulae IIIe to IIIj and containing only one group Y which is a carbon atom carrying a group of the formula II, the group of the formula II can be present in any position. For example, in a compound of the formula I containing a pyrimidine-4-carboxamide moiety of the formula IIIh, the group of the formula II can be present in the 2-position (formula IIIh-1) or the 5-position (formula IIIh-2) or the 6-position (formula IIIh-3) with respect to the ring nitrogen atoms in positions 1 and 3 and the carboxamide group in position 4, the 2-position and the 6-position being preferred and the 6-position being particularly preferred. As in the formulae IIIh-1 to IIIh-3, in the pyridinecarboxamide moieties and diaza-arenecarboxamide moieties mentioned above all ring positions which are not occupied by the group of the formula II or are not nitrogen atoms, carry identical or different groups R¹.

26



Preferably only one of the groups Y in the aromatic ring system CY₅ depicted in the formula I is a carbon atom carrying a group of the formula II, and the other of the groups Y are nitrogen atoms or carbon atoms carrying a group R¹ as outlined above.

The number n preferably is 1, 2, 3 or 4, more preferably 1, 2 or 3, particularly preferably 2.

- 10 The group R⁰ present in the groups of the formula II can be, for example, phenyl, pyridinyl including pyridin-2-yl, pyridin-3-yl and pyridin-4-yl, pyridazinyl including pyridazin-3-yl and pyridazin-4-yl, pyrimidinyl including pyrimidin-2-yl, pyrimidin-4-yl and pyrimidin-5-yl, or pyrazinyl including pyrazin-2-yl. Preferably R⁰ is phenyl, pyridinyl or pyrimidinyl, more preferably phenyl or pyridinyl, particularly preferably phenyl.
- 15 A pyridinyl group representing R⁰ preferably is pyridin-2-yl or pyridin-4-yl, a pyrimidinyl group representing R⁰ preferably is pyrimidin-4-yl. The groups R⁰ can be unsubstituted or substituted by one, two, three, four or five identical or different substituents. Preferably they are unsubstituted or substituted by one, two or three identical or different substituents, particularly preferably they are unsubstituted or substituted by one or two identical or different substituents.
- 20 As outlined above with respect to aryl groups and heteroaryl groups in general, substituents in a group R⁰ can be present in any positions. Thus, for example, a monosubstituted phenyl group representing R⁰ can be 2-substituted, 3-substituted or 4-substituted. Preferably a monosubstituted phenyl group representing R⁰ is 2-substituted or 4-substituted. A disubstituted phenyl group representing R⁰ can be 2,3-substituted, 2,4-substituted,
- 25

2,5-substituted, 2,6-substituted, 3,4-substituted or 3,5-substituted by identical or different substituents. Preferably a disubstituted phenyl group representing R^0 is 2,4-substituted. Thus, in a preferred embodiment of the present invention R^0 is phenyl which is unsubstituted or substituted by one or two identical or different substituents

5 R^2 , where particularly preferably the substituents are present in positions 2 and/or 4.

The groups R^1 are preferably chosen from hydrogen, halogen, hydroxy, nitro, $R^{11}R^{12}N$ - and (C_1-C_8) -alkyloxy, where a (C_1-C_8) -alkyloxy group representing R^1 preferably is (C_1-C_4) -alkyloxy and particularly preferably is methoxy, and where a

10 preferred group $R^{11}R^{12}N$ - representing R^1 preferably is the amino group NH_2 . If an alkyl group or aryl group present in a group R^1 is substituted by one or more identical or different substituents R^{13} it is preferably substituted by one, two, three, four or five, in particular one, two or three, identical or different substituents R^{13} . Examples of groups R^1 in which an alkyl group or aryl group is substituted by R^{13} are

15 aminomethyl, hydroxymethyl, trifluoromethyl, trifluoromethoxy, 2,2,3,3,3-pentafluoropropoxy, 2-methoxyethoxy or 3,4-dimethoxyphenyl.

The number of the groups R^1 which can be present in the aromatic ring system CY_5 depends on the number of the groups of the formula II and the number of ring

20 nitrogen atoms that are present, and can be zero, one, two, three or four. Preferably, one, two or three of the groups R^1 that are present have any one of the meanings of R^1 given above including hydrogen, and a fourth group R^1 that may be present is hydrogen. More preferably, one or two of the groups R^1 that are present have any one of the meanings of R^1 given above including hydrogen, and a third and fourth

25 group R^1 that may be present are hydrogen. For example, in compounds of the formula I which contain a benzamide moiety of the formula IIIa and only one group of the formula II, preferably one, two or three of the four groups R^1 that are present denote hydrogen or a group different from hydrogen, and the fourth group R^1 denotes hydrogen. More preferably in compounds of the formula I which contain a benzamide

30 moiety of the formula IIIa and only one group of the formula II, one or two of the four groups R^1 that are present denote hydrogen or a group different from hydrogen, and the third and the fourth group R^1 denote hydrogen. Moreover, in the case of

compounds of the formula I which contain a benzamide moiety of the formula IIIa and only one group of the formula II, in a preferred embodiment of the present invention one or two groups R^1 are different from hydrogen and three or two groups R^1 are hydrogen. In the case of compounds of the formula I which contain a

- 5 pyridinecarboxamide or a diaza-arenecarboxamide moiety of the formulae IIIb to IIIj and only one group of the formula II, in a preferred embodiment of the present invention all groups R^1 are hydrogen or one group R^1 is different from hydrogen and the remaining groups R^1 are hydrogen. Any groups R^1 that are different from hydrogen can be present in any desired position of the aromatic ring system CY_5 ,
10 provided a sufficiently stable molecule results that is suitable for the desired purpose. For example, if a compound of the formula I contains a benzamide moiety of the formula IIIa and only one group of the formula II and one or two groups R^1 that are different from hydrogen, those groups R^1 can be present in any of the positions 2, 3, 4, 5 and 6 (with respect to the amide group $C(=O)-NH$ in the 1-position), as far as the
15 respective positions are not occupied by the group of the formula II. If in the case of a compound of the formula I containing a benzamide moiety of the formula IIIa and a single group of the formula II in the 3-position (with respect to the amide group $C(=O)-NH$ in the 1-position) a single group R^1 that is different from hydrogen is present, that group R^1 preferably is present in the 4-position or in the 5-position,
20 particularly preferably in the 4-position. If in the case of a compound of the formula I containing a benzamide moiety of the formula IIIa and a single group of the formula II in the 3-position (with respect to the amide group $C(=O)-NH$ in the 1-position) two groups R^1 that are different from hydrogen are present, those groups are preferably present in positions 4 and 5.

25

- Besides having the before-mentioned preferred denotations, in further preferred embodiments of the present invention the ring system CY_5 and substituents R^1 together form a polycyclic aromatic ring system. If two groups R^1 bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an
30 aromatic ring condensed to the ring CY_5 depicted in formula I, the resulting bicyclic aromatic ring system preferably comprises two condensed 6-membered rings. One of the two condensed 6-membered rings, i. e. the ring CY_5 which is depicted in the

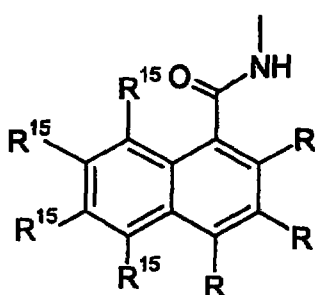
formula I and which carries the groups of the formula II, contains zero, one or two ring nitrogen atoms, and the second ring, i.e. the additional ring formed by the two groups R^1 , preferably is a benzene ring comprising only carbon atoms as ring atoms. Thus, in this latter embodiment of the invention the two residues R^1 - which are

5 bonded to adjacent carbon atoms and which together with the carbon atoms to which they are bonded form a condensed benzene ring, can be regarded as forming a divalent residue of the formula $-C(R^{15})=C(R^{15})-C(R^{15})=C(R^{15})-$ the terminal carbon atom of which are bonded to two adjacent carbon atoms in the ring system CY_5 , and in which the groups R^{15} which are identical or different, are chosen from hydrogen

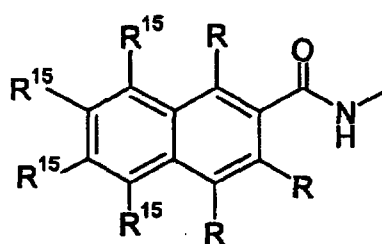
10 and R^{13} . Examples of parent structures from which such a condensed aromatic ring system can be derived are naphthalene, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline and phthalazine. The amide group $C(=O)-NH-$ and the groups of the formula II can be located in any position in the ring which corresponds to the ring CY_5 depicted in the formula I. Thus the compounds of the formula I can

15 inter alia contain, for example, a naphthalene-1-carboxamide moiety of the formula IIIk, a naphthalene-2-carboxamide moiety of the formula IIIl, a quinoline-2-carboxamide moiety of the formula IIIl, a quinoline-3-carboxamide moiety of the formula IIIo, a quinoline-4-carboxamide moiety of the formula IIIp, an isoquinoline-1-carboxamide moiety of the formula IIIq, an isoquinoline-3-carboxamide moiety of the

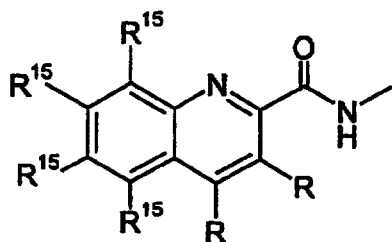
20 formula IIIr or a quinazoline-2-carboxamide moiety of the formula IIIs,



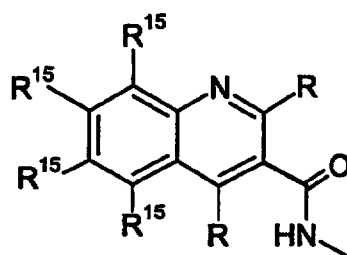
IIIk



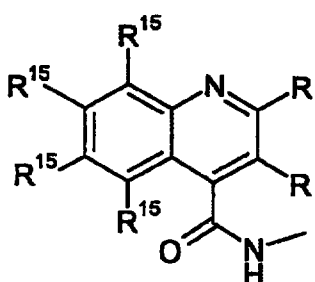
IIIl



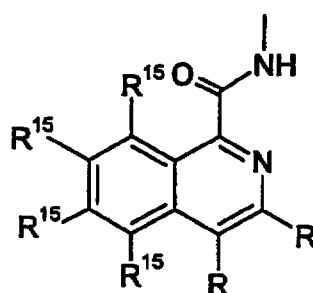
IIIln



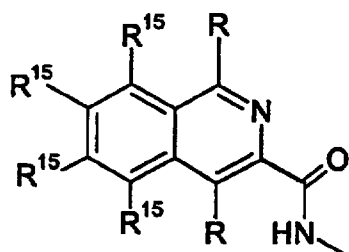
IIIlo



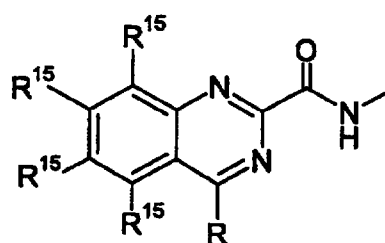
IIIlp



IIIlq



IIIlr



IIIls

5

in all of which one or two of the groups R are identical or different groups of the formula II and the remaining of the groups R are identical or different groups R¹, and the groups R¹⁵ are identical or different groups chosen from hydrogen and R¹³. As in
 10 the cases were the ring system CY₅ is a monocyclic ring, groups R representing groups of the formula II can be present in any position. For example, if a compound of the formula I contains a naphthalene-1-carboxamide moiety of the formula IIIk and

only one group of the formula II is present, it can be present in positions 2, 3 and 4 of the naphthalene system of which the 3-position is preferred. If a compound of the formula I contains a naphthalene-2-carboxamide moiety of the formula IIIm and only one group of the formula II is present, it can be present in positions 1, 3 and 4 of the naphthalene system of which the 4-position is preferred. If a compound of the formula I contains a quinoline-2-carboxamide moiety of the formula IIIn and only one group of the formula II is present, it can be present in positions 3 and 4 of the quinoline system of which the 4-position is preferred.

- 10 The groups R^2 which may be present in the group R^0 are preferably chosen from halogen and (C_1-C_4) -alkyl, where alkyl groups representing R^2 are unsubstituted or substituted by one or more identical or different halogen atoms. Particularly preferably substituents R^2 are identical or different halogen atoms, in particular halogen atoms chosen from fluorine, chlorine and bromine. If an alkyl group present in a group R^2 is substituted by one or more identical or different halogen atoms it is preferably substituted by one, two, three, four or five, in particular one, two or three, identical or different halogen atoms. Examples of groups R^2 in which an alkyl group is substituted by halogen atoms are trifluoromethyl, trifluoromethoxy or 2,2,3,3,3-pentafluoropropoxy.

20

- If the groups alkyl, aryl and Het present in R^3 , R^4 and R^5 are substituted by one or more identical or different substituents R^{13} , they are preferably substituted by one, two, three, four or five, in particular one, two or three, identical or different substituents R^{13} which substituents can be present in any positions, provided that a stable molecule results which is suitable for the desired purpose. R^3 preferably is hydrogen or (C_1-C_6) -alkyl, where the alkyl group representing R^3 is unsubstituted or substituted by one or more identical or different substituents R^{13} . Preferably one of the groups R^4 and R^5 is hydrogen or (C_1-C_4) -alkyl, in particular hydrogen, and the other of the groups R^4 and R^5 is chosen from hydrogen, (C_1-C_{12}) -alkyl, (C_6-C_{14}) -aryl-, (C_1-C_4) -alkyl-, (C_6-C_{14}) -aryl-, Het- and Het- (C_1-C_4) -alkyl-, where the groups alkyl, aryl and Het present in R^4 and R^5 are unsubstituted or substituted by one or more identical or different substituents R^{13} , or R^4 and R^5 together with the nitrogen atom to

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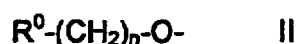
which they are bonded form a saturated 3-membered to 8-membered heterocyclic ring which in addition to the nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen. A heterocyclic ring formed by R^4 and R^5 together with the nitrogen atom to which they are bonded preferably contains no additional ring heteroatom or one additional ring heteroatom chosen from nitrogen, oxygen and sulfur. Examples of such heterocyclic rings are aziridine, azetidine, pyrrolidine, 1,2-oxazolidine, 1,3-oxazolidine, 1,2-thiazolidine, 1,3-thiazolidine, piperidine, morpholine, thiomorpholine, piperazine, perhydroazepine or perhydroazocine all of which are bonded via a ring nitrogen atom and can be substituted as outlined above. Preferred heterocyclic rings formed by R^4 and R^5 together with the nitrogen atom to which they are bonded are aziridine, azetidine, pyrrolidine and piperidine.

If alkyl and aryl groups present in R^{11} and R^{12} are substituted by one or more identical or different substituents R^{13} , they are preferably substituted by one, two, three, four or five, in particular one, two or three, identical or different substituents R^{13} which substituents can be present in any positions, provided that a stable molecule results which is suitable for the desired purpose. A heterocyclic ring formed by R^{11} and R^{12} together with the nitrogen atom to which they are bonded preferably does not contain a further ring heteroatom or contains one further ring heteroatom chosen from nitrogen, oxygen and sulfur in addition to the nitrogen atom carrying R^{11} and R^{12} . The ring heteroatoms can be present in any desired positions. Preferably the heterocyclic ring is saturated. If it is unsaturated it preferably contains one or two double bonds in the ring. Preferably the heterocyclic ring is a 5-membered or 6-membered ring. Examples of such heterocyclic rings are aziridine, azetidine, pyrrolidine, pyrroline, 1,2-oxazolidine, 1,3-oxazolidine, 2,3-dihydro-1,3-oxazole, 1,2-thiazolidine, 1,3-thiazolidine, 2,3-dihydro-1,3-thiazole, piperidine, 1,2-dihydropyridine, 1,4-dihydropyridine, 1,2,3,4-tetrahydropyridine, 1,2,3,6-tetrahydropyridine, morpholine, thiomorpholine, piperazine, perhydroazepine or perhydroazocine all of which are bonded via a ring nitrogen atom. A heterocyclic ring formed by R^{11} and R^{12} together with the nitrogen atom to which they are bonded can be unsubstituted or substituted as outlined above with respect to heterocyclic groups in general. In

particular, in a heterocyclic ring formed by R^{11} and R^{12} together with the nitrogen atom to which they are bonded one or two ring carbon atoms can be substituted by an oxo group, i. e. can carry a doubly bonded oxygen atom, resulting in one or two carbonyl groups $>C=O$ as ring members. Carbon atoms substituted by oxo can be present in any positions, including the positions adjacent to ring heteroatoms and in particular the positions adjacent to the nitrogen atom carrying the groups R^{11} and R^{12} . Examples of such oxo-substituted heterocyclic ring are pyrrolidine-2,5-dione, imidazolidine-2,4-dione, oxazolidine-2,4-dione, pyrrolidine-2-one, imidazolidin-2-one, pyrazolidine-3,5-dione, piperidine-2-one, piperazine-2-one, morpholine-3-one, piperidine-2,6-dione, etc.

Preferred compounds of the formula I are those compounds in which one or more of the groups or residues or numbers have preferred denotations or have one or more specific denotations of the denotations listed in their respective definitions and the general explanations relating to the respective groups and residues. All combinations of such preferred denotations and specific denotations are a subject of the present invention. As the compounds of the formula I in general, just so all preferred compounds of the formula I are a subject of the present invention in all their stereoisomeric forms and mixtures thereof in any ratio, and in the form of their physiologically tolerable salts. Further, also all preferred compounds of the formula I are a subject of the present invention in the form of their prodrugs and other derivatives as explained above, for example in the form of their esters or amides such as unsubstituted amides, (C_1-C_8) -alkyl amides and other amides, or their acyl prodrugs or carbamate prodrugs.

For example, preferred compounds of the formula I are compounds in which one of the groups Y is a carbon atom carrying a group of the formula II,



and zero, one or two of the groups Y are nitrogen atoms, and the remaining groups Y are carbon atoms carrying a group R^1 , where the groups Y are independent of each other and can be identical or different;

5 A is R^4R^5N- ;

k is 3;

n is 2;

10

R^0 is phenyl which is unsubstituted or substituted by one or two identical or different substituents;

in all their stereoisomeric forms and mixtures thereof in any ratio, and their

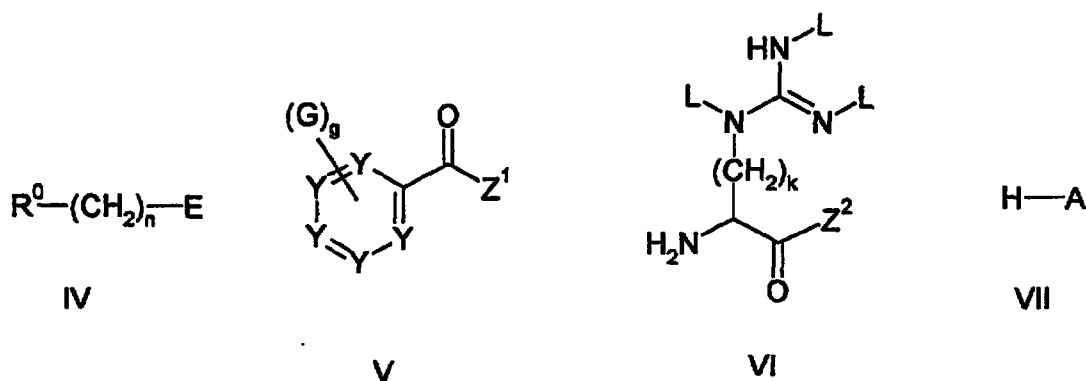
15 physiologically tolerable salts.

The present invention also relates to processes of preparation by which the compounds of the formula I are obtainable. The compounds of the formula I can generally be prepared by linking of two or more fragments (or building blocks) which
20 can be derived retrosynthetically from the formula I. In the preparation of the compounds of the formula I it can generally be advantageous or necessary in the course of the synthesis to introduce functional groups which could lead to undesired reactions or side reactions in a synthesis step in the form of precursors which are later converted into the desired functional groups, or to temporarily block functional
25 groups by a protective group strategy suited to the synthesis problem. Such strategies are well known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991). As examples of precursor groups nitro groups may be mentioned which can later be converted by reduction, for example by catalytic hydrogenation, into amino groups.

30 Protecting groups (or blocking groups) that may be present on functional groups include allyl, tert-butyl, benzyl, tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) and 9-fluorenylmethyloxycarbonyl (Fmoc) as protecting groups for hydroxy, carboxylic

acid, amino and guanidino groups.

In particular, in the preparation of the compounds of the formula I building blocks can be connected by performing one or more condensation reaction such as amide
 5 couplings or ester formations, i. e. by forming amide bonds or ester bonds between a carboxylic acid group of one building block and an amino group or hydroxy group of another building block, or by establishing an ether linkage between a hydroxy group or a halogen atom of one building block and an hydroxy group of another building block. For example, compounds of the formula I can be prepared by linking the
 10 building blocks of the formulae IV, V, VI and VII



by means of forming in a manner known per se an amide bond between the
 15 carboxylic acid derivative group $\text{CO}-\text{Z}^1$ depicted in formula V and the NH_2 group depicted in formula VI, by forming in a manner known per se one or two ether linkages between building blocks of the formulae IV and V in which groups E and/or groups G are hydroxy groups, and by optionally forming in a manner known per se an amide bond or an ester bond between the carboxylic acid derivative group $\text{CO}-\text{Z}^2$
 20 and the amino or oxy group to which the hydrogen atom depicted in formula VII is bonded.

In the compounds of formulae IV, V, VI and VII the groups A, L and R^0 and n and k are defined as above, but functional groups in these compounds can also be present
 25 in the form of precursor groups which are later converted into the groups present in

- the compounds of the formula I, or functional groups can be present in protected form. One or two of the groups Y in the compounds of the formula V are carbon atoms to which the groups G are bonded, zero, one, two or three of the groups Y are nitrogen atoms, and the remaining groups Y are carbon atoms carrying a group R^1 ,
5 where R^1 is defined as above but where functional groups in R^1 can also be present in the form of precursor groups which are later converted into the groups present in the compounds of the formula I, or functional groups can be present in protected form. If compounds of the formula I are to be prepared in which one group of the formula II is present, the number g of the groups G that are present in the
10 compounds of the formula V is one. If compounds of the formula I are to be prepared in which two groups of the formula II are present the number g is two. The groups G which can be identical or different, are hydroxy groups or nucleophilically substitutable leaving groups, for example halogen like fluorine, chlorine, bromine or iodine. The group E in the compounds of the formula IV just so is a hydroxy group or
15 a nucleophilically substitutable leaving group, for example halogen like chlorine, bromine or iodine, or a sulfonyloxy group like tosyloxy, methylsulfonyloxy or trifluoromethylsulfonyloxy. At least one of the two groups E and G which are reacted to establish an ether linkage via which the group $R^0-(CH_2)_n$ is attached, has to be a hydroxy group. The groups Z^1 and Z^2 which can be identical or different, are hydroxy
20 or nucleophilically substitutable leaving groups, i. e. the groups COZ^1 and COZ^2 in the compounds of the formulae V and VI are carboxylic acid groups $COOH$ or activated derivatives of carboxylic acids like acid chlorides, esters like (C_1-C_4) -alkyl esters or activated esters, or mixed anhydrides.
- 25 The starting compounds of the formulae IV, V, VI and VII and other compounds which are employed in the synthesis of the compounds of formula I for introducing certain structural units, are commercially available or can be readily prepared from commercially available compounds by or analogously to procedures described below or in the literature which is readily available to those skilled in the art.
- 30 For the preparation of the compounds of formula I first the compounds of the formulae IV and V may be linked and the resulting intermediate product then be

condensed with a compound of the formula VI to give an intermediate product which is finally condensed with a compound of the formula VII to give a compound of the formula I. Just so, first the compounds of the formulae VI and VII may be condensed and the resulting intermediate product then be condensed with a compound of the formula V to give an intermediate product which is finally linked to a compound of the formula IV to give a compound of the formula I. The intermediate obtained from the compounds of the formula VI and VII may also be condensed with an intermediate obtained by condensing the compounds of the formulae IV and V. There are various other possibilities how the compounds of the formulae IV, V, VI and VII can be coupled to give compounds of the formula I. After any such reaction step in the course of such syntheses protecting and deprotecting steps and conversions of precursor groups into the desired final groups may be carried out and further modifications may be made. For example, a group like R^1 that is different from hydrogen may already be present in the compound of formula V which is employed into the coupling reaction with the compound of formula VI or with the intermediate obtained from the compounds of formula VI and VII, but such a group R^1 may also be introduced only after performing one coupling reaction or both coupling reactions. The synthetic strategy for the preparation of a compound of the formula I can thus be varied broadly, and it depends on the individual case which synthetic procedure is preferred.

Various general methods for the formation of an amide bond that can be employed in the synthesis of the compounds of formula I are known to those skilled in the art, for example, from peptide chemistry. An amide coupling or ester coupling step can favorably be carried out by employing a free carboxylic acid, i. e. a compound of the formula V or VI or an intermediate coupling product in which a group like COZ^1 or COZ^2 reacting in that step is a $COOH$ group, activating that carboxylic acid group, preferably in situ, by means of a customary coupling reagent such as a carbodiimide like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC), or a carbonyldiazole like carbonyldiimidazole, or a uronium salt like O-((cyano-(ethoxycarbonyl)methylene)amino)-1,1,3,3-tetramethyluronium tetrafluoroborate (TOTU) or O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium

hexafluorophosphate (HATU), or a chloroformic acid ester like ethyl chloroformate or isobutyl chloroformate, or tosyl chloride, or propylphosphonic acid anhydride, or others, and then reacting the activated carboxylic acid derivative with an amino compound or hydroxy compound of the formula VI or VII. An amide bond can also be
5 formed by reacting an amino compound with a carboxylic acid halide, in particular a carboxylic acid chloride, which can be prepared in a separate step or in situ from a carboxylic acid and, for example, thionyl chloride, or an carboxylic acid ester or thioester, for example a methyl ester, ethyl ester, phenyl ester, nitrophenyl ester, pentafluorophenyl ester, methylthio ester, phenylthio ester or pyridin-2-ylthio ester, i.
10 e. with a compound of the formula V or VI or with a intermediate coupling product in which a group like Z^1 or Z^2 is chlorine, methoxy, ethoxy, optionally substituted phenyloxy, methylthio, phenylthio or pyridin-2-ylthio.

The activation reactions and coupling reactions are usually performed in the
15 presence of an inert solvent (or diluent), for example in the presence of an aprotic solvent like dimethylformamide (DMF), tetrahydrofuran (THF), dimethylsulfoxide (DMSO), hexamethyl phosphoric triamide (HMPT), 1,2-dimethoxyethane (DME), dioxane, or others, or in a mixture of such solvents. Depending on the specific process, the reaction temperature may be varied over a wide range and be, for
20 example, from about - 20 °C to the boiling temperature of the solvent or diluent. Also depending on the specific process, it may be necessary or advantageous to add in a suitable amount one or more auxiliary agents, for example a base like a tertiary amine, such as triethylamine or diisopropylethylamine, or an alkali metal alcoholate, such as sodium methoxide or potassium tert-butoxide, for adjusting the pH or
25 neutralizing an acid that is formed or for liberating the free base of an amino compound that is employed in the form of an acid addition salt, or an N-hydroxyazole like 1-hydroxybenzotriazole, or a catalyst like 4-dimethylaminopyridine. Details on methods for the preparation of activated carboxylic acid derivatives and the formation of amide bonds and ester bonds as well as source literature are given in various
30 standard references like, for example, J. March, Advanced Organic Chemistry, 4th ed., John Wiley & Sons, 1992; or Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg Thieme Verlag.

The formation of the ether linkage between the building blocks of the formulae IV and V by condensation of the groups E and G can be performed by various methods which are known per se and which are familiar to those skilled in the art. If in a
5 compound of the formula IV wherein n is different from zero, the group E is halogen, sulfonyloxy or another nucleophilically substitutable leaving group, and the group G is hydroxy, the reaction is between a substituted alkyl halide etc. and an aromatic, i. e. phenolic, or a heteroaromatic hydroxy group, and corresponds to the well known Williamson reaction. If E is hydroxy and G is halogen or another nucleophilically
10 substitutable leaving group, the reaction is between an alcohol or phenol and an aryl or heteroaryl halide etc. and is an aromatic nucleophilic substitution. The latter reaction can be carried in case the aromatic ring in the compound of the formula V is activated by electron-withdrawing substituents like nitro or by ring nitrogen atoms. Details for performing these reactions, for example with regard to solvents or to the
15 addition of bases, can be found in the above-mentioned references like J. March, loc. cit., and Houben-Weyl, loc. cit. A versatile method which can favorably be used to form the ether linkage is the condensation of compounds of the formulae IV and V wherein both E and G are hydroxy, under the conditions of the Mitsunobu reaction. In such a reaction a hydroxy compound is activated by reaction with an azodicarboxylic
20 acid ester like diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and a phosphane like triphenylphosphane or tributylphosphane, and becomes susceptible to nucleophilic substitution by, for example, a second hydroxy compound. The reaction can usually be carried under mild conditions in an aprotic solvent like an ether, for example tetrahydrofuran or dioxane, at temperatures from about 0° C to
25 about room temperature. Details on the Mitsunobu reaction are given, for example, in O. Mitsunobu, *Synthesis* (1981) 1 - 28, or in the examples below.

Protective groups that may still be present in the products obtained in the above reactions are then removed by standard procedures. For example, tert-butyl
30 protecting groups, in particular a tert-butyl ester group which is a protected form of a COOH group, can be deprotected, i. e. converted into the carboxylic acid group in the case of an tert-butyl ester, by treatment with trifluoroacetic acid. Benzyl groups can

be removed by hydrogenation. Fluorenylmethoxycarbonyl groups can be removed by secondary amines like piperidine. As already explained, after the coupling reaction also functional groups can be generated from suitable precursor groups or, if desired, further reactions can be carried out on the coupling products by standard processes, for example acylation reactions or esterification reactions. In addition, a conversion into a physiologically tolerable salt or a prodrug of a compound of the formula I can then be carried out by known processes.

The reactions described above and 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. The compounds of the formula I can be prepared, for example, according to the methods of solid phase chemistry by a process which comprises

- a) coupling a compound of the formula VI wherein Z^2 is hydroxy and the amino group is protected by the Fmoc group and the L-substituted guanidino group is a protected guanidino group, to an acid sensitive linker attached to a resin or in general to a solid support, and cleaving off the protecting group Fmoc,
- b) coupling a compound of the formula V wherein Z^1 is hydroxy to the free amino group,
- c) coupling a compound of the formula IV to the intermediate attached to the resin by reacting the groups E and G to give an ether linkage, for example coupling a compound of the formula IV in which E is hydroxy to the intermediate in which G is hydroxy under Mitsunobu conditions in the presence of an azodicarboxylate and triphenylphosphane, and
- d) cleaving off the compound obtained according to steps a) through c) from the resin by means of trifluoroacetic acid.

The resin or the linker used in this process may be of a type such that the carboxy group in the compound of the formula VI which is coupled to the resin or the linker, respectively, is transformed into an amide group $C(=O)-NH_2$, for example a Knorr Linker or a Rink amide resin.

In general, a reaction mixture containing a final compound of the formula I or an intermediate is worked up and, if desired, the product is then purified by customary processes known to those skilled in the art. For example, a synthesized compound
5 can be purified using well known methods such as crystallization, chromatography or reverse phase high performance 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 NMR, IR and mass spectrometry (MS) can be used for characterizing a compound of the invention.

10

The compounds of the present invention are serine protease inhibitors which inhibit the activity of the blood coagulation enzymes factor Xa and/or factor VIIa. In particular, they are highly active inhibitors of factor Xa. They are specific serine protease inhibitors inasmuch as they do not substantially inhibit the activity of other
15 proteases involved in the blood coagulation and/or the fibrinolysis pathway whose inhibition is not desired, such as plasmin and thrombin, in particular thrombin (using the same concentration of the inhibitor). The activity of the compounds of the formula I can be determined, for example, in the assays described below or in other assays known to those skilled in the art. With respect to factor Xa inhibition, a preferred
20 embodiment of the invention comprises compounds which have a $K_i \leq 1 \mu\text{M}$, particularly preferably $\leq 0.1 \mu\text{M}$, for factor Xa inhibition as determined in the assay described below, with or without concomitant factor VIIa inhibition, and which preferably do not substantially inhibit the activity of other proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the same
25 concentration of the inhibitor). The compounds of the invention inhibit 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. With respect to factor VIIa inhibition, a preferred embodiment of the invention comprises compounds which have a $K_i \leq 10 \mu\text{M}$ for factor VIIa inhibition as
30 determined in the assay described below, with or without concomitant factor Xa inhibition, and which preferably do not substantially inhibit the activity of other

proteases involved in coagulation and fibrinolysis whose inhibition is not desired (using the same concentration of the inhibitor).

Because of their factor Xa and/or factor VIIa inhibitory activity the compounds of the formula I are useful pharmacologically active compounds which are suitable, for example, for influencing blood coagulation (or blood clotting) and fibrinolysis and for the therapy and prophylaxis of, for example, cardiovascular disorders, thromboembolic diseases or restenoses. The compounds of the formula I and their physiologically tolerable salts and their prodrugs can be administered to animals, preferably to mammals, and in particular to humans as pharmaceuticals for therapy or prophylaxis. They can be administered on their own, or in mixtures with one another or in the form of pharmaceutical preparations which permit enteral or parenteral administration and which contain, as active constituent, an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to customary pharmaceutically acceptable carrier substances and/or additives.

The present invention therefore also relates to the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the production of pharmaceuticals for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for the production of pharmaceuticals for the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses. The invention also relates to the use of the compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs for the inhibition of factor Xa and/or factor VIIa or for influencing blood coagulation or fibrinolysis or for the therapy or prophylaxis of the diseases mentioned above or below, for example for use in the therapy and prophylaxis of cardiovascular disorders, thromboembolic diseases or restenoses, and to methods of treatment aiming at such purposes including methods for said therapies and prophylaxes. The present invention

furthermore relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula I and/or its physiologically tolerable salts and/or its prodrugs in addition to a customary pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable
5 carrier substances or excipients and/or auxiliary substances or additives.

The pharmaceuticals 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. Administration,
10 however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or 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.

15 The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carriers being used in addition to the compound(s) of the formula I and/or its (their) physiologically tolerable salts and/or its
20 (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. Carrier substances for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carrier substances for the production of solutions, for
25 example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carrier substances for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 to about 90 % by weight of the compounds of the formula I and/or
30 their physiologically tolerable salts and/or their prodrugs. The amount of the active ingredient of the formula I and/or its physiologically tolerable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 to about 1000 mg,

preferably from about 1 to about 500 mg.

In addition to the active ingredients of the formula I and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical
5 preparations can contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain
10 two or more compounds of the formula I and/or their physiologically tolerable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula I the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be
15 combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula I allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula I and/or its physiologically tolerable salts and/or
20 its prodrugs, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

As inhibitors of factor Xa and/or factor VIIa the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for the
25 therapy and prophylaxis of conditions in which the activity of factor Xa and/or factor VIIa plays a role or has an undesired extent, or which can favorably be influenced by inhibiting factor Xa and/or factor VIIa or decreasing their activities, or for the prevention, alleviation or cure of which an inhibition of factor Xa and/or factor VIIa or a decrease in their activity is desired by the physician. As inhibition of factor Xa
30 and/or factor VIIa influences blood coagulation and fibrinolysis, the compounds of the formula I and their physiologically tolerable salts and their prodrugs are generally suitable for reducing blood clotting, or for the therapy and prophylaxis of conditions in

which the activity of the blood coagulation system plays a role or has an undesired extent, or which can favorably be influenced by reducing blood clotting, or for the prevention, alleviation or cure of which a decreased activity of the blood coagulation system is desired by the physician. A specific subject of the present invention thus
5 are the reduction or inhibition of unwanted blood clotting, in particular in an individual, by administering an effective amount of a compound I or a physiologically tolerable salt or a prodrug thereof, as well as pharmaceutical preparations therefor.

Conditions in which a compound of the formula I can be favorably used include, for
10 example, cardiovascular disorders, thromboembolic diseases or complications associated, for example, with infection or surgery. The compounds of the present invention can also be used to reduce an inflammatory response. Examples of specific disorders for the treatment or prophylaxis of which the compounds of the formula I can be used are coronary heart disease, myocardial infarction, angina pectoris,
15 vascular restenosis, for example restenosis following angioplasty like PTCA, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular clotting disorder. Examples of related complications associated with surgery are thromboses like deep vein and proximal vein thrombosis which can occur following surgery. In view of their pharmacological activity the compounds of the
20 invention can replace or supplement other anticoagulant agents such as heparin. The use of a compound of the invention can result, for example, in a cost saving as compared to other anticoagulants.

When using the compounds of the formula I the dose can vary within wide limits and,
25 as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established
30 using clinical approaches well known in the medical art. In general, the daily dose for achieving the desired results in an adult weighing about 75 kg is from about 0.01 to about 100 mg/kg, preferably from about 0.1 to about 50 mg/kg, in particular from

about 0.1 to about 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or
5 downwards from the daily dose indicated.

A compound of the formula I can also advantageously be used as an anticoagulant outside an individual. For example, an effective amount of a compound of the invention can be contacted with a freshly drawn blood sample to prevent coagulation
10 of the blood sample. Further, a compound of the formula I and its salts can be used for diagnostic purposes, for example in in vitro diagnoses, and as an auxiliary in biochemical investigations. For example, a compound of the formula I can be used in an assay to identify the presence of factor Xa and/or factor VIIa or to isolate factor Xa and/or factor VIIa in a substantially purified form. A compound of the invention can be
15 labeled with, for example, a radioisotope, and the labeled compound bound to factor Xa and/or factor VIIa is then detected using a routine method useful for detecting the particular label. Thus, a compound of the formula I or a salt thereof can be used advantageously as a probe to detect the location or amount of factor Xa and/or factor VIIa activity in vivo, in vitro or ex vivo.

20

Furthermore, the compounds of the formula I can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

25

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not limit the present invention.

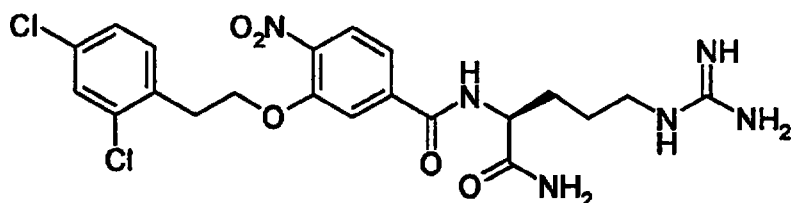
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Examples

Abbreviations used:

5	Arginine	Arg
	tert-Butyl	tBu
	Dichloromethane	DCM
	Diethyl azodicarboxylate	DEAD
	Diisopropyl azodicarboxylate	DIAD
10	N,N'-Diisopropylcarbodiimide	DIC
	N,N-Diisopropyl-N-ethylamine	DIEA
	N,N-Dimethylformamide	DMF
	Dimethylsulfoxide	DMSO
	N-Ethylmorpholine	NEM
15	9-Fluorenylmethyloxycarbonyl	Fmoc
	N-Hydroxybenzotriazole	HOBt
	Methanol	MeOH
	2,2,4,6,7-Pentamethyldihydro- benzofuran-5-sulfonyl	PBF
20	Tetrahydrofuran	THF
	Trifluoroacetic acid	TFA
	O-((Cyan(ethoxycarbonyl)methylene)amino)- 1,1,3,3-tetramethyluronium tetrafluoroborate	TOTU
25	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	
30	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: (S)-4-Nitro-N-(1-carbamoyl-4-guanidinobutyl)-3-[2-(2,4-dichlorophenyl)ethoxy]benzamide



5

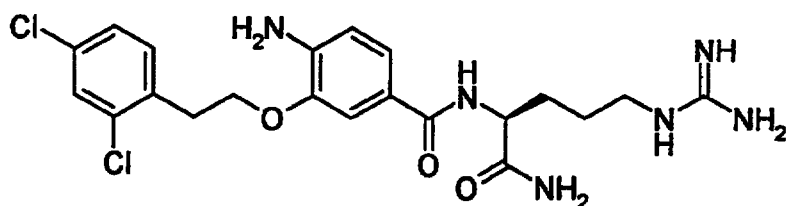
In a reaction vial 300 mg of Tentagel[®] resin functionalized with Rink linker (loading 0.28 mmol/g) was coupled with 600 mg of Fmoc-Arg(Boc)₂ in the presence of 151 mg of HOBt and 172 mg of DIC in 3 ml of dry DMF. Coupling was continued overnight at room temperature and was repeated for additional 2 h. The functionalized resin was Fmoc-deprotected by reaction with 50% piperidine in DMF for 15 min. The unprotected resin was washed and coupled with 183 mg of 3-hydroxy-4-nitrobenzoic acid in the presence of 152 mg of HOBt and 176 mg of DIC in 3 ml of dry DMF for 3 h at room temperature. The resin was washed with DMF, MeOH and DCM and dried in vacuo for 3 h. The dried resin was washed with anhydrous THF and mixed with 267 mg of triphenylphosphane and 201 mg of 2-(2,4-dichlorophenyl)ethanol in 2 ml of anhydrous THF. The suspended resin was cooled in a refrigerator for 20 min and mixed with 180 µl of DEAD dissolved in 1 ml of THF. The mixture was coupled for 15 h at room temperature. The resin was washed with THF, DMF, MeOH, DCM and cleaved with TFA/water (95/5) for 2 h at room temperature. The solution of the final product was filtered off and the filtrate was evaporated to dryness. The residual product was lyophilized from a mixture of acetonitrile and water. The lyophilized solid was purified by HPLC and the final product characterized by electro-spray mass (ES-MS) spectrometry.

MS: 511 (M+H)⁺

25

Example 2: (S)-4-Amino-N-(1-carbamoyl-4-guanidinobutyl)-3-[2-(2,4-dichlorophenyl)ethoxy]benzamide

49

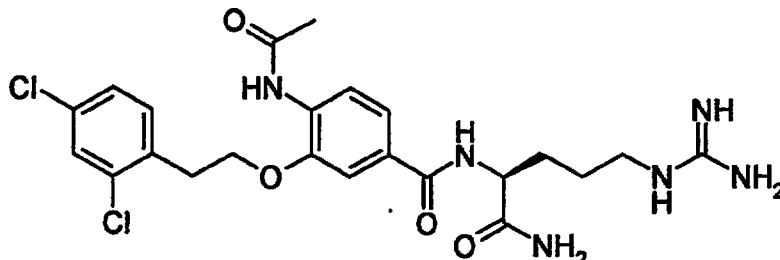


This compound was prepared as outlined in Example 1. Before cleaving the final compound from the resin, the resin was mixed with 210 mg of tin chloride and 300 μ l of acetic acid in 2.5 ml of DMF. The suspended resin was agitated at room temperature for 8 h. The resin was washed, dried and split into three parts. One part was cleaved and processed as outlined in Example 1 to give the title compound. The second and third part were used in Examples 3 and 4.

MS: 481 (M+H)⁺

10

Example 3: (S)-4-Acetylamino-N-(1-carbamoyl-4-guanidinobutyl)-3-[2-(2,4-dichlorophenyl)ethoxy]benzamide



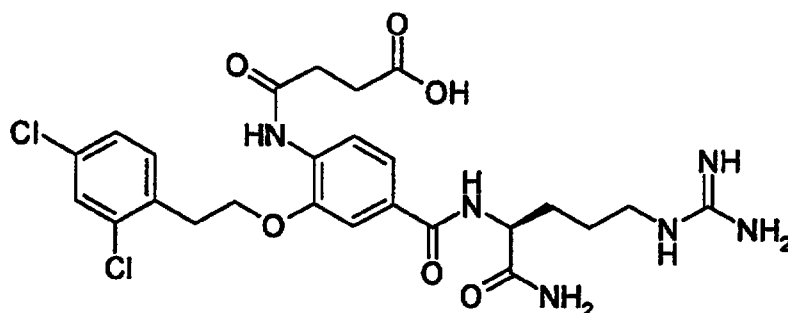
15

The second part of the resin obtained in Example 2 (105 mg) was washed with DCM containing 10% DIEA and coupled with a mixture of DCM and acetic anhydride (1/1) at room temperature for 15 h. The resin was washed, dried, the final product cleaved off and processed as in Example 1.

20 MS: 523 (M+H)⁺

Example 4: (S)-N-[4-(1-Carbamoyl-4-guanidinobutylcarbamoyl)-2-[2-(2,4-dichlorophenyl)ethoxy]phenyl]succinamic acid

50

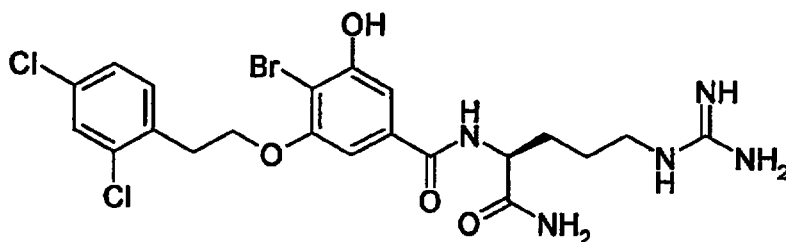


The third part of the resin obtained in Example 2 (116 mg) was coupled with 160 mg of succinic anhydride analogously as described in Example 3. The resin was washed,
5 dried, and the final product cleaved off and processed as in Example 1.

MS: 580.9 (M+H)⁺

Example 5: (S)-4-Bromo-N-(1-carbamoyl-4-guanidinobutyl)-3-[2-(2,4-dichlorophenyl)-ethoxy]-5-hydroxybenzamide

10

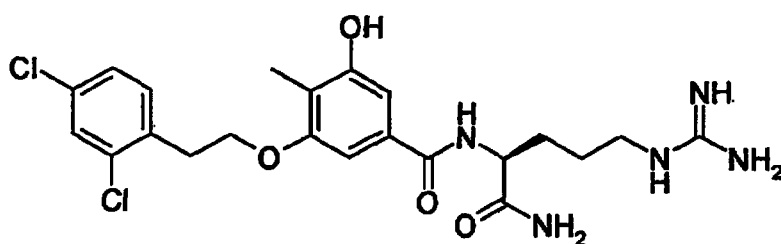


Rink resin (500 mg; loading 0.3 mmol/g) functionalized with Arg(Boc)₂ was coupled with 176 mg of 3,5-dihydroxy-4-bromobenzoic acid in the presence of DIC (110 mg)
15 and HOBt (78 mg) in DMF. The resin was then washed and treated with a 30% solution of benzyltrimethylammonium hydroxide in DMF for 1 h. The resin was washed with DMF, 10% acetic acid in DMF, DMF, and DCM and dried in vacuo for 3 h. The dried resin was washed with anhydrous THF and mixed with 0.2 mmol of triphenylphosphane and 0.2 mmol of 2-(2,4-dichlorophenyl)ethanol in 2 ml of dry
20 THF. The suspension of the resin was cooled in a refrigerator for 16 min and 50 μ l (0.2 mmol) of DIAD in 0.5 ml of dry THF were added. Coupling was continued overnight at room temperature. The resin was washed with dry THF and the coupling

was repeated for additional 8 h. The resin was washed, dried and the final product cleaved off and processed as outlined in Example 1.

MS: 561.8 (M+H)⁺

- 5 Example 6: (S)-N-(1-Carbamoyl-4-guanidinobutyl)-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxy-4-methylbenzamide

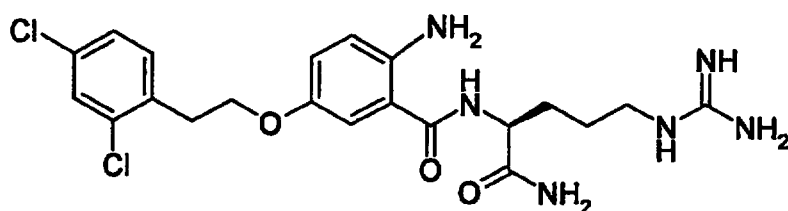


- 10 Rink resin (239 mg; loading 0.43 mmol/g) functionalized with Arg(Boc)₂ was coupled with 106 mg of 3,5-dihydroxy-4-methylbenzoic acid in the presence of DIC (85 mg) and HOBt (90 mg) in DMF (1.5 ml). The resin was then washed and treated with a 15% solution of benzyltrimethylammonium hydroxide in DMF for 45 min. The resin was washed with DMF, 10% acetic acid in DMF, DMF and DCM and dried in vacuo
- 15 for 4 h. The dried resin was washed with anhydrous THF and mixed with 145 mg (0.5 mmole) of triphenylphosphane and 25 μ l of bistrimethylsilylacetamide in THF and kept at room temperature for 1 h. In a separate vial a mixture of 100 mg (0.2 mmol) of 2-(2,4-dichlorophenyl)ethanol and 100 μ l of DIAD in dry THF was prepared. The reaction mixture was added to the resin which had previously been cooled in a
- 20 refrigerator for 10 min. Coupling was continued at room temperature overnight. The resin was washed, dried and the final product cleaved off and processed as outlined in Example 1.

MS: 496.1 (M+H)⁺

- 25 Example 7: (S)-2-Amino-N-(1-carbamoyl-4-guanidino-butyl)-5-[2-(2,4-dichlorophenyl)ethoxy]benzamide

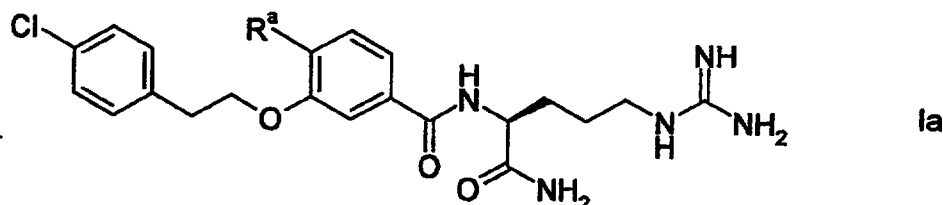
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- Rink resin (306 mg; loading 0.43 mmol/g) functionalized with Arg(Boc)₂ was coupled with 146 mg of 5-hydroxy-2-nitrobenzoic acid in the presence of DIC (136 mg) and
- 5 HOBt (140 mg) in DMF (2 ml) for 3 h at room temperature. The resin was then washed and treated with a 15% solution of benzyltrimethylammonium hydroxide in DMF for 60 min. The resin was washed with DMF, 10% acetic acid in DMF, DMF and DCM and dried in vacuo for 4 h. The dried resin was washed with anhydrous THF and mixed with 534 mg (2 mmol) of triphenylphosphane, 422 mg (2 mmol) of 2-(2,4-
- 10 dichlorophenyl)ethanol and 400 μ l (2 mmol) of DIAD in dry THF. The mixture was kept overnight at room temperature. The resin was washed and treated with 415 mg of tin dichloride monohydrate in 2 ml of DMF and 0.5 ml of trifluoroethanol. The reduction was continued overnight at room temperature. The resin was washed, dried and the final product cleaved off and processed as outlined in Example 1.
- 15 MS: 481 (M+H)⁺

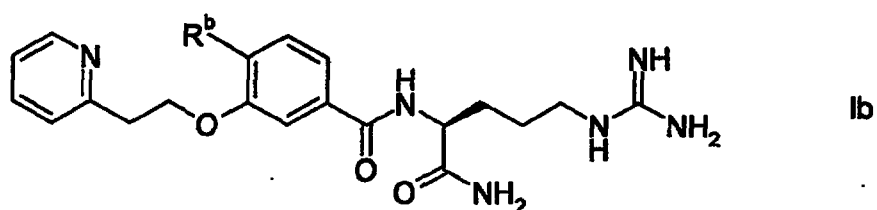
Analogously to the above examples the following example compounds were prepared.

- 20 Example compounds of the formula Ia:



	R^a	MS (M+H) ⁺
Example 8	H	432.2
Example 9	CH ₃	446
Example 10	CH ₃ O	462.3
5 Example 11	NO ₂	477

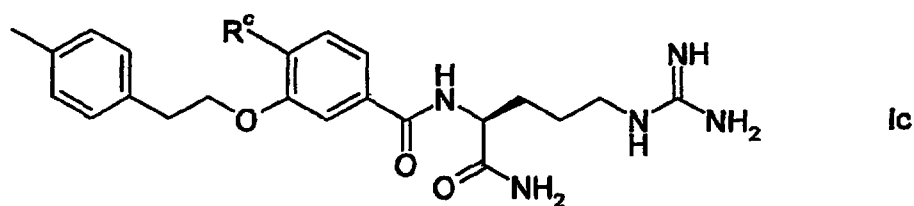
Example compounds of the formula Ib:



10

	R^b	MS (M+H) ⁺
Example 12	H	399.2
Example 13	CH ₃	413.2
Example 14	CH ₃ O	429.2
15 Example 15	NO ₂	444.3

Example compounds of the formula Ic:



20

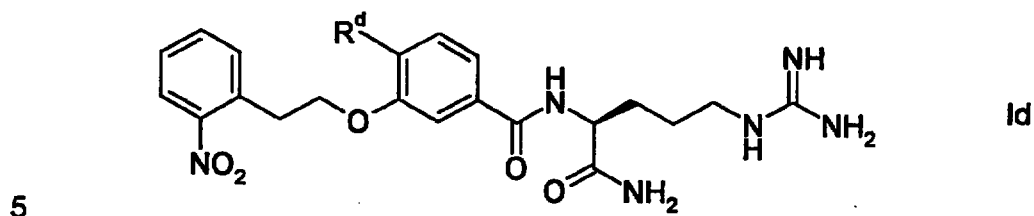
	R^c	MS (M+H) ⁺
Example 16	H	412.2
Example 17	CH ₃	426.2
Example 18	CH ₃ O	442.3
25 Example 19	NO ₂	457.3

Example 20

NH₂

427.2

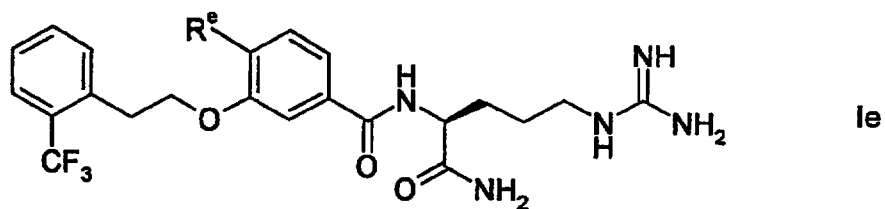
Example compounds of the formula Id:



	R ^d	MS (M+H) ⁺
Example 21	H	443.3
Example 22	CH ₃	457.3
10 Example 23	CH ₃ O	473.3
Example 24	NO ₂	488.3
Example 25	NH ₂	458.3

Example compounds of the formula Ie:

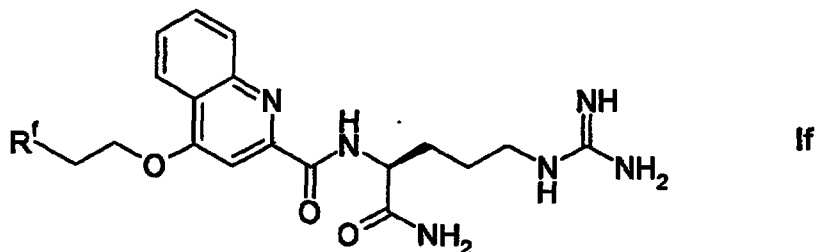
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	R ^e	MS (M+H) ⁺
Example 26	H	466.3
20 Example 27	CH ₃	480.3
Example 28	CH ₃ O	496.3
Example 29	NO ₂	511.3
Example 30	NH ₂	481.3

25

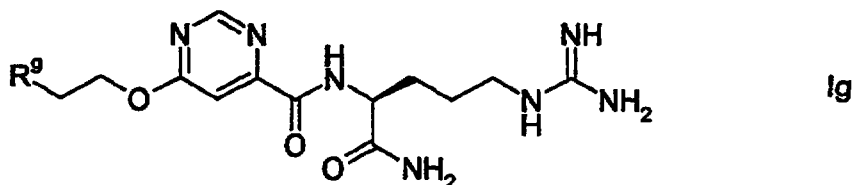
Example compounds of the formula If:



5	R'	MS (M+H) ⁺
Example 31	4-nitrophenyl	494.3
Example 32	2,4,6-trimethylphenyl	491.3
Example 33	4-cyanophenyl	474.3
Example 34	2,4-dichlorophenyl	517.3

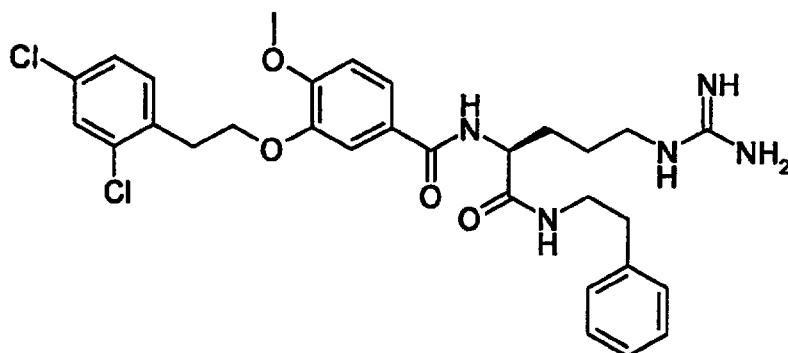
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Example compounds of the formula Ig:



15	R^9	MS (M+H) ⁺
Example 35	2,4-dichlorophenyl	468.3
Example 36	2,4-dimethoxyphenyl	474.3
Example 37	2,4,6-trimethylphenyl	442.3

20 Example 38: (S)-3-[2-(2,4-Dichlorophenyl)ethoxy]-N-(4-guanidino-1-[(2-phenylethyl)carbamoyl]butyl)-4-methoxybenzamide



a) 3-[2-(2,4-Dichlorophenyl)ethoxy]-4-methoxybenzoic acid ethyl ester

To a solution of 10 g (38.3 mmol) of triphenylphosphane in 100 ml of THF were
 5 added 6.7 g (3.83 mmol) of DEAD within 5 min at room temperature. After 30 min at
 room temperature 5 g (25.5 mmol) of 3-hydroxy-4-methoxybenzoic acid ethyl ester
 and 4.87 g (25.5 mmol) of 2-(2,4-dichlorophenyl)ethanol were added and the mixture
 was stirred at room temperature for 12 h. The solvent was removed and the residue
 was separated by chromatography to give 3.6 g (38%) of the title compound.

10

b) 3-[2-(2,4-Dichlorophenyl)ethoxy]-4-methoxybenzoic acid

A solution of 3.6 g (9.8 mmol) of 3-[2-(2,4-dichlorophenyl)ethoxy]-4-methoxybenzoic
 acid ethyl ester in 30 ml of ethanol and 5.4 ml of 2N sodium hydroxide solution was
 stirred at room temperature for 12 h. The precipitate was filtered off. The obtained
 15 solid was stirred with 5 ml of 2N HCl and filtered to give 2.44 g (73%) of the title
 compound.

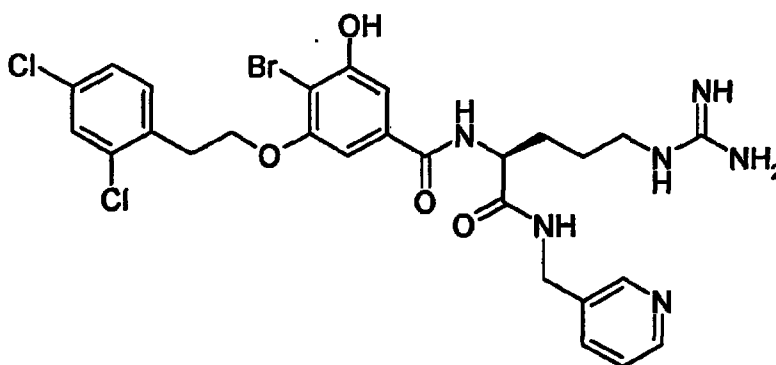
c) (S)-3-[2-(2,4-Dichlorophenyl)ethoxy]-N-{4-guanidino-1-[(2-phenylethyl)carbamoyl]butyl}-4-methoxybenzamide

20 A solution of 78 mg (0.23 mmol) of Arg-(2-phenylethyl)amide, 100 mg (0.23 mmol) of
 3-[2-(2,4-dichlorophenyl)ethoxy]-4-methoxybenzoic acid, 99 mg (0.3 mmol) of TOTU
 and 78 mg (0.6 mmol) of DIEA in 1.5 ml of DMF was stirred at room temperature for
 2 h. 10 ml of DCM was added to the solution which was then washed with water and
 dried with sodium sulfate. The solvent was removed and the residue was precipitated
 25 with diethyl ether and methanol to give 32 mg (22%) of the title compound.

MS: 600.3 (M+H)⁺

Example 39: (S)-4-Bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-N-{4-guanidino-1-[(pyridin-3-ylmethyl)carbamoyl]butyl}-5-hydroxybenzamide

5



a) 4-Bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxybenzoic acid ethyl ester

To a solution of 17.8 g (67.9 mmol) of triphenylphosphane, 8.8 ml (67.9 mmol) of 2-(2,4-dichlorophenyl)ethanol and 16 g (61.3 mmol) of 4-bromo-3,5-dihydroxybenzoic acid ethyl ester in 25 ml of THF was added a solution of 10.6 ml (67.9 mmol) of DEAD in 40 ml of THF within 45 min between 6° and 18°C. After 16 h at room temperature the solvent was removed and the residue was stirred with cyclohexane/ethyl acetate (1/1) and filtered. The solid residue was stirred with cyclohexane and filtered. The remaining solid was separated by chromatography (cyclohexane/ethyl acetate (1/1)) to give 25.6 g (96 %) of the title compound.

MS: 433.1 (M+H)⁺

b) 4-Bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxybenzoic acid

A solution of 25.6 g (59 mmol) of 4-bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxybenzoic acid ethyl ester in 300 ml of ethanol and 2.36 g (65 mmol) of sodium hydroxide in 15 ml of water was stirred at room temperature for 12 h. The solvent was removed and the residue was distributed between water and ethyl acetate. The aqueous solution was acidified with 1 N HCl and the precipitate was filtered to give 4.35 g (31%) of the title compound.

MS: 407.2 (M+H)⁺

c) (S)-4-Bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-N-{4-guanidino-1-[(pyridin-3-ylmethyl)-carbamoyl]butyl}-5-hydroxybenzamide

- 5 25 mg (0.11 mmol) of dicyclohexylcarbodiimide were added to a solution of 40 mg (0.1 mmol) of 4-bromo-3-[2-(2,4-dichlorophenyl)ethoxy]-5-hydroxybenzoic acid, 74 mg (0.1 mmol) of Arg(PBF)-(pyridin-3-ylmethyl)amide, 14 mg (0.1 mmol) of HOBt and 25 μ l of NEM. After 12 h at room temperature the solvent was removed and the residue distributed between water and ethyl acetate. The organic layer was dried with
- 10 sodium sulfate, filtered and the solvent was removed. 1 ml of TFA was added to the residue and the mixture stirred for 2 h at room temperature. The product was precipitated by the addition of water and ethyl acetate and filtered off to give 43 mg (49%) of the title compound.

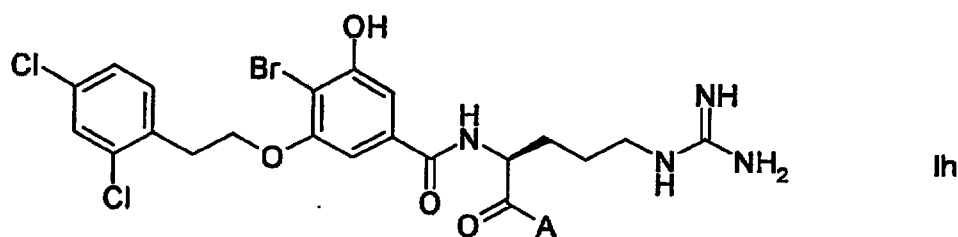
MS: 653.3 (M+H)⁺

15

Analogously to the above examples the following example compounds were prepared.

Example compounds of the formula 1h:

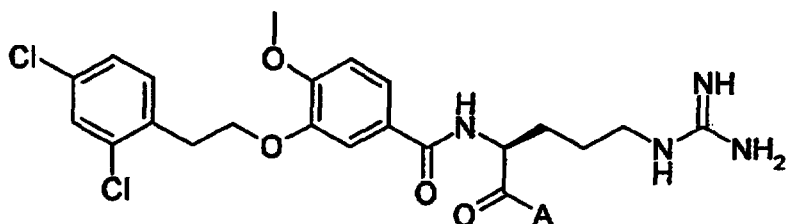
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	A	MS (M+H) ⁺
Example 40	(pyridin-4-ylmethyl)amino	653.3
25 Example 41	benzylamino	652.2
Example 42	3-methoxybenzylamino	682.2
Example 43	4-chlorobenzylamino	686.2
Example 44	4-methoxybenzylamino	682.3

Example 45	dimethylamino	590.2
Example 46	hydroxy	563.2
Example 47	n-propyloxy	605.2

5 Example compounds of the formula II



II

	A	MS (M+H) ⁺
10 Example 48	dimethylamino	524.3
Example 49	hydroxy	497.3
Example 50	n-propyloxy	539.3

15 Pharmacological testing

The ability of the compounds of the formula I to inhibit factor Xa or factor VIIa or other enzymes like thrombin, plasmin, or trypsin can be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 %, i. e. the IC₅₀ value, which is related to the inhibition constant K_i. Purified enzymes are used in chromogenic assays. The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis is determined by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. For calculating the inhibition constant K_i, the IC₅₀ value is corrected for competition with substrate using the formula

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

wherein K_m is the Michaelis-Menten constant (Chen and Prusoff, *Biochem. Pharmacol.* 22 (1973), 3099-3108; I. H. Segal, *Enzyme Kinetics*, 1975, John Wiley & Sons, New York, 100-125; which are incorporated herein by reference).

5 a) Factor Xa Assay

- In the assay for determining the inhibition of factor Xa activity 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) was used. The IC_{50} was determined by combining in appropriate wells of a Costar half-area microtiter plate 25 μl human factor Xa (Enzyme Research Laboratories, Inc.;
10 South Bend, Indiana) 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(α)-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin, Ohio) in TBS-PEG.
- 15 The assay was performed by pre-incubating the compound of formula I plus enzyme for 10 min. Then the assay was initiated by adding substrate to obtain a final volume of 100 μl . The initial velocity of chromogenic substrate hydrolysis was 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
20 min after addition of substrate). The enzyme concentration was 0.5 nM and substrate concentration was 140 μM .

b) Factor VIIa Assay

- The inhibitory activity towards factor VIIa/tissue factor activity was determined using a
25 chromogenic assay essentially as described in J. A. Ostrem et al., *Biochemistry* 37 (1998) 1053-1059, which is incorporated herein by reference. Kinetic assays were conducted at 25 °C in half-area microtiter plates (Costar Corp., Cambridge, Massachusetts) using a kinetic plate reader (Molecular Devices Spectramax 250). A
30 typical assay consisted of 25 μl human factor VIIa and TF (5 nM and 10 nM, respective final concentration) combined with 40 μl of inhibitor dilutions in 10% DMSO/TBS-PEG buffer (50 mM Tris, 15 mM NaCl, 5 mM CaCl_2 , 0.05 % PEG 8000, pH 8.15). Following a 15 minute preincubation period, the assay was initiated by the

addition of 35 μ l of the chromogenic substrate S-2288 (D-Ile-Pro-Arg-p-nitroanilide, Pharmacia Hepar Inc., 500 μ M final concentration).

The following test results (inhibition constants K_i (FXa) for inhibition of factor Xa and
5 K_i (FVIIa) for inhibition of factor VIIa) were obtained.

Example Compound	K_i (FXa) (μ M)	K_i (FVIIa) (μ M)
Example 1	0.048	188
Example 2	0.076	
Example 3	0.67	
Example 4	0.354	42
Example 5	0.018	58
Example 6	0.038	7.5
Example 8	1.1	
Example 11	0.192	
Example 16	6.15	
Example 32	13	13
Example 34	0.75	9.8
Example 39	0.445	>200
Example 45	0.031	>200
Example 46	0.059	>200
Example 47	0.021	>200
Example 48	0.56	>200
Example 50	0.729	>200

The following tests can serve to investigate the inhibition of selected other
coagulation enzymes and other serine proteases by the compounds of formula I and
10 thus to determine their specificity.

c) 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.;
5 South Bend, Indiana). The enzyme concentration is 175 μ M.

d) 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-
10 nitroanilide; Kabi) and the enzyme is human plasmin (Kabi). The enzyme concentration is 5 nM and the substrate concentration is 300 μ M.

e) Trypsin Assay

TBS-PEG buffer containing 10 mM $CaCl_2$ is used for this assay. The IC_{50} is
15 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, Missouri) and the enzyme is bovine pancreatic trypsin (Type XIII, TPCK treated; Sigma). The enzyme concentration is 50 nM and the substrate concentration is 300 μ M.

20

Rat Arteriovenous Shunt Model of Thrombosis

The antithrombotic efficacy of the compounds of the invention can be assessed using rat extracorporeal arteriovenous (AV) shunt. The AV shunt circuit consists of a 20 cm length of polyethylene (PE) 60 tubing inserted into the right carotid artery, a 6 cm
25 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.

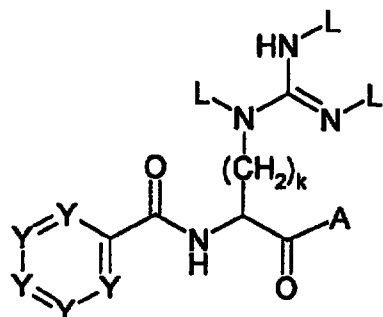
30 The test compound is administered by continuous infusion into the tail vein using a syringe pump and butterfly catheter. The compound is administered for 30 min, then the shunt is opened and blood allowed to flow for a period of 15 min (total of 45 min

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.

Patent claims

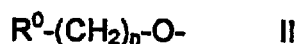


1. A compound of the formula I



in which

one or two of the groups Y are carbon atoms carrying a group of the formula II,



and zero, one, two or three of the groups Y are nitrogen atoms, and the remaining groups Y are carbon atoms carrying a group R^1 , where the groups Y are independent of each other and can be identical or different;

L is chosen from hydrogen, (C_1-C_8) -alkylcarbonyl, (C_6-C_{14}) -aryl- (C_1-C_4) -alkylcarbonyl, (C_6-C_{14}) -arylcarbonyl, (C_1-C_8) -alkyloxycarbonyl, (C_6-C_{14}) -aryl- (C_1-C_4) -alkyloxycarbonyl and (C_6-C_{14}) -aryloxycarbonyl, where the aryl groups present in L are unsubstituted or substituted by one or more identical or different substituents R^{13} , and where all groups L are independent of each other and can be identical or different;

A is chosen from R^3O- and R^4R^5N- ;

k is 1, 2, 3 or 4;



n is 0, 1, 2, 3 or 4;

- R^0 is chosen from phenyl and monocyclic 6-membered heteroaryl containing one or
 5 two nitrogen atoms as ring heteroatoms, where the group R^0 is unsubstituted or substituted by one or more identical or different groups R^2 ;

- R^1 is chosen from hydrogen, halogen, nitro, hydroxy, (C_1-C_8) -alkyloxy-, (C_6-C_{14}) -aryl, (C_1-C_8) -alkyl, hydroxycarbonyl- (C_1-C_8) -alkylureido-, (C_1-C_8) -alkyloxycarbonyl- (C_1-C_8) -
 10 alkylureido-, (C_1-C_8) -alkylsulfonyl- and $R^{11}R^{12}N$ -, where the groups R^1 are independent of each other and can be identical or different, and where alkyl and aryl groups present in R^1 are unsubstituted or substituted by one or more identical or different substituents R^{13} ,

or

- 15 two groups R^1 bonded to adjacent ring carbon atoms together with the carbon atoms to which they are bonded form an aromatic ring condensed to the ring depicted in formula I, where the ring formed by the two groups R^1 is unsubstituted or substituted by one or more identical or different substituents R^{13} ;
- 20 R^2 is chosen from halogen, nitro, (C_1-C_8) -alkyl, cyano, hydroxy, amino and (C_1-C_8) -alkyloxy-, where alkyl groups present in R^2 are unsubstituted or substituted by one or more identical or different halogen atoms;

- R^3 , R^4 and R^5 are chosen from hydrogen, (C_1-C_{12}) -alkyl, (C_6-C_{14}) -aryl- (C_1-C_4) -alkyl-,
 25 (C_6-C_{14}) -aryl-, Het- and Het- (C_1-C_4) -alkyl-, where R^4 and R^5 are independent of each other and can be identical or different, and where the groups alkyl, aryl and Het present in R^3 , R^4 and R^5 are unsubstituted or substituted by one or more identical or different substituents R^{13} ,

or

- 30 R^4 and R^5 together with the nitrogen atom to which they are bonded form a saturated 3-membered to 8-membered monocyclic heterocyclic ring which in addition to the



nitrogen atom carrying R^4 and R^5 can contain one or two identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen;

R^{11} and R^{12} which are independent of each other and can be identical or different,
5 are chosen from hydrogen, (C_1-C_8) -alkyl, (C_6-C_{14}) -aryl- (C_1-C_4) -alkyl-, Het- (C_1-C_4) -alkyl-, hydroxycarbonyl- (C_1-C_8) -alkyl-, (C_1-C_8) -alkyloxycarbonyl- (C_1-C_8) -alkyl-, hydroxycarbonyl- (C_1-C_8) -alkylcarbonyl-, (C_1-C_8) -alkyloxycarbonyl- (C_1-C_8) -alkylcarbonyl- and (C_1-C_8) -alkylcarbonyl-, where alkyl and aryl groups present in R^{11} and R^{12} are unsubstituted or substituted by one or more identical or different
10 substituents R^{13} ,

or

R^{11} and R^{12} together with the nitrogen atom to which they are bonded form a saturated or unsaturated 5-membered to 8-membered monocyclic heterocyclic ring which in addition to the nitrogen atom carrying R^{11} and R^{12} can contain one or two
15 identical or different ring heteroatoms chosen from oxygen, sulfur and nitrogen, and in which one or two of the ring carbon atoms can be substituted by oxo to form $C=O$ group(s);

R^{13} is chosen from halogen, nitro, cyano, hydroxy, (C_1-C_8) -alkyl, (C_1-C_8) -alkyloxy,
20 trifluoromethyl and amino;

Het is a residue of a saturated, partially unsaturated or aromatic monocyclic or bicyclic, 3-membered to 10-membered heterocyclic ring system containing one, two, three or four identical or different heteroatoms chosen from nitrogen, oxygen and
25 sulfur;

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

30 2. A compound of the formula I as claimed in claim 1, in which one of the groups Y is a carbon atom carrying a group of the formula II, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.



3. A compound of the formula I as claimed in claims 1 and/or 2, in which zero, one or two of the groups Y are nitrogen atoms, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

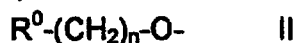
5

4. A compound of the formula I as claimed in one or more of claims 1 to 3, in which R^1 is chosen from hydrogen, halogen, hydroxy, nitro, $R^{11}R^{12}N$ - and (C_1-C_8) -alkyloxy, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

10

5. A compound of the formula I as claimed in one or more of claims 1 to 4, in which A is R^4R^5N -, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically tolerable salts.

15 6. A compound of the formula I as claimed in one or more of claims 1 to 5, in which one of the groups Y is a carbon atom carrying a group of the formula II,



20 and zero, one or two of the groups Y are nitrogen atoms, and the remaining groups Y are carbon atoms carrying a group R^1 , where the groups Y are independent of each other and can be identical or different;

A is R^4R^5N -;

25

k is 3;

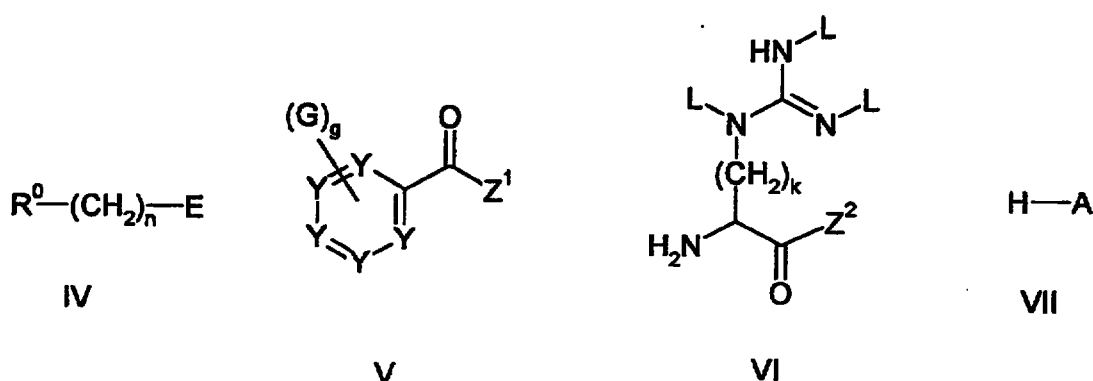
n is 2;

30 R^0 is phenyl which is unsubstituted or substituted by one or two identical or different substituents;



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

7. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 6, comprising linking compounds of the formulae IV, V, VI and VII,



- 10 in which R^0 , A, L, k and n are defined as in claims 1 to 6, one or two of the groups Y in the compounds of the formula V are carbon atoms to which the groups G are bonded, zero, one, two or three of the groups Y are nitrogen atoms, and the remaining groups Y are carbon atoms carrying a group R^1 where R^1 is defined as in claims 1 to 6, but where in R^0 , R^1 , A and L functional groups can also be present in protected form or in the form of precursor groups, and in which one of the two groups E and G is hydroxy and the other is hydroxy or a nucleophilically substitutable leaving group, g is one or two, and Z^1 and Z^2 are hydroxy or nucleophilically substitutable leaving groups.
- 20 8. A pharmaceutical preparation, comprising at least one compound of the formula I as claimed in one or more of claims 1 to 6 and/or its physiologically tolerable salts and a pharmaceutically acceptable carrier.
9. A compound of the formula I as claimed in one or more of claims 1 to 6 and/or its
- 25 physiologically tolerable salts for use as an inhibitor of factor Xa and/or factor VIIa.



10. A compound of the formula I as claimed in one or more of claims 1 to 6 and/or its physiologically tolerable salts for inhibiting or reducing blood clotting or inflammatory response or for use in the therapy or prophylaxis of cardiovascular disorders,
- 5 thromboembolic diseases or restenoses.