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(54) INDOLE DERIVATIVES AS INHIBITORS OF FACTOR XA

INDOLDERIVATE ALS FAKTOR XA INHIBITOREN

UTILISATION DE DERIVES INDOLIQUES COMME INHIBITEURS DU FACTEUR XA

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(73) Proprietor: **Aventis Pharma Deutschland GmbH
65929 Frankfurt am Main (DE)**

(72) Inventors:

- **DEFOSSE, Elisabeth
D-65510 Idstein (DE)**
- **HEINELT, Uwe
D-65187 Wiesbaden (DE)**

- **KLINGLER, Otmar
D-63110 Rodgau (DE)**
- **ZOLLER, Gerhard
D-61137 Schöneck (DE)**
- **AL-OBEIDI, Fahad
Tucson, AZ 85704 (US)**
- **WALSER, Armin
Tucson, AZ 85718 (US)**
- **WILDGOOSE, Peter
D-61440 Oberursel (DE)**
- **MATTER, Hans
D-63505 Langenselbold (DE)**

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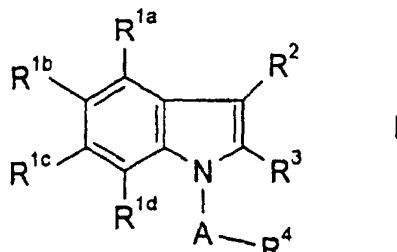
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Description

[0001] The present invention relates to the inhibition of blood clotting proteins, and more particularly, to indole derivatives of the formula I,

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in which R^{1a}, R^{1b}, R^{1c}, R^{1d}, R², R³, R⁴ and A are defined as indicated below. The compounds of the formula I are inhibitors of the blood clotting enzyme factor Xa. The invention also relates to processes for the preparation of the compounds of the formula I, to methods of inhibiting factor Xa activity and of inhibiting blood clotting, to the use of the compounds of formula I in the treatment and prophylaxis of diseases which can be cured or prevented by the inhibition of factor Xa activity such as thromboembolic diseases, and to the use of the compounds of formula I in the preparation of medicaments to be applied in such diseases. The invention further relates to compositions containing a compound of the formula I in admixture or otherwise in association with an inert carrier, in particular pharmaceutical compositions containing a compound of the formula I together with pharmaceutically acceptable carrier substances and/or auxiliary substances.

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[0002] The ability to form blood clots is vital to survival. In certain disease states, however, the formation of blood clots within the circulatory system is itself a source of morbidity. It is nevertheless not desirable in such disease states to completely inhibit the clotting system because life threatening hemorrhage would ensue. In order to reduce the instances of the intravascular formation of blood clots those skilled in the art have endeavored to develop an effective inhibitor of factor Xa, or prothrombinase, the enzyme which is incorporated into the prothrombinase complex where it serves to activate thrombin during clot formation. Appropriate concentrations of such an inhibitor would increase the level of prothrombinase forming agents required to initiate clotting, but would not unduly prolong the clotting process once a threshold concentration of thrombin had been obtained.

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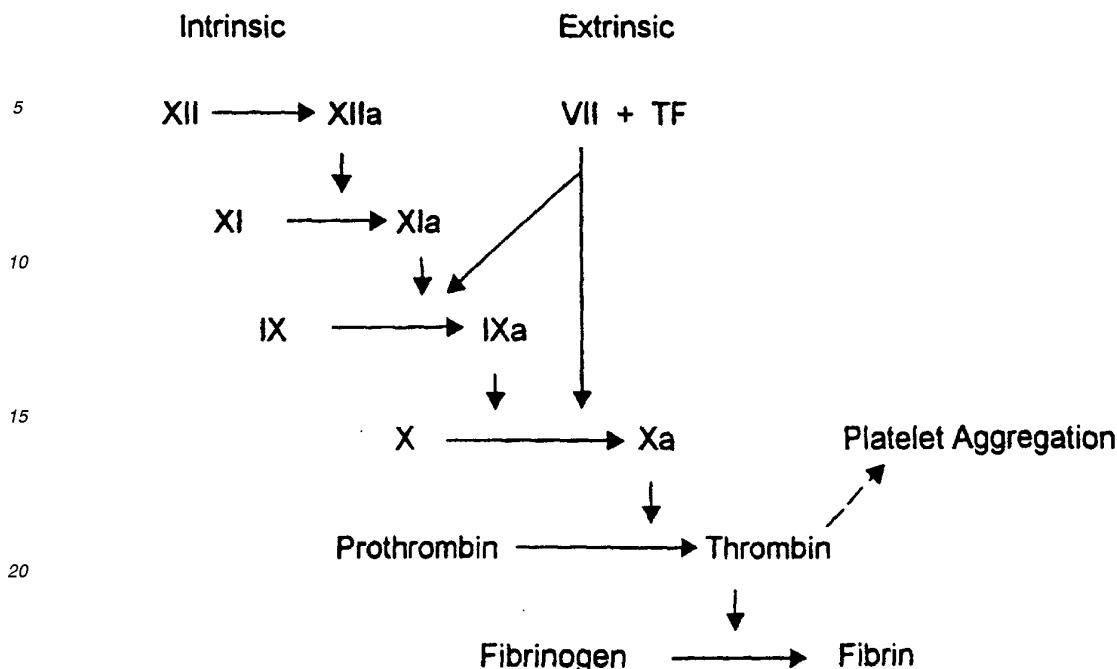
[0003] Blood coagulation is a complex process involving a progressively amplified series of enzyme activation reactions in which plasma zymogens are sequentially activated by limited proteolysis. Mechanistically the blood coagulation cascade has been divided into intrinsic and extrinsic pathways, which converge at the activation of factor X; subsequent generation of the thrombin proceeds through a single common pathway (see Scheme 1).

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Scheme 1: Blood coagulation cascade

- [0004] Present evidence suggests that the intrinsic pathway plays an important role in the maintenance and growth of fibrin formation, while the extrinsic pathway is critical in the initiation phase of blood coagulation. It is generally accepted that blood coagulation is physically initiated upon formation of a tissue factor/factor VIIa complex. Once formed, this complex rapidly initiates coagulation by activating factors IX and X. The newly generated activated factor X, i. e. factor Xa, then forms a one-to-one complex with factor Va and phospholipids to form a prothrombinase complex, which is responsible for converting soluble fibrinogen to insoluble fibrin via the activation of thrombin from its precursor prothrombin. As time progresses, the activity of the factor VIIa/tissue factor complex (extrinsic pathway) is suppressed by a Kunitz-type protease inhibitor protein, TFPI, which, when complexed to factor Xa, can directly inhibit the proteolytic activity of factor VIIa/tissue factor. In order to maintain the coagulation process in the presence of an inhibited extrinsic system, additional factor Xa is produced via the thrombin-mediated activity of the intrinsic pathway. Thus, thrombin plays a dual autocatalytic role, mediating its own production and the conversion of fibrinogen to fibrin.
- [0005] The autocatalytic nature of thrombin generation is an important safeguard against uncontrolled bleeding and it ensures that, once a given threshold level of prothrombinase is present, blood coagulation will proceed to completion, effecting, for example, an end of the hemorrhage. Thus, it is most desirable to develop agents that inhibit coagulation without directly inhibiting thrombin. However, despite the long standing recognition of the desirability of such an inhibitor, there is at present no effective specific Xa inhibitor in clinical use.
- [0006] In many clinical applications there is a great need for the prevention of intravascular blood clots or for some anti-coagulant treatment. The currently available drugs are not satisfactory in many specific clinical applications. For example, nearly 50 % of patients who have undergone a total hip replacement develop deep vein thrombosis (DVT). The currently approved therapies are fixed dose low molecular weight heparin (LMWH) and variable dose heparin. Even with these drug regimes 10 % to 20 % of patients develop DVT and 5 % to 10 % develop bleeding complications.
- [0007] Another clinical situation for which better anticoagulants are needed concerns subjects undergoing transluminal coronary angioplasty and subjects at risk for 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, administration of heparin after termination of the procedures is of little value and can be detrimental.
- [0008] The most widely used blood-clotting inhibitors are heparin and the related sulfated polysaccharides, LMWH and heparin sulfate. These molecules exert their anti-clotting effects by promoting the binding of a natural regulator of

the clotting process, anti-thrombin III, to thrombin and to factor Xa. The inhibitory activity of heparin primarily is directed toward thrombin, which is inactivated approximately 100 times faster than factor Xa. Although relative to heparin, heparin sulfate and LMWH are somewhat more potent inhibitors of Xa than of thrombin, the differences in vitro are modest (3 to 30 fold) and effects in vivo can be inconsequential. Hirudin and hirulog are two additional thrombin-specific anticoagulants presently in clinical trials. However, these anticoagulants, which inhibit thrombin, also are associated with bleeding complications.

[0009] Preclinical studies in baboons and dogs have shown that specific inhibitors of factor Xa prevent clot formation without producing the bleeding side effects observed with direct thrombin inhibitors. Such factor Xa inhibitors include, for example, 2,7-bis-(4-amidinobenzylidene)-cycloheptanone and N(α)-tosyl-glycyl-3-amidinophenylalanine methyl ester ("TENSTOP"), which have effective inhibitory concentrations (Ki's) of about 20 nM and 800 nM, respectively. (+)- α -(2S)-2-(4-((3S)-1-acetimidoyl-3-pyrrolidinyl)oxy)phenyl)-3-(7-amidino-2-naphthyl)propanoic acid also is representative of a class of factor Xa inhibitors (Katakura et al., Biochem. Biophys. Res. Comm. 197 (1993), 965-972). Thus far, however, these compounds have not been developed clinically.

[0010] Several specific inhibitors of factor Xa have been reported. Both synthetic and protein inhibitors of factor Xa have been identified including, for example, antistasin ("ATS") and tick anticoagulant peptide ("TAP"). ATS, which is isolated from the leech, Haementeria officinalis, contains 119 amino acids and has a Ki for factor Xa of 0.05 nM. TAP, which is isolated from the tick, Ornithodoros moubata, contains 60 amino acids and has a Ki for factor Xa of about 0.5 nM.

[0011] 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.

[0012] Subcutaneous ATS also was found to be an effective treatment in a thromboplastin-induced model of disseminated intravascular coagulation (DIC). TAP effectively prevents "high-shear" arterial thrombosis and "reduced flow" caused by the surgical placement of a polyester ("DACRON") graft at levels that produced a clinically acceptable prolongation of the activated partial thromboplastin time (aPTT), i.e., less than about two fold prolongation. By comparison, standard heparin, even at doses causing a five fold increase in the aPTT, did not prevent thrombosis and reduced flow within the graft. The aPTT is a clinical assay of coagulation which is particularly sensitive to thrombin inhibitors.

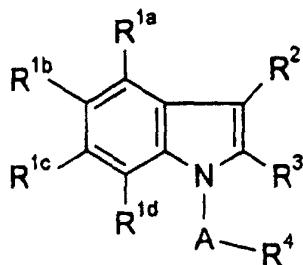
[0013] ATS and TAP have not been developed clinically. One major disadvantage of these two inhibitors is that administration of the required repeated doses causes the generation of neutralizing antibodies, thus limiting their potential clinical use. Moreover, the sizes of TAP and ATS render oral administration impossible, further restricting the number of patients able to benefit from these agents.

[0014] Other compounds having a factor Xa inhibitory activity have been described. WO-A-95/29 189, for example, discloses factor Xa inhibitors which have a peptide like structure, and WO-A-97/08 165 discloses cyclic guanidines which inhibit factor Xa. In WO-A-97/21 437 naphthyl-substituted benzimidazoles are described which have an inhibitory activity against factor Xa and factor IIa and which can be used as anti-coagulants, and in WO-A-97/30 971 factor Xa inhibitory m-amidino phenyl analogs are described. But there is still a need for further factor Xa inhibitors having improved properties like a favorable pharmacological activity profile.

[0015] A specific inhibitor of factor Xa would have substantial practical value in the practice of medicine. In particular, a factor Xa inhibitor would be effective under circumstances where the present drugs of choice, heparin and related sulfated polysaccharides, are ineffective or only marginally effective. Thus, there exists a need for a low molecular weight factor Xa-specific blood clotting inhibitor that is effective, but does not cause unwanted side effects. The present invention satisfies this need by providing novel factor Xa activity inhibiting indole derivatives of the formula I and by providing related advantages as well.

[0016] As used herein, the term "factor Xa activity" refers to the ability of factor Xa, by itself or in the assembly of subunits known as the prothrombinase complex, to catalyze the conversion of prothrombin to thrombin. When used in reference to factor Xa activity, the term "inhibition" includes both the direct and indirect inhibition of factor Xa activity. Direct inhibition of factor Xa activity can be accomplished, for example, by the binding of a compound of the formula I to factor Xa or to prothrombinase so as to prevent the binding of prothrombin to the prothrombinase complex active site. Indirect inhibition of factor Xa activity can be accomplished, for example, by the binding of a compound of the invention to soluble factor Xa so as to prevent its assembly into the prothrombinase complex. As used herein, the term "specific" when used in reference to the inhibition of factor Xa activity means that a compound of the formula I can inhibit factor Xa activity without substantially inhibiting the activity of other specified proteases, including plasmin and thrombin (using the same concentration of the inhibitor). Such proteases are involved in the blood coagulation and fibrinolysis cascade. The present invention provides novel compounds which inhibit factor Xa activity but do not substantially inhibit the activity of other proteases involved in the blood coagulation pathway.

[0017] Thus, a subject of the present invention are indole derivatives of the formula I,



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wherein

two of the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} independent of one another are hydrogen, F, Cl, Br, I, methyl, (C₁-C₄)-alkoxy, phenyl-(C₁-C₄)-alkoxy-, OH or NR^{5a}R^{5b}, and are identical or different, and the other two of the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} are hydrogen;

R^{5a} is hydrogen or ((C₁-C₄)-alkoxy)carbonyl-;

R^{5b} is hydrogen;

R² is hydrogen, Cl or Br;

R³ is -CO-NHR¹⁰;

R⁷ is hydroxy, (C₁-C₄)-alkoxy, phenyl-(C₁-C₄)-alkoxy- or -NR^{5a}R^{5b};

R¹⁰ is (C₁-C₁₀)-alkyl-, phenyl-(C₁-C₄)-alkyl- or naphthyl-(C₁-C₄)-alkyl-, where the (C₁-C₁₀)-alkyl- residue, the phenyl residue and the naphthyl residue are unsubstituted or substituted by one, two or three identical or different residues R¹¹;

R¹¹ is -N(R¹²)₂, -OR¹², -CO-N(R¹³)₂, -CO-R⁷, R^{15b}, (C₁-C₁₄)-alkyl, phenyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b}, naphthyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b}, quinolinyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b} and/or substituted at the nitrogen atom by R¹⁴, isoquinolinyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b} and/or substituted at the nitrogen atom by R¹⁴, pyridyl which is unsubstituted or substituted at the nitrogen atom by R¹⁴, or Het which is unsubstituted or substituted by R^{15a}, where

30 residues R¹¹ if present more than one time in the molecule, are independent of each other and can be identical or different;

[0018] Het is the residue of a 5-membered or 6-membered saturated heterocyclic ring containing 1 or 2 identical or different ring heteroatoms selected from the series consisting of nitrogen, oxygen and sulfur;

each residue R¹² independent of the denotation of another residue R¹² is hydrogen, (C₁-C₄)-alkyl, phenyl, phenyl-(C₁-C₄)-alkyl-, naphthyl, naphthyl-C₁-C₄-alkyl-, pyrrolidinyl, piperidinyl, pyrrolidinyl-(C₁-C₄)-alkyl- or piperidinyl-(C₁-C₄)-alkyl-, where each pyrrolidinyl residue and each piperidinyl residue is unsubstituted or substituted at the nitrogen atom by phenyl-(C₁-C₄)-alkyl- or R^{15a};

each residue R¹³ independent of the denotation of another residue R¹³ is hydrogen, (C₁-C₄)-alkyl, phenyl, phenyl-(C₁-C₄)-alkyl-, naphthyl or naphthyl-(C₁-C₄)-alkyl-, or the two residues R¹³ together with the nitrogen atom to which they are bonded form a 5-membered or 6-membered saturated heterocyclic ring which can contain an additional nitrogen atom or oxygen atom in the ring where the additional nitrogen atom in the ring is unsubstituted or substituted by (C₁-C₄)-alkyl or phenyl-(C₁-C₄)-alkyl-;

R¹⁴ is (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₁-C₆)-alkynyl, phenyl-(C₁-C₆)-alkyl- or ((C₁-C₆)-alkoxy)carbonyl-(C₁-C₆)-alkyl-, where phenyl present in R¹⁴ denotes an unsubstituted phenyl residue, the substitution by these residues at the nitrogen atom of the heterocyclic residue leading to a positively charged group having X⁻ as the counterion; or R¹⁴ is oxido this substitution at the nitrogen atom of the heterocyclic residue leading to an N-oxide; and where residues R¹⁴ if present more than one time in the molecule, are independent of each other and can be identical or different;

R^{15a} is (C₁-C₆)-alkyl, ((C₁-C₆)-alkyl)-C(=NH)-, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N⁺(R^{16a})₂(-O⁻), -(CH₂)_t-N⁺(R^{16a})₃ X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ or -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷, where ((C₁-C₆)-alkyl)-C(=NH)- is bonded to a ring nitrogen atom, and where residues R^{15a} if present more than one time in the molecule, are independent of each other and can be identical or different;

R^{15b} is (C₁-C₆)-alkyl, hydroxy, (C₁-C₄)-alkoxy, F, Cl, Br, I, NO₂, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N⁺(R^{16a})₂(-O⁻), -(CH₂)_t-N⁺(R^{16a})₃ X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CO-OR¹⁸, -(CH₂)_t-CO-N(R¹⁸)₂, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ or -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷, where alkyl can be substituted 1, 2, 3, 4, 5, 6, or 7 times by fluoro, and where

55 residues R^{15b} if present more than one time in the molecule, are independent of each other and can be identical or different;

t is 0, 1, 2 or 3, where numbers t, if present more than one time in the molecule, are independent of each other and can be identical or different;

each residue R¹⁶ independent of the denotations of another residue R¹⁶ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₁-C₆)-alkynyl, phenyl-(C₁-C₆)-alkyl- or ((C₁-C₆)-alkoxy)carbonyl-(C₁-C₆)-alkyl-, where phenyl present in R¹⁶ denotes an unsubstituted phenyl residue, and where groups containing residues R¹⁶ if present more than one time in the molecule, are independent of each other and can be identical or different;

5 each residue R^{16a} independent of the denotations of another residue R^{16a} is (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₁-C₆)-alkynyl, phenyl-(C₁-C₆)-alkyl- or ((C₁-C₆)-alkoxy)carbonyl-(C₁-C₆)-alkyl-, where phenyl present in R^{16a} denotes an unsubstituted phenyl residue, and where groups containing residues R^{16a} if present more than one time in the molecule, are independent of each other and can be identical or different;

10 each residue R¹⁷ independent of the denotation of another residue R¹⁷ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl-, (C₁-C₆)-alkoxycarbonyl-, (C₁-C₆)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl-, phenylcarbonyl-, phenoxy carbonyl-, phenyl-(C₁-C₆)-alkoxycarbonyl-, hydroxy, (C₁-C₆)-alkoxy, phenyl-(C₁-C₆)-alkoxy- or amino, and additionally in the groups -(CH₂)_nC(=NR¹⁷)-NHR¹⁷ and -(CH₂)_nNH-C(=NR¹⁷)-NHR¹⁷ the two residues R¹⁷ together with the C(=N)-NH group to which they are bonded, can form a 5-membered or 6-membered heterocyclic ring, and where phenyl present in R¹⁷ denotes an unsubstituted phenyl residue, and where groups containing residues R¹⁷ if present more than one time in the molecule, are independent of each other and can be identical or different;

15 each residue R¹⁸ independent of the denotation of another residue R¹⁸ is hydrogen or (C₁-C₄)-alkyl; A is a methylene residue -CH₂;

R⁴ is phenyl which is substituted by one residue R^{15c} in the meta position;

R^{15c} is -C(=NR¹⁷)-NHR¹⁷ wherein the residues R¹⁷ are hydrogen;

20 X⁻ is a physiologically acceptable anion;

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

[0019] In general, residues or substituents which can occur more than once in compounds of the formula I can all independently of one another have the meanings indicated, and can in all cases be identical or different.

[0020] Alkyl residues present in the compounds of the formula I can be straight-chain or branched. This also applies when they carry substituents or occur as substituents in other residues such as, for example, in alkoxy residues, alkyl-carbonyl residues, alkoxy carbonyl residues or phenylalkyl residues. An alkyl residue like (C₁-C₆)-alkyl comprises alkyl residues having 1, 2, 3, 4, 5 or 6 carbon atoms, an alkyl residue like (C₁-C₁₀)-alkyl in addition alkyl residues having 7, 8, 9 or 10 carbon atoms, an alkyl residue like (C₁-C₁₄)-alkyl in addition alkyl residues having 11, 12, 13 or 14 carbon atoms. Examples of alkyl residues are methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, isopropyl, isobutyl, isopentyl, isoheptyl, isoctyl, neopentyl, 3-methylpentyl, sec-butyl, tert-butyl and tert-pentyl. A group of preferred alkyl residues is formed by the residues methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl. Examples of fluoro-substituted alkyl groups are trifluoromethyl, pentafluoroethyl, heptafluoropropyl or 2,2,2-trifluoroethyl, in particular trifluoromethyl.

[0021] Further, as used herein, the term alkyl comprises acyclic alkyl residues as well as alkyl residues which contain one or more alicyclic ring system. Thus, in addition to acyclic alkyl residues the term alkyl expressly also comprises cycloalkyl residues which are bonded via a ring carbon atom, and cycloalkyl-alkyl residues which are bonded via a carbon atom in an acyclic subunit. This also applies when alkyl residues carry substituents or occur as substituents in other residues such as, for example, in alkoxy residues, alkylcarbonyl residues, alkoxy carbonyl residues or phenylalkyl residues. Cycloalkyl residues representing alkyl residues or being contained in alkyl residues can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Of course, the term alkyl comprises only such cyclic residues which are stable in view of the number of carbon atoms present in the alkyl residue considered. As monocyclic alkyl residues have to contain at least three carbon atoms in the ring a (C₁-C₄)-alkyl residue, for example, comprises also (C₃-C₄)-monocycloalkyl residues, a (C₁-C₆)-alkyl residue comprises also (C₃-C₆)-monocycloalkyl residues, a (C₁-C₁₀)-alkyl residue comprises also (C₃-C₁₀)-monocycloalkyl residues or a (C₁-C₁₄)-alkyl residue comprises also (C₃-C₁₄)-monocycloalkyl residues. Bicyclic and tricyclic alkyl residues preferably contain 6, 7, 8, 9, 10, 11, or 12 carbon atoms. Thus, a (C₁-C₁₀)-alkyl residue, for example, comprises also (C₆-C₁₀)-bicycloalkyl residues and (C₆-C₁₀)-tricycloalkyl residues, or a (C₁-C₁₄)-alkyl residue comprises also (C₆-C₁₄)-bicycloalkyl residues and (C₆-C₁₄)-tricycloalkyl residues, both preferably comprising bicycloalkyl residues and tricycloalkyl residues having 7 or more carbon atoms. Examples of cyclic alkyl residues or of alkyl-substituted alkyl residues wherein the alkyl group regarded as a substituent is a cyclic residue, are cyclopropyl, cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclopropylbutyl, cyclopropylpentyl, cyclopropylhexyl, cyclopropylheptyl, cyclobutyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclobutylbutyl, cyclobutylpentyl, cyclobutylhexyl, cyclopentyl, cyclopentylmethyl, cyclopentylenethyl, cyclopentylpropyl, cyclopentylbutyl, cyclopentylpentyl, cyclohexyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, cyclohexylbutyl, cycloheptyl, cyclooctyl, octahydroindenyl, bicyclo[4.2.0]octyl, octahydronatalenyl, bicyclo[3.3.1]nonyl, tetradecahydrophenanthryl, dodecahydrophenalenyl, octahydro-1,4-ethano-indenyl, adamantyl or adamantylmethyl, wherein the ethyl, propyl, butyl, pentyl, hexyl and heptyl groups carrying the cyclic groups can be straight-chain or branched as described above. The cyclic groups can be bonded via any suitable carbon atom. Residues derived from bridged hydrocarbons can be bonded via bridgehead carbon atoms or carbon atoms in the bridges. Adamantyl, for example, can be 1-adamantyl or

2-adamantyl.

[0022] Alkenyl residues and alkynyl residues can also be straight-chain or branched. Examples of alkenyl residues are vinyl, 1-propenyl, 2-propenyl (= allyl), butenyl, 3-methyl-2-but enyl, pentenyl and hexenyl, examples of alkynyl residues are ethynyl, 1-propynyl, 2-propynyl (= propargyl), butynyl, pentynyl and hexynyl.

[0023] The above statements relating to alkyl residues correspondingly apply to divalent alkyl residues, i. e. to alkylene residues or alkanediyl residues. Examples of saturated divalent alkyl residues are methylene (-CH₂), methylenemethylene (-CH(CH₃)-), dimethylmethylenes (-C(CH₃)₂), ethylene (-CH₂-CH₂), methylethylene (-CH(CH₃)-CH₂- and -CH₂-CH(CH₃)-), trimethylene -(CH₂)₃- or tetramethylene -(CH₂)₄-.

[0024] 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 phenyl is substituted twice, the substituents can be in the 2,3-position, the 2,4-position, the 2,5-position, the 2,6-position, the 3,4-position or the 3,5-position. In phenyl residues carrying three substituents the substituents can be in the 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.

[0025] Naphthyl residues can be 1-naphthyl and 2-naphthyl. In substituted naphthyl residues the substituents can be in any positions, i. e. in monosubstituted 1-naphthyl residues in the 2-, 3-, 4-, 5-, 6-, 7-, or 8-position and in mono-substituted 2-naphthyl residues in the 1-, 3-, 4-, 5-, 6-, 7-, or 8-position.

[0026] Examples of pyridyl residues are 2-pyridyl, 3-pyridyl and 4-pyridyl. Also if a pyridyl residue present in a compound of the formula I is substituted at the nitrogen atom by an oxido group -O⁻, i. e. if a pyridine N-oxide residue is present in a compound of the formula I, it can be bonded via the 2-position, the 3-position or the 4-position of the pyridine ring. This also applies to pyridyl residues in which the nitrogen atom is substituted by an alkyl group etc. this substitution leading to a positively charged pyridinium group.

[0027] Quinolinyl and isoquinolinyl residues can be 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl and 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, respectively. In substituted quinolinyl and isoquinolinyl residues the substituents can be present in any desired positions, for example in a monosubstituted 4-quinolinyl residue in the 2-, 3-, 5-, 6-, 7- or 8-position and in a monosubstituted 1-isoquinolinyl residue in the 3-, 4-, 5-, 6-, 7- or 8-position. Also if a quinolinyl or isoquinolinyl residue present in a compound of the formula I is substituted at the nitrogen atom by an oxido group -O⁻, i. e. if a quinoline or isoquinoline N-oxide residue is present in a compound of the formula I, it can be bonded via any desired position. This also applies to quinolinyl and isoquinolinyl residues in which the nitrogen atom is substituted by an alkyl group etc. this substitution leading to a positively charged quinolinium or isoquinolinium group.

[0028] Groups like alkyl groups, phenyl groups, naphthyl groups, quinolinyl groups or isoquinolinyl groups which occur in or which represent groups like R¹⁰ or R¹¹ and which can carry as substituents one or more of the groups representing R^{15b}, can preferably carry not more than two, in particular not more than one of the groups -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N+(R^{16a})₂(-O⁻), -(CH₂)_t-N+(R^{16a})₃ X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CO-OR¹⁸, -(CH₂)_t-CO-N(R¹⁸)₂, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_tC(=NR¹⁷)-NHR¹⁷ and -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷. Of groups like (C₁-C₆)-alkyl, hydroxy, (C₁-C₄)-alkoxy, F, Cl, Br, I, NO₂, and fluoro-substituted alkyl which can be present as substituents in such alkyl groups, phenyl groups etc., there usually can be present also more than one or more than two groups, for example one, two or three identical or different groups, either in addition to the first listed groups -(CH₂)_t-N(R¹⁶)₂ etc., or without one of the first listed groups being present.

[0029] Unless stated otherwise, aryl groups like phenyl or naphthyl that are present in the compounds of the formula I can in general be unsubstituted or can be substituted in any desired positions by one or more, for example one, two or three, identical or different substituents, for example substituents like (C₁-C₄)-alkyl such as methyl or tert-butyl, hydroxy, (C₁-C₄)-alkoxy such as methoxy, ethoxy or tert-butoxy, methylenedioxy, ethylenedioxo, F, Cl, Br, I, cyano, nitro, trifluoromethyl, hydroxymethyl, formyl, acetyl, amino, mono- or di-(C₁-C₄)-alkylamino, ((C₁-C₄)-alkyl)carbonylamino, hydroxycarbonyl, ((C₁-C₄)-alkoxy)carbonyl, carbamoyl, phenyl, benzyl, phenoxy or benzyloxy.

[0030] In general, not more than two nitro groups can be present in the compounds of the formula I.

[0031] Examples of the 5-membered or 6-membered saturated heterocyclic rings that can be formed by the two residues R¹³ together with the nitrogen atom to which they are bonded are pyrrolidine, piperidine, piperazine or morpholine.

[0032] Examples of Het are pyrrolidine, piperidine, perhydroazepine, tetrahydrofuran, perhydropyrane, tetrahydrothiophene, perhydrothiopyran, pyrazolidine, imidazolidine, hexahydroazepidine, hexahydroimididine, piperazine, di-oxolane, perhydrodioxane, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, perhydro-1,2-oxazine, perhydro-1,3-oxazine, perhydro-1,4-oxazine (morpholine), perhydro-1,3-thiazine and perhydro-1,4-thiazine (thiomorpholine). Preferred groups Het include, for example, groups containing one nitrogen atom as ring heteroatom like pyrrolidine or piperidine. Substituents present in Het can be bonded to any position unless stated otherwise. A ring nitrogen atom present in Het can carry one or two substituents. When a ring nitrogen atom carries two substituents, i. e. when it is quaternized, it is positively charged, and the compound of the formula I then also comprises an anion X⁻ as counterion. In general a group Het can carry one or more than one substituents, for example one, two, three, four or five identical or different substituents. Of the groups representing R^{15a} which can be present as substituents in a group Het, preferably

only one or two, in particular not more than one, of the groups $((C_1\text{-}C_6)\text{-alkyl})\text{-}C(=\text{NN})\text{-}$, $-(CH_2)_t\text{-N}(R^{16})_2$, $-(CH_2)_t\text{-N}^+(R^{16a})_2(-O^-)$, $-(CH_2)_t\text{-N}^+(R^{16a})_3 X^-$, $-(CH_2)_t\text{-NHR}^{17}$, $-(CH_2)_t\text{-CN}$, $-(CH_2)_t\text{-CS-N}(R^{18})_2$, $-(CH_2)_t\text{-C}(=\text{NR}^{17})\text{-NHR}^{17}$ and $-(CH_2)_t\text{-NH-C}(=\text{NR}^{17})\text{-NHR}^{17}$ can be present as a substituent in Het whereas, for example, $(C_1\text{-}C_6)\text{-alkyl}$ substituents can be present once or more than once in Het, for example one, two, three or four times, either without a substituent from the first group being present or in addition to substituents from the first group. These statements correspondingly apply to substituents in other heterocyclic rings. A group Het and similar heterocyclic groups can in general be substituted by substituents like, for example, $(C_1\text{-}C_6)\text{-alkyl}$ groups and also other substituents, for example phenyl- $(C_1\text{-}C_4)\text{-alkyl}$ -groups like a benzyl group.

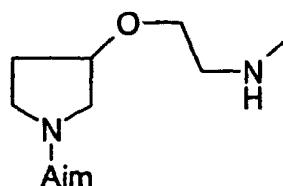
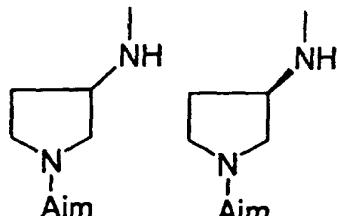
[0033] Examples of 5-membered or 6-membered heterocyclic rings which can be formed by two residues R^{17} together with the $C(=\text{N})\text{-NH}$ group to which they are bonded, are 4,5-dihydro-1H-imidazole and 1,4,5,6-tetrahydropyrimidine.

[0034] Examples of the substituent $((C_1\text{-}C_6)\text{-alkyl})\text{-C}(=\text{NH})\text{-}$ which is attached to the ring nitrogen atom of a heterocycle are the acetimidoyl residue, i. e. the residue $CH_3\text{-C}(=\text{NH})\text{-}$, or the residues $CH_3\text{-CH}_2\text{-C}(=\text{NH})\text{-}$, $CH_3\text{-CH}_2\text{-CH}_2\text{-C}(=\text{NH})\text{-}$ or $(CH_3)_2\text{CH-C}(=\text{NH})\text{-}$.

[0035] In the following some groups containing the substituent $((C_1\text{-}C_6)\text{-alkyl})\text{-C}(=\text{NH})\text{-}$ are listed which can be present in the residue R^3 . The following groups correspond to the group -NHR^{10} in the definition of the compounds of the formula I and are bonded to the CO group in the group -CO-NHR^{10} via the nitrogen atom having a free bond which is indicated in the following formulae by the line starting from an NH group. In the following formulae the substituent $((C_1\text{-}C_6)\text{-alkyl})\text{-C}(=\text{NH})\text{-}$ is abbreviated as Aim-.

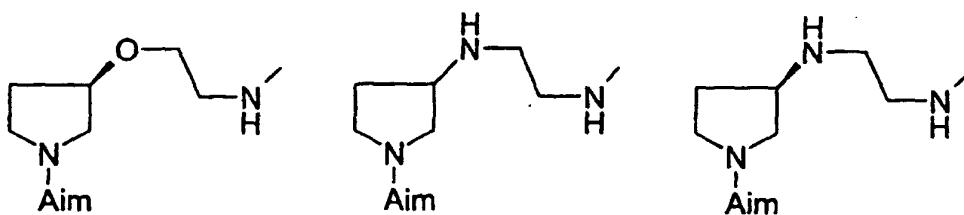
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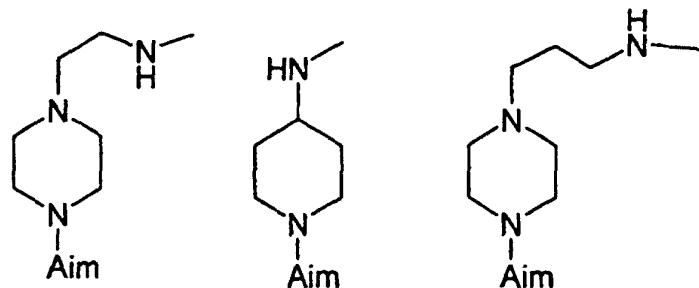
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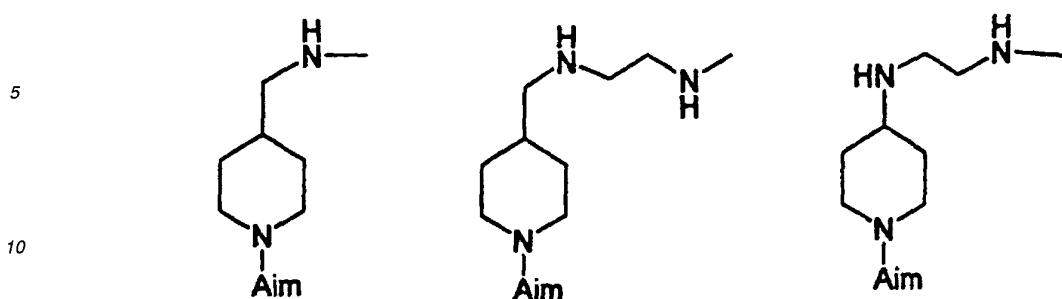
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[0036] A residue represented by the formula $-(CH_2)_t-N^+(R^{16a})_2(-O^-)$ is the residue of an amine oxide.

15 [0037] Physiologically acceptable anions X^- which are present in the compounds of the formula I when a positively charged group like a quaternary ammonium group or a pyridinium, quinolinium or isoquinolinium group is present, can be anions derived from suitable inorganic acids or organic carboxylic acids or sulfonic acids. Suitable acids are, in particular, pharmaceutically utilizable or non-toxic acids. Examples of such acids are those given below as examples of acids which can form physiologically acceptable salts with compounds of the formula I containing basic groups. If a compound of the formula I contains an anion X^- and simultaneously is present as an acid addition salt formed at a basic group, the anion X^- can be the same as or different from the anion introduced by salt formation.

20 [0038] Physiologically acceptable salts of the compounds of the formula I are, in particular, pharmaceutically utilizable or non-toxic salts. Such salts are formed, for example, from compounds of the formula I which contain acid groups, for example carboxylic acid or sulfonic acid groups. Examples of such salts are salts containing cations of alkali metals or alkaline earth metals, such as, for example, sodium, potassium, magnesium or calcium salts, or salts containing the unsubstituted ammonium cation NH_4^+ or organic ammonium cations, the latter including cations obtained from physiologically acceptable organic amines, such as, for example, methylamine, ethylamine, triethylamine, ethanolamine, tris(2-hydroxyethyl)amine or amino acids by protonation, and suitable quaternary ammonium cations like, for example, tetramethylammonium.

25 [0039] Compounds of the formula I which contain basic groups, for example one or more amino groups and/or amidino groups and/or guanidino groups, form acid addition salts with, for example, inorganic acids, organic carboxylic acids and organic sulfonic acids. Examples of such acids the anions of which can be present in physiologically acceptable salts of the compounds of formula I are hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, acetic acid, benzoic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, p-toluenesulfonic acid or naphthalenesulfonic acids.

30 [0040] The present invention also covers inner salts, zwitterions or betaines of the compounds of the formula I.

35 [0041] Physiologically acceptable salts of the compounds of formula I can be prepared according to standard procedures, for example by combining the compound of the formula I with the desired base, for example with an alkaline metal hydroxide or carbonate or hydrogen carbonate or an amine, or with the desired acid in a solvent or diluent. A physiologically acceptable salt of a compound of the formula I can also be prepared from another salt by cation exchange or anion exchange by standard procedures. Moreover, the present invention also covers salts of the compounds of the formula I which are, for example, obtained during the chemical synthesis of the compounds and which are less suitable for the desired use of the compounds of the formula I but which can be used as starting materials for the subsequent preparation of a desired physiologically acceptable salt. The present invention further covers solvates of the compounds of the formula I, for example hydrates or alcoholates.

40 [0042] The compounds of the formula I can be present in stereoisomeric forms. The present invention covers all possible stereoisomers. For example, the compounds of the formula I according to the invention can contain optically active carbon atoms which independently of one another can have R configuration or S configuration. The compounds of the formula I can thus be present in the form of individual enantiomers or individual diastereomers or in the form of enantiomeric mixtures including racemates or diastereomeric mixtures. The present invention relates both to pure enantiomers and mixtures of enantiomers in all ratios, and to pure diastereomers and mixtures of diastereomers in all ratios. The invention covers mixtures of two stereoisomers as well as mixtures of more than two stereoisomers, and all ratios of stereoisomers in the mixtures. The compounds of the formula I can also be present as E isomers or Z isomers (or cis isomers or trans isomers). The present invention relates to both pure E isomers and Z isomers and to mixtures of E isomers and Z isomers in all ratios.

45 [0043] Diastereomers, including E/Z isomers, can be separated into the individual isomers, for example by chromatography. Mixtures of enantiomers including racemates can be separated into the two enantiomers by chromatography on chiral phases or by resolution according to standard procedures like crystallization of diastereomeric salts obtained

with auxiliary agents. Stereochemically pure compounds, for example pure enantiomers, can also be obtained by employing into the synthesis optically active starting materials, or by using stereoselective reactions.

[0044] The compounds of the formula I according to the invention can further contain mobile hydrogen atoms, i.e. they can be present in various tautomeric forms. The present invention relates to all these tautomers.

[0045] The present invention further covers derivatives of the compounds of the formula I in which functional groups are masked or protected by suitable groups, for example by common protective groups. Such functional groups are, for example, carboxylic acid groups which can be present as ester groups or amide groups, or acylatable nitrogen containing groups which can be present as acyl derivatives. The present invention also covers other derivatives and prodrugs of the compounds of the formula I which may be designed in order to enhance the property profile of the compounds of the formula I and which may be prepared according to techniques well known to one skilled in the art, and it covers active metabolites of the compounds of the formula I.

[0046] A specific group of compounds of the formula I is formed by those compounds wherein two of the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} independently of each other are hydrogen, F, Cl, Br, I, methyl, (C₁-C₄)-alkoxy, phenyl-(C₁-C₄)-alkoxy-, OH or NR^{5a}R^{5b}, and are identical or different, and the other two of the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} are hydrogen;

R^{5a} is hydrogen or ((C₁-C₄)-alkoxy)carbonyl-;

R^{5b} is hydrogen;

R² is hydrogen, Cl or Br;

R³ is -CO-NHR¹⁰;

R⁷ is hydroxy, (C₁-C₄)-alkoxy, phenyl-(C₁-C₄)-alkoxy- or -NR^{5a}R^{5b};

R¹⁰ is (C₁-C₈)-alkyl-, phenyl-(C₁-C₄)-alkyl- or naphthyl-(C₁-C₄)-alkyl-, where the (C₁-C₈)-alkyl- residue, the phenyl residue and the naphthyl residue are unsubstituted or substituted by one or two identical or different residues R¹¹;

R¹¹ is -NHR¹², -OR¹², -CO-R⁷, R^{15b}, cyclohexyl, phenyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b}, naphthyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b}, pyridyl which is unsubstituted or substituted at the nitrogen atom by R¹⁴, or Het which is unsubstituted or substituted by R^{15a}, where residues R¹¹ if present more than one time in the molecule, are independent of each other and can be identical or different;

Het is the residue of a 5-membered or 6-membered saturated heterocyclic ring containing 1 or 2 identical or different ring heteroatoms selected from the series consisting of nitrogen, oxygen and sulfur;

R¹² is hydrogen, pyrrolidinyl, piperidinyl, pyrrolidinyl-(C₁-C₄)-alkyl- or piperidinyl-(C₁-C₄)-alkyl-, where each pyrrolidinyl residue and each piperidinyl residue is unsubstituted or substituted at the nitrogen atom by phenyl-(C₁-C₄)-alkyl- or R^{15a};

each residue R¹³ independently of the denotation of another residue R¹³ is hydrogen, (C₁-C₄)-alkyl or phenyl-(C₁-C₄)-alkyl-, or the two residues R¹³ together with the nitrogen atom to which they are bonded form a 5-membered or 6-membered saturated heterocyclic ring which can contain an additional nitrogen atom or oxygen atom in the ring where the additional nitrogen atom in the ring is unsubstituted or substituted by (C₁-C₄)-alkyl or phenyl-(C₁-C₄)-alkyl-;

R¹⁴ is (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₁-C₆)-alkynyl, phenyl-(C₁-C₆)-alkyl- or ((C₁-C₆)-alkoxy)carbonyl-(C₁-C₆)-alkyl-, where phenyl present in R¹⁴ denotes an unsubstituted phenyl residue, the substitution by these residues at the nitrogen atom of the heterocyclic residue leading to a pyridinium group having X⁻ as the counterion; or R¹⁴ is oxido this substitution at the nitrogen atom of the pyridinyl residue leading to a pyridine N-oxide; and where residues R¹⁴ if present more than one time in the molecule, are independent of each other and can be identical or different;

R^{15a} is (C₁-C₆)-alkyl, ((C₁-C₆)-alkyl)-C(=NH)-, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N⁺(R^{16a})₂(-O⁻), -(CH₂)_t-N⁺(R^{16a})₃ X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ or -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷, where ((C₁-C₆)-alkyl)-C(=NH)- is bonded to a ring nitrogen atom, and where residues R^{15a} if present more than one time in the molecule, are independent of each other and can be identical or different;

R^{15b} is (C₁-C₆)-alkyl, hydroxy, F, Cl, Br, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N⁺(R^{16a})₂(-O⁻), -(CH₂)_t-N⁺(R^{16a})₃ X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ or -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷, where residues R^{15b} if present more than one time in the molecule, are independent of each other and can be identical or different;

t is 0, 1, 2 or 3, where numbers t, if present more than one time in the molecule, are independent of each other and can be identical or different;

each residue R¹⁶ independently of the denotations of another residue R¹⁶ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₁-C₆)-alkynyl, phenyl-(C₁-C₆)-alkyl- or ((C₁-C₆)-alkoxy)carbonyl-(C₁-C₆)-alkyl-, where phenyl present in R¹⁶ denotes an unsubstituted phenyl residue, and where groups containing residues R¹⁶ if present more than one time in the molecule, are independent of each other and can be identical or different;

each residue R^{16a} independently of the denotations of another residue R^{16a} is (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₁-C₆)-alkynyl, phenyl-(C₁-C₆)-alkyl- or ((C₁-C₆)-alkoxy)carbonyl-(C₁-C₆)-alkyl-, where phenyl present in R^{16a} denotes an unsubstituted phenyl residue, and where groups containing residues R^{16a} if present more than one time in the molecule, are independent of each other and can be identical or different;

each residue R¹⁷ independently of the denotation of another residue R¹⁷ is hydrogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkylcarbonyl-, (C₁-C₆)-alkoxycarbonyl-, (C₁-C₆)-alkylcarbonyloxy-(C₁-C₆)-alkoxycarbonyl-, phenylcarbonyl-, phenoxy carbonyl-, phenyl-(C₁-C₆)-alkoxycarbonyl-, hydroxy, (C₁-C₆)-alkoxy, phenyl-(C₁-C₆)-alkoxy- or amino, and additionally in the groups -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ and -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷ the two residues R¹⁷ together with the C(=N)-NH group to which they are bonded, can form a 5-membered or 6-membered heterocyclic ring, and where phenyl present in R¹⁷ denotes an unsubstituted phenyl residue, and where groups containing residues R¹⁷ if present more than one time in the molecule, are independent of each other and can be identical or different;

each residue R¹⁸ independently of the denotation of another residue R¹⁸ is hydrogen or (C₁-C₄)-alkyl; A is a methylene residue -CH₂-;

R⁴ is phenyl which is substituted by one residue R^{15c} in the meta position;

R^{15c} is -C(=NR¹⁷)-NHR¹⁷ wherein the residues R¹⁷ are hydrogen;

X⁻ is a physiologically acceptable anion;

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

[0047] As with any group of structurally related compounds which possess a particular generic utility, certain groups and configurations are preferred for compounds of the formula I in their end-use application.

[0048] Preferred compounds of the formula I are those wherein the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} independently of one another are selected from the series consisting of hydrogen; methyl, F, Br, hydroxy, methoxy, benzyloxy and -NHR^{6a}.

[0049] Preferred compounds of the formula I are also those wherein three or all four of the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} are hydrogen. Preferred compounds of the formula I are also those wherein the residues R^{1c} and R^{1d} are hydrogen.

[0050] Preferred compounds of the formula I are also those wherein the residues R^{1a} and R^{1b} are hydrogen or one or two of the residues R^{1a} and R^{1b} are different from hydrogen. Particularly preferred compounds of the formula I are those wherein one of the residues R^{1a} and R^{1b} is hydrogen and the other of the residues R^{1a} and R^{1b} is hydrogen or is different from hydrogen. Especially preferred are compounds of the formula I wherein one of the residues R^{1a} and R^{1b} is selected from the series consisting of hydrogen, methyl, F, Br, hydroxy, methoxy, benzyloxy and -NHR^{5a} and the other of the residues R^{1a} and R^{1b} as well as the residues R^{1c} and R^{1d} are hydrogen.

[0051] Preferred compounds of the formula I are also those wherein the residue R^{5a} is hydrogen or tert-butyloxycarbonyl.

[0052] Preferred compounds of the formula I are also those wherein R¹⁰ is (C₁-C₁₀)-alkyl, phenyl-(C₁-C₄)-alkyl- or naphthyl-(C₁-C₄)-alkyl-, where the (C₁-C₁₀)-alkyl residue and the phenyl residue are substituted by one, two or three identical, or different residues R¹¹ and the naphthyl residue is unsubstituted or substituted by one, two or three identical or different residues R¹¹, and particularly the (C₁-C₁₀)-alkyl residue and the phenyl residue are substituted by one, two or three identical or different residues R¹¹ and the naphthyl residue is unsubstituted.

[0053] Preferred compounds of the formula I are also those wherein R¹¹ is R^{15b}, (C₁-C₁₄)-alkyl, quinolinyl, isoquinolinyl or pyridyl, where quinolinyl, isoquinolinyl, and pyridyl are unsubstituted or substituted at the nitrogen atom by R¹⁴. A (C₁-C₁₄)-alkyl residue representing R¹¹ preferably has up to 12, more preferably up to 10 carbon atoms.

[0054] Preferred compounds of the formula I are also those wherein R¹⁴ is (C₁-C₆)-alkyl.

[0055] Preferred compounds of the formula I are also those wherein R^{15b} is (C₁-C₆)-alkyl where the alkyl residue can be substituted 1, 2, 3, 4, 5, 6 or 7 times by fluoro, or R^{15b} is F, Cl, I, -(CH₂)_t-N⁺(R^{16a})₃X⁻ or -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷.

[0056] Preferred compounds of the formula I are also those wherein t is 0 or 1, in particular 0, where numbers t, if present more than one time in the molecule, are independent of each other and are identical or different.

[0057] Preferred compounds of the formula I are also those wherein R^{16a} is (C₁-C₆)-alkyl, (C₁-C₆)-alkynyl or phenyl-(C₁-C₆)-alkyl.

[0058] Preferred compounds of the formula I are also those wherein R¹⁷ is hydrogen.

[0059] Especially preferred compounds of the formula I are those wherein two or more residues are defined as indicated before for preferred compounds of the formula I, or residues can have one or some of the specific denotations of the residues given in their general definitions or in the definitions of preferred compounds before. All possible combinations of definitions given for preferred definitions and of specific denotations of residues explicitly are a subject of the present invention.

[0060] Also with respect to all preferred compounds of the formula I all their stereoisomeric forms and mixtures thereof in any ratio and their physiologically acceptable salts explicitly are a subject of the present invention, as well as are their prodrugs. Similarly, also in all preferred compounds of the formula I all residues that are present more than one time in the molecule are independent of each other and can be identical or different.

[0061] The compounds of the formula I can be prepared by utilizing procedures and techniques which per se are well known and appreciated by one of ordinary skill in the art. Starting materials or building blocks for use in the general synthetic procedures that can be applied in the preparation of the compounds of formula I are readily available to one of ordinary skill in the art. In many cases they are commercially available or have been described in the literature.

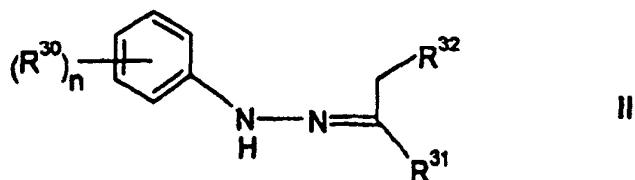
Otherwise they can be prepared from readily available precursor compounds analogously to procedures described in the literature, or by procedures or analogously to procedures described in this application.

[0062] In general, compounds of the formula I can be prepared, for example in the course of a convergent synthesis, by linking two or more fragments which can be derived retrosynthetically from the formula I. More specifically, suitably substituted starting indole derivatives are employed as building blocks in the preparation of the compounds of formula I. If not commercially available such indole derivatives can be prepared according to the well-known standard procedures for the formation of the indole ring system such as, for example, the Fischer indole synthesis, the Madelung indole synthesis, the indole synthesis starting from N-chloroanilines and β -ketosulfides described by Gassman et al., the Bischler indole synthesis, the Reissert indole synthesis, or the Nenitzescu indole synthesis. By choosing suitable precursor molecules, these indole syntheses allow the introduction of a variety of substituents into the various positions of the indole system which can then be chemically modified in order to finally arrive at the molecule of the formula I having the desired substituent pattern. As one of the comprehensive reviews in which numerous details and literature references on the chemistry of indoles and on synthetic procedures for their preparation can be found, volume 25, "Indoles, Part One", W. J. Houlihan (ed.), 1972, out of the series "The Chemistry of Heterocyclic Compounds", A. Weissberger and E. C. Taylor (ed.), John Wiley & Sons, is referred to.

[0063] Examples of the many commercially available indole derivatives that are suitable as starting materials for the preparation of the compounds of formula I, are the following (the acids listed are commercially available as the free acids themselves and/or as the methyl or ethyl esters): indole-2-carboxylic acid, indole-2,3-dicarboxylic acid, 5-fluoroindole-2-carboxylic acid, 5-chloro-indole-2-carboxylic acid, 5-bromo-indole-2-carboxylic acid, 5-methoxy-indole-2-carboxylic acid, 5-hydroxy-indole-2-carboxylic acid, 5,6-dimethoxy-indole-2-carboxylic acid, 4-benzoyloxy-indole-2-carboxylic acid, 5-benzoyloxy-indole-2-carboxylic acid, 6-benzoyloxy-5-methoxy-indole-2-carboxylic acid, 5-methyl-indole-2-carboxylic acid, 7-methyl-indole-2-carboxylic acid, 4-methoxy-indole-2-carboxylic acid, 6-methoxy-indole-2-carboxylic acid, 4,6-dimethoxy-indole-2-carboxylic acid, 4,6-dichloro-indole-2-carboxylic acid, 5-nitro-indole-2-carboxylic acid, 7-nitro-indole-2-carboxylic acid, 7-tert-butylcarbonylamino-indole-2-carboxylic acid, 5-bromo-3-methyl-indole-2-carboxylic acid.

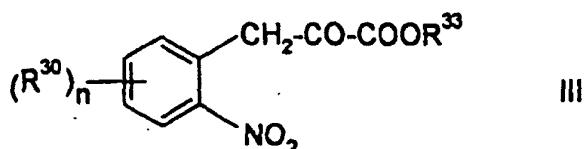
[0064] If starting indole derivatives are to be synthesized this can be done, for example, according to the well known indole syntheses mentioned above. In the following they are explained briefly, however, they are standard procedures comprehensively discussed in the literature, and are well known to one skilled in the art.

[0065] The Fischer indole synthesis comprises the acid cyclization of phenylhyrazones, for example of the general formula II,



40 which can be obtained by various methods and in which R³⁰, R³¹ and R³² and n can have a wide variety of denotations. Besides hydrogen and alkyl, R³¹ and R³² can especially denote ester groups or methyl or ethyl groups carrying an ester group as substituent thus allowing the introduction into the indole molecule of the CO moiety occurring in the group R³ in the compounds of the formula I. As examples of the many literature references describing the synthesis of indole derivatives according to the Fischer synthesis, besides the above-mentioned book edited by Houlihan, the following articles are mentioned: F.G. Salituro et al., J. Med. Chem. 33 (1990), 2944; N.M. Gray et al., J. Med. Chem. 34 (1991); 1283; J. Sh. Chikvaidze et al., Khim. Geterotsikl. Soedin. (1991), 1508; S. P. Hiremath et al., Indian J. Chem. 19 (1980), 770; J. Bornstein, J. Amer. Chem. Soc. 79 (1957), 1745.

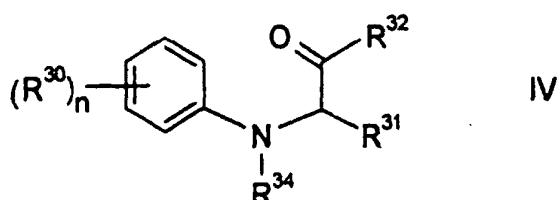
45 **[0066]** The Reissert indole synthesis comprises the reductive cyclization of o-nitrophenylpyruvic acids or esters thereof, for example of the general formula III,



in which the groups R^{30} can have a wide variety of denotations and can be present in all positions of the benzene ring. The Reissert indole synthesis leads to derivatives of indole-2-carboxylic acids. The pyruvic acid derivatives of the formula III can be obtained by condensation of oxalic acid esters with substituted o-nitrotoluenes. As literature references, besides the above-mentioned book edited by Houlihan and the literature articles mentioned therein, for example the articles by H. G. Lindwall and G. J. Mantell, J. Org. Chem. 18 (1953), 345 or by H. Burton and J. L. Stoves, J. Chem. Soc. (1937), 1726 are mentioned.

[0067] According to the Bischler indole synthesis α -anilinoketones, for example of the general formula IV,

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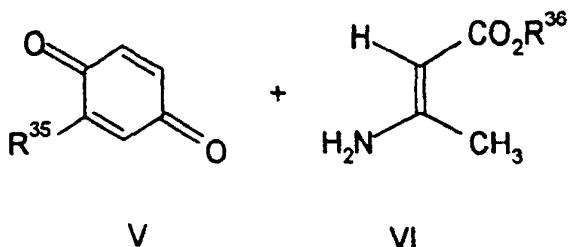


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can be cyclized to indole derivatives.

[0068] The Nenitzescu indole synthesis provides a valuable route to indole-3-carboxylic acid derivatives carrying a hydroxy group in the 5-position. It comprises the reaction of a para-benzoquinone with a β -aminocrotonate, for example of the compounds of the formulae V and VI.

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[0069] A further route to specifically substituted indole derivatives proceeds via 2,3-dihydroindoles (indolines) which can be easily obtained by reduction of indoles, for example by hydrogenation, or by cyclization of suitable phenylethylamine derivatives. Indolines can undergo a variety of electrophilic aromatic substitution reaction allowing the introduction of various substituents into the benzene nucleus which cannot directly be introduced by such reactions into the benzene nucleus of the indole molecule. The indolines can then be dehydrogenated to the corresponding indoles, for example with reagents like chloranil or palladium together with a hydrogen acceptor. Again, details on these syntheses can be found in the above-mentioned book edited by Houlihan.

[0070] Depending on the substituents in the starting materials, in certain indole syntheses mixtures of positional isomers may be obtained which, however, can be separated by modern separation techniques like, for example, preparative HPLC.

[0071] Further, in order to obtain the desired substituents in the benzene nucleus and in the heterocyclic nucleus of the indole ring system in the formula I, the functional groups introduced into the ring system during the indole synthesis can be chemically modified. For example, indoles carrying a hydrogen atom in the 3-position can also be obtained by saponification and subsequent decarboxylation of indoles carrying an ester group in the respective position. Halogen atoms can be introduced into the 3-position, for example by reacting the respective indolinone with a halogenating agent such as phosphorus pentachloride analogously to the method described by J. C. Powers, J. Org. Chem. 31 (1966), 2627. The starting indolinones for such a synthesis can be obtained from 2-aminophenyl acetic acids. Starting indole derivatives for the preparation of compounds of the formula I carrying a halogen substituent in the 3-position can also be obtained according to procedures described in the literature like the following. Chlorination of 1H-indole-2-carboxylic acid ethyl ester in the 3-position by reaction with sulfonyl chloride in benzene yields 3-chloro-1H-indole-2-carboxylic acid ethyl ester (Chem. Abstr. 1962, 3441i - 3442b). 3-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester can be synthesized analogously to J. Het. Chem 33 (1996), 1627 by reaction of 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester with pyridinium bromide perbromide in pyridine.

[0072] Especially the groups present in the benzene nucleus of the indole ring system can be modified by a variety

of reactions and thus the desired residues R^{1a}, R^{1b}, R^{1c} and R^{1d} be obtained. For example, nitro groups can be reduced to amino group with various reducing agents, such as sulfides, dithionites, complex hydrides or by catalytic hydrogenation. A reduction of a nitro group may also be carried out at a later stage of the synthesis of a compound of the formula I, and a reduction of a nitro group to an amino group may also occur simultaneously with a reaction performed on another functional group, for example when reacting a group like a cyano group with hydrogen sulfide or when hydrogenating a group. In order to introduce the residue R^{5a}, amino groups can then be modified according to standard procedures for acylation, for example by reaction with activated carboxylic acid derivates such as acid chlorides, anhydrides, activated esters or others or by reaction with carboxylic acids in the presence of an activating agent.

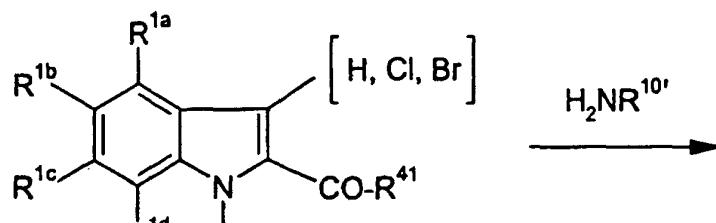
[0073] Ester groups present in the benzene nucleus can be hydrolyzed to the corresponding carboxylic acids which after activation can then be reacted with amines or alcohols under standard conditions. Ether groups present at the benzene nucleus, for example benzyloxy groups or other easily cleavable ether groups, can be cleaved to give hydroxy groups which then can be reacted with a variety of agents, for example etherification agents or activating agents allowing replacement of the hydroxy group by other groups. Sulfur-containing groups can be reacted accordingly.

[0074] The before-mentioned reactions for the conversion of functional groups are in general extensively described in textbooks of organic chemistry and in treatises like Houben-Weyl, "Methoden der Organischen Chemie" (Methods of Organic Chemistry), Georg Thieme Verlag, Stuttgart, Germany, or "Organic Reactions", John Wiley & Sons, New York, in which details on the reactions and primary source literature can be found. Due to the fact that in the present case the functional groups are attached to an indole ring it may in certain cases become necessary to specifically adapt reaction conditions or to choose specific reagents from a variety of reagents that can in principle be employed into a conversion reaction, or otherwise to take specific measures for achieving a desired conversion, for example to use protection group techniques. However, finding out suitable reaction variants and reaction conditions in such cases does not cause any problems for one skilled in the art.

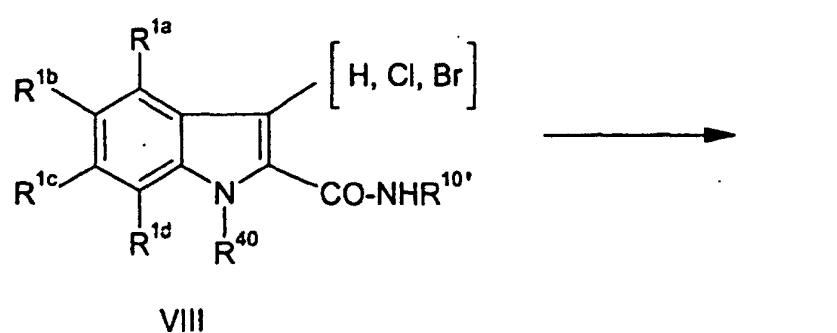
[0075] The structural elements present in the residues in the 1-position of the indole ring in the compounds of the formula I and in the CONHR¹⁰ group present in the 2-position of the indole ring can be introduced into the starting indole derivative obtainable as outlined above by consecutive reaction steps like those outlined below using procedures which per se are well known to one skilled in the art.

[0076] The residues NHR¹⁰ that can be present in R³ can be introduced, for example, by condensing a corresponding carboxylic acid of the formula VII or a derivative thereof with a compound or with compounds of the formula H₂NR^{10'}, i. e. with an amine, to give a compound of the formula VIII. The compound of the formula VIII thus obtained can already contain the desired final groups, i. e. the groups NHR^{10'} and R⁴⁰ can be the groups NHR¹⁰ and R^{4-A-} defined as for the formula I, or optionally in the compound of the formula VIII thus obtained subsequently the residue NHR^{10'} and the residue R⁴⁰ are converted into the residues NHR¹⁰ and R^{4-A-}, respectively, to give the desired compound of the formula I.

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[0077] Thus, the residue $\text{NHR}^{10'}$ and the residue $\text{R}^{10'}$ contained therein can have the denotations of NHR^{10} and R^{10} , respectively, given above, or in addition in the residues $\text{NHR}^{10'}$ and $\text{R}^{10'}$ functional groups can also be present in the form of groups that can subsequently be transformed into the final groups NHR^{10} and R^{10} , i. e. functional groups can be present in the form of precursor groups or of derivatives, for example in protected form. Examples of precursor groups are cyano groups which may in a later step be transformed into carboxylic acid derivatives or by reduction into aminomethyl groups, or nitro groups which may be transformed by reduction like catalytic hydrogenation into amino groups.

[0078] The residue R^{40} in the compounds of the formulae VII and VIII can denote the group $-\text{A}-\text{R}^4$ as defined above which finally is to be present in the desired target molecule of the formula I, or it can denote a group which can subsequently be transformed into the group $-\text{A}-\text{R}^4$, for example a precursor group or a derivative of the group $-\text{A}-\text{R}^4$ in which functional groups are present in protected form, or R^{40} can denote a hydrogen atom or a protective group for the nitrogen atom of the indole ring. Similarly, the residues R^{1a} , R^{1b} , R^{1c} and R^{1d} in the formulae VII and VIII are defined as above, however, for the synthesis of the compounds of the formula I these residues, too, can in principle be present at the stage of the condensation of a compound of the formula VII with a compound of the formula $\text{H}_2\text{NR}^{10'}$ giving a compound of the formula VIII in the form of precursor groups or in protected form.

[0079] The residues R^{41} in the compounds of the formula VII which can be identical or different, can be, for example, hydroxy or ($\text{C}_1\text{-C}_4$)-alkoxy, i. e., the groups COR^{41} present in the compounds of the formula VII can be, for example, the free carboxylic acids or esters thereof like alkyl esters. The groups COR^{41} can also be any other activated derivative of a carboxylic acid which allows amide formation with a compound of the formula $\text{H}_2\text{NR}^{10'}$. The group COR^{41} can be, for example, an acid chloride, an activated ester like a substituted phenyl ester, an azolide like an imidazolide, an azide or a mixed anhydride, for example a mixed anhydride with a carbonic acid ester or with a sulfonic acid, which derivatives can all be prepared from the carboxylic acid by standard procedures and can be reacted with an amine of the formula $\text{H}_2\text{NR}^{10'}$ under standard conditions. A carboxylic acid group COOH representing COR^{41} in a compound of the formula VII can be obtained, for example, from an ester group introduced into the indole system during an indole synthesis by standard hydrolysis procedures.

[0080] The compounds of the formula I, in which the group CONHR^{10} is an amide group, can be prepared from amines and compounds of the formula VII in which COR^{41} is a carboxylic acid group or an ester thereof by common amination reactions. For the preparation of the amides the compounds of the formula VII in which COR^{41} is a carboxylic acid group can be condensed under standard conditions with amines of the formula $\text{H}_2\text{NR}^{10'}$ by means of common coupling reagents used in peptide synthesis. Such coupling reagents are, for example, carbodiimides like dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide, carbonyldiazoles like carbonyldiimidazole and similar reagents, propylphosphonic anhydride, O-((cyano-(ethoxycarbonyl)-methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) and many others.

[0081] If the residue R^{4-A} present in an indole of the formula I or the residue R^{40} present in an indole of the formula VII, or a residue in which functional groups within the residue R^{4-A} or R^{40} are present in protected form or in the form of a precursor group, have not already been introduced during a preceding step, for example during a synthesis of the indole nucleus, these residues can, for example, be introduced into the 1-position of the indole system by conventional literature procedures well known to one skilled in the art for N-alkylation of ring nitrogen atoms of heterocycles. The starting indole derivative that is to be employed in such a reaction carries a hydrogen atom in the 1-position. N-Alkylation of a ring nitrogen atom can, for example, be performed under standard conditions, preferably in the presence of a base, using an alkylating compound of the formula $\text{R}^{4-A}-\text{LG}$ or of the formula $\text{R}^{40}-\text{LG}$, wherein the atom in the group A or in the group R^{40} bonded to the group LG in this case is an aliphatic carbon atom of an alkyl moiety and LG is a leaving group, for example halogen like chlorine, bromine or iodine, or a sulfonyloxy group like tosyloxy, mesyloxy or trifluormethylsulfonyloxy. LG may, for example, also be a hydroxy group which, in order to achieve the alkylation reaction, is activated by a conventional activating agent.

[0082] A guanidino function present in a compound of the formula I can be introduced by conversion of an amino function which, for example, may be obtained by reduction of a nitro function or a cyano function, using the following reagents:

- 50 1. O-Methylisourea (S. Weiss and H. Krommer, Chemiker-Zeitung 98 (1974), 617-618)
2. S-Methylisothiourea (R. F. Borne, M. L. Forrester and I. W. Waters, J. Med. Chem. 20 (1977), 771-776)
3. Nitro-S-methylisothiourea (L. S. Hafner and R. E. Evans, J. Org. Chem. 24 (1959), 1157)
4. Formamidinosulfonic acid (K. Kim, Y.-T. Lin and H. S. Mosher, Tetra. Lett. 29 (1988), 3183-3186)
5. 3,5-Dimethyl-1-pyrazolylformamidinium nitrate (F. L. Scott, D. G. O'Donovan and J. Reilly, J. Amer. Chem. Soc. 75 (1953), 4053-4054)
6. N,N'-Di-tert-butyloxycarbonyl-S-methylisothiourea (R. J. Bergeron and J. S. McManis, J. Org. Chem. 52 (1987), 1700-1703)
7. N-Alkoxy carbonyl-, N,N'-dialkoxy carbonyl-, N-alkyl carbonyl- and N,N'-dialkyl carbonyl-S-methylisothiourea (H.

Wollweber, H. Kölling, E. Niemers, A. Widdig, P. Andrews, H.-P. Schulz and H. Thomas, Arzneim. Forsch./Drug Res. 34 (1984), 531-542).

[0083] Amidines can be prepared from the corresponding cyano compounds by addition of alcohols, for example methanol or ethanol, in an acidic anhydrous medium, for example dioxane, methanol or ethanol, and subsequent aminolysis, for example treatment with ammonia in alcohols such as, for example, isopropanol, methanol or ethanol (G. Wagner, P. Richter and Ch. Garbe, Pharmazie 29 (1974), 12-55). Further methods of preparing amidines are the addition of hydrogen sulfide to a cyano group, followed by alkylation, for example by methylation with an agent like methyl iodide, of the resulting thioamide and subsequent reaction with ammonia (GDR Patent No. 235 866), or the addition of hydroxylamine which may be obtained from a hydroxylammonium salt with a base, to the cyano group followed by conversion of the amidoxime to the amidine, for example by catalytic hydrogenation (see, for example, R. P. Mull et al., J. Med. Pharm. Chem. 5 (1962), 651; B. J. Broughton et al., J. Med. Chem. 18 (1975), 1117).

[0084] Compounds of the formula I in which a group $((C_1-C_6)\text{-alkyl})\text{-}C(=\text{NH})$ -bonded to a nitrogen atom is present can be prepared from a precursor compound containing said nitrogen atom as an NH group, for example, by the following methods. The precursor compound containing the NH group is reacted with a mono- or bis-benzylloxycarbonyl (Z) protected alkylamidine of the formulae $((C_1-C_6)\text{-alkyl})\text{-}C(=\text{NH})\text{-NH-Z}$ or $((C_1-C_6)\text{-alkyl})\text{-}C(=\text{NZ})\text{-NH-Z}$ of which the bis-protected reagent is more reactive than the mono-protected one (Y. Sugimura et al., Heterocycles 24 (1986), 1331 - 1345; J. Eustache and A. Grob, Tetrahedron Lett. 36 (1995), 2045 - 2046). In another method, the precursor compound containing the NH group is reacted with an imino ether, for example, of the formula $((C_1-C_6)\text{-alkyl})\text{-}C(=\text{NH})\text{-O-}(C_1-C_4)\text{-alkyl}$ which in turn is available under standard conditions from a nitrile of the formula $((C_1-C_6)\text{-alkyl})\text{-CN}$ by addition of an alcohol in the presence of an acid. If two or more NH groups are present in the compound to be reacted with the imino ether or the Z-protected alkylamidine protection group strategies can be used to achieve the desired result, as is well known to one skilled in the art.

[0085] An imino ether which can be regarded as an activated nitrile, is also a versatile intermediate in case it is prepared from a cyano group that is present in a compound which already contains the indole system and which has been obtained as an intermediate during the synthesis of a compound of the formula I. For example, a cyano group that is present in the residue R⁴⁰ in a compound of the formulae VII or VIII or in another residue can be reacted according to standard procedures to give an imino ether. Such an imino ether can be reacted, for example, with hydroxylamine to give an amidoxime group standing in place of the former cyano group. Again, in such reactions as in all reactions employed in the synthesis of the compounds of the formula I, depending on the individual case it may be favorable in order to avoid undesired reactions or secondary reactions to apply protection group techniques and to temporarily block groups like, for example, amino groups or carboxylic acid groups by protective groups suited to the specific synthesis problem.

[0086] Compounds of the formula I in which an amine oxide moiety or a pyridine N-oxide, quinoline N-oxide or iso-quinoline N-oxide moiety is present can be obtained by oxidation of the amines or of the nitrogen heterocycles according to standard procedures as are described, for example, in J. March, Advanced Organic Chemistry, 3. ed., p. 1088.

[0087] The compounds of the formula I can also be prepared, for example, by synthesizing the compounds stepwise on a solid phase according to customary methods of solid phase chemistry which are well known to one skilled in the art and which are illustrated by the examples below.

[0088] As is demonstrated in the pharmacological tests described below, the compounds of the formula I inhibit factor Xa activity. They can therefore advantageously be used as pharmaceuticals, especially when it is desired to reduce factor Xa activity or to produce effects that can be achieved by inhibiting factor Xa activity in a system, such as influencing coagulation or inhibiting blood clotting. Thus, the present invention also relates to the compounds of the formula I for use as pharmaceuticals as well as to the compounds of the formula I for use in the production of medicaments, especially of medicaments for treatment or prophylaxis of the conditions and diseases mentioned below and above. Further, the present invention provides a method of specifically inhibiting factor Xa activity by contacting factor Xa with a compound of the formula I, wherein a compound of the invention inhibits factor Xa catalytic activity either directly, within the prothrombinase complex or as a soluble subunit, or indirectly, by inhibiting the assembly of factor Xa into the prothrombinase complex. A preferred embodiment of the invention comprises such compounds of the formula I which can inhibit factor Xa activity with a $K_i \leq 100 \mu\text{M}$ and, more preferably, with a $K_i \leq 2 \mu\text{M}$ as determined in the factor Xa assay described below.

[0089] Inhibition of factor Xa activity or the production of effects achieved by such an inhibition can take place, for example, *in vivo*, i. e. in an individual. As used herein, the term "individual" means a vertebrate, including a mammal such as, for example a mouse, a rat, a rabbit, a dog, a pig and especially a human, in which factor Xa is involved in the coagulation cascade. It can also take place outside the body of an individual, for example, in an extracorporeal circulation or in the treatment of blood samples from an individual, and generally *in vitro*. *In vitro* uses of the compounds of the formula I are, for example, the use as a biochemical tool or reagent in scientific or analytical investigations or the use in *in vitro* diagnoses. Further, a compound of the formula I can advantageously be used as an anticoagulant

which can be contacted with a blood sample to prevent coagulation. For example, an effective amount of a compound of the formula I can be contacted with a freshly drawn blood sample to prevent coagulation of the blood sample.

[0090] As used herein, the term "effective amount" when used in this connection means an amount of a compound of the formula I that inhibits factor Xa activity to the desired extent. The skilled artisan would recognize that an effective amount of a compound of the invention can be determined using the methods disclosed herein or otherwise known in the art.

[0091] In view of the disclosed utility of the compounds of the formula I, the skilled artisan also would recognize that an agent such as heparin can be replaced with a compound of the invention. Such a use of a compound of the formula I can result, for example, in a cost saving as compared to other anticoagulants, or in less side effects.

[0092] In a further embodiment, the present invention provides a method of inhibiting factor Xa in a patient in need thereof, comprising administering to said patient an effective factor Xa inhibitory amount of a compound of the formula I. As used herein, the term "patient" refers especially to a warm-blooded animal including a mammal and particularly a human. A patient is in need of treatment to inhibit factor Xa when the patient is suffering from a disease state that can be beneficially influenced by inhibiting factor Xa activity or that is expected by the clinician to be beneficially influenced by inhibiting factor Xa activity. The identification of those patients who are in need of treatment to inhibit factor Xa is well within the ability and knowledge of one skilled in the art. A clinician skilled in the art can readily identify, for example by the use of clinical tests, physical examination and medical/family history, those patients who are in need of such a treatment.

[0093] Since a compound of the formula I can inhibit factor Xa activity, such a compound can be used for reducing or inhibiting blood clotting in an individual. Thus, the present invention further provides a method of reducing or inhibiting the formation of blood clots in an individual, especially in a patient in need thereof, by administering a therapeutically effective amount of a compound of the formula I.

[0094] A "therapeutically effective amount" relating to the production in an individual of an effect like inhibition or reduction of blood clotting, or an "effective factor Xa inhibitory amount" of a compound of the formula I means the amount or the dose of a compound of the formula I that has to be administered to an individual in order to achieve or to maintain the desired effect, or to inhibit factor Xa activity in the individual to the desired extent. Such an effective amount or dose to be administered has to be adjusted to the individual circumstances in each case. It can be readily determined by the use of conventional techniques using the methods described herein or otherwise known in the art, and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to the species of the patient; its size, age, and general health; the specific disease involved; the degree or the involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the pharmaceutical preparation administered; the dose regimen selected; and the use of concomitant medication. An appropriate dosage can be established using clinical approaches well known in the medical art.

[0095] In general, in view of the above factors it is evident that the effective factor Xa inhibitory amount or the therapeutically effective amount of a compound of the formula I will vary and can be varied within wide limits. Usually, an effective amount of a compound of the formula I will vary from about 0.01 milligram per kilogram of body weight per day (mg/kg per day) to about 20 mg/kg per day. A daily dose of from about 0.1 mg/kg to about 10 mg/kg usually is preferred. These data refer to an adult human of about 75 kg of body weight. However, depending on the individual circumstances it may be necessary to deviate upward or downward from the doses given. In particular when administering relatively large quantities, it can be favorable to subdivide the daily dose into several, for example 2, 3 or 4 subdose administrations.

[0096] A compound of the formula I can be administered to an individual for the treatment of a variety of clinical conditions including, for example, the treatment and prophylaxis of cardiovascular disorders or complications associated, for example, with infection or surgery. Examples of cardiovascular disorders include restenosis, for example restenosis following angioplasty, reocclusion prophylaxis including reocclusion prophylaxis following lysis or dilatation (PTCA), conditions after coronary bypass operations, arterial, venous and microcirculatory disease states, cardiac infarction, angina pectoris including unstable angina pectoris, thromboembolic diseases, thromboses, embolism, adult respiratory distress syndrome, multi-organ failure, stroke and disseminated intravascular coagulation clotting disorder. Examples of related complications associated with surgery include, for example, deep vein and proximal vein thrombosis, which can occur following surgery. In general, a compound of the invention is useful as a medicament for reducing or inhibiting or preventing unwanted coagulation or blood clotting or thrombus formation in an individual.

[0097] The compounds of the formula I, their physiologically acceptable salts and other suitable derivatives thereof like prodrugs can be administered as medicaments or pharmaceuticals in the above-mentioned methods of treatment or prophylaxis on their own, in mixtures with each other or in the form of pharmaceutical compositions which comprise, as the active ingredient, an effective amount of at least one compound of the formula I and/or of a physiologically acceptable salt and/or another suitable derivative thereof in admixture or otherwise in association with a pharmaceutically acceptable carrier.

[0098] In effecting treatment of a patient, compounds of the formula I or pharmaceutical compositions comprising them can be administered in any form or mode which makes the compounds of the formula I bioavailable in effective amounts, including oral and parenteral routes. For example, they can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred but depending on the specific case other modes of administration can also be favorable, for example in an acute stage of a disease intravenous administration by means of injection or infusion. One skilled in the art can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

[0099] Pharmaceutical compositions or medicaments comprising a compound of the formula I and/or a physiologically acceptable salt and/or another suitable derivative thereof can be made by combining by standard procedures the compounds of the formula I and/or their physiologically acceptable salts and/or other suitable derivatives thereof with one or more pharmaceutically acceptable carrier substances and/or auxiliary substances the proportion and nature of which are determined by the chosen route of administration and standard pharmaceutical practice. The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The pharmaceutical compositions will, in general, contain an effective amount of one or more compounds of the formula I and/or their physiologically acceptable salt and/or other suitable derivatives thereof together with a suitable amount of a carrier so as to comprise the proper dosage for administration to an individual. The pharmaceutical compositions may be adapted for oral or parenteral use and may be administered to the patient in the form of, for example, tablets, capsules, suppositories, solutions, suspensions, ointments, tinctures, nasal sprays, aerosol mixtures, implants, rods, microcapsules or the like. Thus, together with the claimed compounds of the formula I the present invention provides useful pharmaceutical compositions or medicaments for inhibiting factor Xa activity, for inhibiting blood clotting and for the treatment and prophylaxis of the above-mentioned diseases in an individual. The present invention further encompasses a process for the preparation of pharmaceutical compositions or medicaments which comprise at least one compound of the formula I and/or a physiologically acceptable salt and/or another suitable derivative thereof, as well as it encompasses the use of the compounds of the formula I and/or physiologically acceptable salts and/or other suitable derivatives thereof for the preparation of medicaments, especially of medicaments for the treatment or prophylaxis of the above-mentioned diseases.

[0100] Pharmaceutically acceptable carrier and auxiliary substances are referred to as substances or compositions that are non-toxic to an individual or have acceptable toxicity as determined by the appropriate regulatory agency. The carrier substance or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. As used herein, the term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers such as liquid carriers, for example water, saline, phosphate buffered saline, an emulsion such as an oil/water or water/oil emulsion, or solid or semi-solid carriers such as, for example, lactose, corn starch, fats, waxes, etc. Suitable pharmaceutical carriers and their formulations are well known in the art and are described, for example, by Martin in Remington's Pharmaceutical Sciences, 15th Ed., Mack Publishing Co., Easton 1975, which is incorporated herein by reference also with respect to other aspects of the ingredients and of the preparation of pharmaceutical compositions.

[0101] Examples of auxiliary substances are fillers, disintegrants, binders, glidants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, dyes, flavorants, aromatizing agents, thickeners, diluents, buffering substances, solubilizing agents, agents for achieving a slow-release effect, salts for altering the osmotic pressure, coating agents, antioxidants, etc.

[0102] For the purpose of oral administration, the compounds of the formula I and/or of their physiologically acceptable salts and/or other suitable derivatives thereof may be incorporated with excipients or inert diluents or edible carriers and used in the form of, for example, tablets, film tablets, coated tablets, pills, troches, capsules, granules, solutions, suspensions, emulsions, elixirs, syrups, wafers, chewing gums and the like, or they may be enclosed in gelatin capsule. The pharmaceutical compositions for oral administration may be varied depending upon the particular form. Usually such pharmaceutical compositions contain at least 1 % of the active ingredient of the formula I and/or of a physiologically acceptable salt and/or another suitable derivative thereof and may conveniently contain up to about 90 % of the weight of the unit. Preferably the content of the compounds of the formula I and/or their physiologically acceptable salts and/or other suitable derivatives is from about 4 % to about 70 % by weight. Preferably the amount of the active ingredient present in the compositions is such that a unit dosage form suitable for administration will be obtained.

[0103] The tablets, pills, capsules, troches and the like may also contain, for example, one or more of the following carrier and auxiliary substances: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide. Further, sweetening agents such as sucrose or saccharin may be added or flavoring agents such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain various other materials which modify the

physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, for example sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0104] For the purpose of, for example, parenteral administration the compounds of the formula I and/or physiologically acceptable salts thereof and/or other suitable derivatives thereof may be incorporated into a solution or a suspension. The solutions or suspensions may, for example, also include one or more of the following carrier and auxiliary substances: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates; agents for the adjustment of toxicity such as sodium chloride or dextrose. The content of the compounds of the formula I and/or of their physiologically acceptable salt and/or other suitable derivatives thereof in the preparations for parenteral administration may be varied. Usually they contain at least 0.1 % by weight of the compound of the formula I and/or of a physiologically acceptable salt and/or another suitable derivative thereof and up to 90 % by weight. Preferably the content of the compound of the formula I and/or the physiologically acceptable salts thereof and/or other suitable derivatives thereof is from about 0.1 % to 50 %. The parenteral preparations can be enclosed, for example, in ampules, disposable syringes, multiple dose vials made of glass or plastic, or infusion bottles. Suitable excipients for microcapsules, implants and rods are, for example, mixed polymers of glycolic acid and lactic acid.

[0105] Generally, the amount of the compounds of the formula I and/or physiologically acceptable salts thereof and/or other suitable derivatives thereof that is present in a pharmaceutical composition is from about 0.5 mg to about 1 g, preferably from about 1 mg to about 500 mg. Besides one or more compounds of the formula I and/or one or more physiologically acceptable salts thereof and/or one or more other suitable derivatives thereof as active compounds the pharmaceutical compositions according to present invention may also contain one or more other pharmacologically active compounds. Any materials used in preparing the various pharmaceutical compositions should be pharmaceutically pure and non-toxic in the amounts used.

[0106] In another, more general embodiment the present invention provides compositions comprising at least one compound of the formula I and/or a salt thereof and/or another suitable derivative thereof in admixture or otherwise in association with one or more inert carriers. These compositions are useful, for example, as assay standards, as convenient means of making bulk shipments, as pharmaceutical compositions or as starting materials for the production of pharmaceutical compositions. The amount of a compound of the formula I in such a composition will generally vary from about 0.001 % to about 90 % by weight. Inert carriers can be any material which does not degrade or otherwise covalently react with a compound of the formula I. Examples of suitable inert carriers are water; aqueous buffers, such as, for example, those which are generally useful in High Performance Liquid Chromatography (HPLC) analysis; organic solvents, such as acetonitrile, ethyl acetate, hexane and the like; and pharmaceutically acceptable carrier and/or auxiliary substances.

[0107] The compounds of the formula I can also be used as starting materials or chemical intermediates in the preparation of other compounds, especially in the preparation of other pharmacologically active compounds. Examples for such conversions of compounds of the invention into other compounds of the invention are discussed above and are given in detail below. For this use, besides the compounds of the formula I and their physiologically acceptable salts also other salts of the compounds of the formula I can be useful which are not suitable or less suitable for use as pharmaceuticals. Thus, the present invention also relates to compounds of the formula I and their salts in general as chemical intermediates, especially as intermediates in the preparation of pharmacologically active compounds. A subject of the invention also are intermediates which are used in the syntheses of the compounds of the formula I described above and below, and their use as chemical intermediates, especially as intermediates in the preparation of pharmacologically active compounds.

[0108] The following tests can serve to investigate the pharmacological activity and to illustrate the utility of the compounds of the present invention as factor Xa inhibitors.

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

[0109] The ability of a compound of the formula I to inhibit factor Xa, thrombin, plasmin, elastase and trypsin may be assessed by determining the concentration of the compound of the formula I that inhibits enzyme activity by 50 % (IC_{50}). Purified enzymes are used in chromogenic assays. To determine the inhibition constant K_i , the IC_{50} value is corrected for competition with substrate using the formula

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

wherein Km is the Michaelis-Menten constant (Chen and Prusoff, Biochem. Pharmacol. 22 (1973), 3099-3018 which is incorporated herein by reference).

a. Factor Xa Assay

[0110] TBS-PEG buffer (50 mM Tris-Cl, pH 7.8, 200 mM NaCl, 0.05 % (w/v) PEG-8000, 0.02 % (w/v) NaN₃) is used for this assay. The IC₅₀ is determined by combining in appropriate wells of a Costar half-area microtiter plate 25 µl human factor Xa (Enzyme Research Laboratories, Inc.; South Bend, IN) in TBS-PEG; 40 µl 10 % (v/v) DMSO in TBS-PEG (uninhibited control) or various concentrations of the compound to be tested diluted in 10 % (v/v) DMSO in TBS-PEG; and substrate S-2765 (N(α)-benzyloxycarbonyl-D-Arg-Gly-L-Arg-p-nitroanilide; Kabi Pharmacia, Inc.; Franklin OH) in TBS-PEG.

[0111] The assay is performed by pre-incubating the compound of formula I plus enzyme for 10 min. Then the assay is initiated by adding substrate to obtain a final volume of 100 µl. The initial velocity of chromogenic substrate hydrolysis is measured by the change in absorbance at 405 nm using a Bioteck Instruments kinetic plate reader (Ceres UV900HDI) at 25 °C during the linear portion of the time course (usually 1.5 min after addition of substrate). The concentration of inhibitor that causes a 50 % decrease in the rate of substrate hydrolysis is predicted by linear regression after plotting the relative rates of hydrolysis (compared to the uninhibited control) versus the log of the concentration of the compound of formula I. The enzyme concentration is 0.5 nM and substrate concentration is 140 µM.

b. Thrombin Assay

[0112] TBS-PEG buffer is used for this assay. The IC₅₀ is determined as above for the factor Xa assay, except that the substrate is S-2366 (L-PyroGlu-L-Pro-L-Arg-p-nitroanilide; Kabi) and the enzyme is human thrombin (Enzyme Research Laboratories, Inc.; South Bend IN). The enzyme concentration is 175 µM.

c. Plasmin Assay

[0113] TBS-PEG buffer is used for this assay. The IC₅₀ is determined as described above for the factor Xa assay, except that the substrate is S-2251 (D-Val-L-Leu-L-Lys-p-nitroanilide; Kabi) and the enzyme is human plasmin (Kabi). The enzyme concentration is 5 nM and the substrate concentration is 300 µM.

d. Trypsin Assay

[0114] TBS-PEG buffer containing 10 mM CaCl₂ is used for this assay. The IC₅₀ is determined as described above in the factor Xa assay, except that the substrate is BAPNA (benzoyl-L-Arg-p-nitroanilide; Sigma Chemical Co.; St. Louis MO) and the enzyme is bovine pancreatic trypsin (Type XIII, TPCK treated; Sigma). The enzyme concentration is 50 nM and the substrate concentration is 300 µM.

e. Elastase Assay

[0115] Tris-Cl buffer (pH 7.4, 300 mM NaCl, 2 % (v/v) N-methyl-pyrrolidone, 0.01 % (w/v) NaN₃) is used for this assay. The IC₅₀ is determined as described above for the assay for factor Xa, except that the substrate is succinyl-Ala-Ala-Ala-p-nitroanilide (Calbiochem-Nova Biochem Corp.; San Diego CA) and the enzyme is human neutrophil elastase (Athens Research and Technology, Inc.; Athens GA). The enzyme concentration is 75 nM and the substrate concentration is 600 µM. The control compound is "TENSTOP" (N(α)-tosyl-Gly-p-amidinophenylalanine methyl ester; American Diagnostica, Inc.; Greenwich CT), which is a reversible factor Xa inhibitor (Sturzebecher et al., Thromb. Res. 54 (1989), 245-252; Hauptmann et al., Thromb. Haem. 63 (1990), 220-223, each of which is incorporated herein by reference).

Test 2: Assays for Determining Inhibition of Coagulation

[0116] The effectiveness of the compounds of the formula I may be assessed by the in vitro prothrombin time (PT) assay using pooled human donor plasma. An ex vivo assay may also be used in which plasma is collected at various times after intravenous (iv) administration of a compound of the formula I to rats or to rabbits, or after intraduodenal (id) administration to rats, and analysis using the PT assay to determine plasma half-life. The PT assay is initiated with a thromboplastin dilution selected to obtain an extended and highly reproducible coagulation endpoint, referred to as the "dilute PT assay" as described below. The effectiveness of the compounds may also be determined using an in vivo rat arteriovenous shunt model of thrombosis.

a. In Vitro Dilute Prothrombin Time Assay

[0117] 100 µl prewarmed (37 °C) pooled human platelet poor plasma (PPP) is added to a fibrometer cup (Baxter Diagnostics, Inc.; McGaw Park IL). 50 µl of various concentrations of a compound of the formula I in TBS-BSA with calcium (50 mM Tris-Cl, 100 mM NaCl, 0.1 % (w/v) bovine serum albumin (BSA), 20 mM CaCl₂) is added. In control experiments, TBS-BSA with calcium but without a test compound of the formula I is added for measurement of uninhibited coagulation time. 150 µl diluted prewarmed rabbit thromboplastin (Baxter) with calcium is added to the fibrometer cup and the fibrometer timer is started. A rabbit thromboplastin dilution curve is obtained prior to treating the compound and is used to choose a thromboplastin dilution that allows approximately 30 sec PT time for uninhibited controls. The experimental concentration giving 50 % inhibition of coagulation (EC₅₀) is calculated from the dilution curve times.

[0118] Alternatively, the dilute prothrombin time assay may be conducted using the "research" mode on an Instrumentation Laboratories (IL) ACL3000-plus automated coagulation instrument (IL; Milan, Italy). Thromboplastin is diluted until a clotting time of 30-35 seconds is achieved. This clotting time is taken as 100 % activity. A standard curve for calibration is established by serial 2-fold dilution of the diluted thromboplastin reagent (rabbit brain IL-brand thromboplastin). During the assay, a 50 µl sample (plasma separated by centrifugation) is mixed with 100 µl thromboplastin reagent and nephelometric readings are taken over 169 sec. Coagulation time is determined from the maximal rate of change of light scatter calculated by the instrument. Inhibition is expressed as percent activity as determined by comparison with the calibration curve.

b. Ex Vivo Dilute Prothrombin Time Assay

[0119] A test compound of the formula I is administered iv either through the tail vein (rat) or ear vein (rabbit) following an approved protocol. Blood samples of 1 ml volume are removed at timed intervals after administration of the test compound from a cannulated carotid artery (rat) or auricular artery (rabbit). After centrifugation to obtain PPP, the plasma is immediately stored on ice or frozen.

[0120] For dilute prothrombin time determination, the plasma is prewarmed and assayed as described above. Percent inhibition is calculated from a thromboplastin dilution curve, which is run with each series of samples, and used to determine the time at which approximately 50 % of the initial anticoagulant activity remains in the plasma (T_{1/2}).

[0121] The test compound of the formula I may also be administered to rats using an intraduodenal dosing protocol. Male Sprague-Dawley rats weighing approximately 300 g are anesthetized with a combination of ketamine/xylazine administered subcutaneously, following an approved protocol. The right carotid artery is cannulated for blood sampling. A laparotomy is performed and the duodenum is cannulated with a ball-tip needle and tied into place to ensure that the suture is distal to the point of insertion. An additional tie is placed proximal to the insertion point to prevent leakage of gastric contents. The effectiveness of the suture in preventing a compound from reaching the site of insertion is tested by pressure testing at the conclusion of each experiment. The point of insertion is approximately 4 cm from the duodenal-gastric junction. The compound is administered in 1 ml normal saline. A blood sample of 0.7 ml is drawn prior to administration of the test compound of the formula I and at 15, 30, 60, 90 and 120 min after administration. The plasma is separated by centrifugation and assayed for inhibition of coagulation using the dilute prothrombin time assay.

c. Rat Arteriovenous Shunt Model of Thrombosis

[0122] The anti-thrombotic efficacy of the compounds of the invention may 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 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.

[0123] A test compound of the formula I is administered by continuous infusion into the tail vein using a syringe pump and butterfly catheter (infusion volume 1.02 ml/hr). 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.

[0124] In Table 1 some inhibition constants K_i for factor Xa inhibition by example compounds of the present invention are given. The inhibition constants were determined as described above (Test 1, a., Factor Xa Assay).

Table 1:

Ki values for factor Xa inhibition				
	Example	Ki (Xa) (μM)	Example	Ki (Xa) (μM)
5	2	0.10	97	1.60
10	4	0.090	103	1.7
15	6	0.40	106	0.04
20	21(4)	4.8	110	1.1
25	23	7.0	112	0.013
30	24	0.11	115	0.009
35	27	0.61	117	0.015
40	35	0.009	120	0.0048
45	39	0.007	121	0.13
50	47	0.007	124	0.025
55	56	0.082	125	0.009
60	58	0.014	132	2.0
65	77	0.009	133	0.05
70	78	0.21	137	0.011
75			141	0.72
80			146	0.013

[0125] As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mM" refers to millimolar; "ml" refers to milliliters; "m.p." refers to melting point; "dec." refers to decomposition; " $^{\circ}\text{C}$ " refers to degrees Celsius; " μl " refers to microliters; "nM" refers to nanomolar and " μM " refers to micromolar.

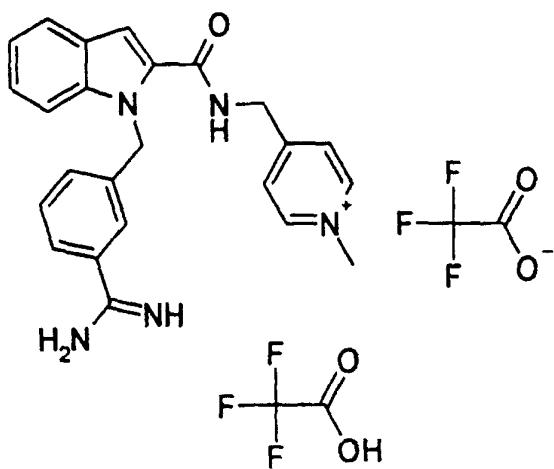
Examples

[0126] The following examples present typical syntheses of the compounds of the formula I. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. The compounds of the examples were characterized by mass spectra (MS) and/or NMR spectra and/or melting points.

Example 1:

[0127] 4-({[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-1-methylpyridinium trifluoroacetate trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester

[0128] A solution of 1.9 g (10 mmol) of 1H-indole-2-carboxylic acid ethyl ester in 15 ml of dimethylformamide was treated with 1.2 g (10.5 mmol) of potassium tert-butoxide. The mixture was stirred at room temperature for 10 minutes to give a clear solution. 2 g (10 mmol) of 3-cyano-benzyl bromide was added and the mixture was slowly heated to 100°C, cooled, acidified with acetic acid and poured on ice-water. The precipitated product was filtered off and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from methylene chloride/methanol to give 2.5 g of colorless crystals with m.p. 93-95°C.

10 2.) 1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid

[0129] A mixture of 0.61 g (2 mmol) of the above 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester, 25 ml of methanol, 2.5 ml of water, and 0.6 g of sodium hydroxide was heated to reflux for 15 minutes. The solvent was evaporated and the residue was partitioned between methylene chloride and 1 N hydrochloric acid. The organic phase was dried and evaporated.

Crystallization from methylene chloride/hexane gave 0.53 g of colorless crystals with m.p. 226-228°C (dec.).

15 3.) 1-(3-Cyano-benzyl)-N-[(4-pyridyl)methyl]-1H-indole-2-carboxamide

[0130] A mixture of 300 mg of the above 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid, 20 ml of methylene chloride, and 10 ml of thionyl chloride was heated to reflux for 4 hours. The solvent and excess reagent were evaporated, at the end azeotropically with toluene. The residue was dissolved in methylene chloride and the solution was treated with 0.3 ml of 4-aminomethylpyridine. The mixture was layered with 10 % aqueous sodium carbonate solution and stirred vigorously for 15 minutes. The organic layer was dried and evaporated and the residue was crystallized from ethyl acetate/ether to yield 280 mg of colorless crystals with m.p. 154-156 °C.

20 4.) N-[(4-pyridyl)methyl]-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

[0131] Hydrogen sulfide was introduced for 15 minutes into an ice-water cooled solution of 250 mg of the above 1-(3-cyano-benzyl)-N-[(4-pyridyl)methyl]-1H-indole-2-carboxamide in 5 ml of pyridine and 4 ml of triethylamine. The mixture was stirred at room temperature for 18 hours in a sealed vial and then partitioned between toluene/pyridine and 10 % aqueous sodium carbonate solution. The organic layer was dried and evaporated and the residue was crystallized from acetone/ether to yield 220 mg of light yellow crystals with m.p. 197-200°C (dec.).

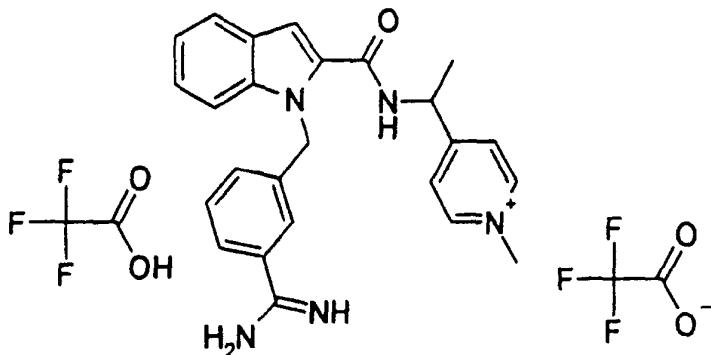
25 5.) 4-({[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-1-methylpyridinium trifluoroacetate trifluoroacetic acid salt

[0132] A mixture of 220 mg of N-[(4-pyridyl)methyl]-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide, 2 ml of dimethylsulfoxide, 5 ml of acetone, and 0.5 ml of methyl iodide was stirred in a sealed vial for 20 hours. The reaction mixture was diluted with toluene and evaporated. The residue was dissolved in acetone and the product was precipitated with ether. The solvents were decanted and the residue was stirred with fresh acetone/ether. The solids were separated and dried in vacuum. This material was dissolved in 20 ml of methanol and the solution was treated with 0.3 ml of acetic acid and 0.4 g of ammonium acetate. The mixture was heated to 55-60°C for 2 hours in a sealed vial. The solvent was evaporated and the bulk of the ammonium acetate was removed under high vacuum. The residue was lyophilized from acetonitrile/water 1:1 containing 1 % of trifluoroacetic acid. Final purification by reverse phase HPLC gave the product with a retention time of 16.14 min and correct molecular weight.

Example 2 :

[0133] (RS)-4-(1-{[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-ethyl)-1-methylpyridinium trifluoroacetate trifluoroacetic acid salt

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- 15 1.) (RS)-1-(3-Cyano-benzyl)-N-[1-(4-pyridyl)-1-ethyl]-1H-indole-2-carboxamide

[0134] A mixture of 280 mg of 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2), 10 ml of methylene chloride, and 4 ml of thionyl chloride was heated to reflux for 4 hours. The solvent and excess reagent were evaporated, at the end azeotropically with hexane. This acid chloride was dissolved in methylene chloride and added to a mixture of 0.3 g (RS)-1-(4-pyridyl)ethylamine dihydrochloride, 20 ml of methylene chloride, and 0.5 ml of diisopropylethylamine. After stirring for 15 minutes, the reaction mixture was layered with 10 % aqueous sodium carbonate and stirred vigorously for another 15 minutes. The organic layer was dried and evaporated and the residue was crystallized from ethyl acetate/ether to yield 300 mg of colorless product with m.p. 176-180°C.

- 25 2.) (RS)-N-[1-(4-Pyridyl)-1-ethyl]-1-[{(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

[0135] Hydrogen sulfide was introduced for 15 minutes into an ice-water cooled solution of 250 mg of the above (RS)-1-(3-cyano-benzyl)-N-[1-(4-pyridyl)-1-ethyl]-1H-indole-2-carboxamide in 5 ml of pyridine and 4 ml of triethylamine. The mixture was stirred at room temperature for 18 hours in a sealed vial and then evaporated. The residue was crystallized from acetone/ether to yield 220 mg of light yellow crystals with m.p. 197-200°C (dec.).

- 30 3.) (RS)-4-(1-{[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-ethyl)-1-methylpyridinium trifluoroacetate trifluoroacetic acid salt

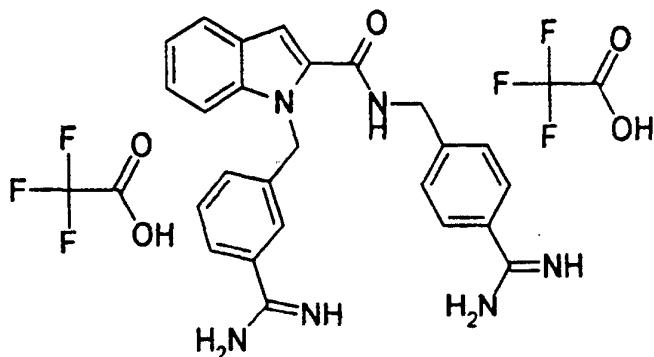
[0136] A mixture of 200 mg of (RS)-N-[1-(4-pyridyl)-1-ethyl]-1-[{(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide, 1.5 ml of dimethylsulfoxide, 5 ml of acetone, and 0.8 ml of methyl iodide was stirred in a sealed vial for 18 hours. The reaction mixture was diluted with toluene and evaporated. The residue was dissolved in acetone and the product was precipitated with ether. The solvents were decanted and the residue was stirred with fresh acetone/ether. The solids were separated, dried in vacuum, and dissolved in 20 ml of methanol. After addition of 0.3 ml of acetic acid and 0.65 g of ammonium acetate the mixture was heated at 55°C in a sealed vial for 3 hours. The solvent and excess ammonium acetate were removed in vacuum and the residue was lyophilized from acetonitrile/water containing 1 % of trifluoroacetic acid. The crude material was purified by reverse phase HPLC to give the desired product with retention time of 16.6 min and correct molecular weight.

- 45 Example 3:

[0137] 1-(3-Amidino-benzyl)-N-(4-amidino-benzyl)-1H-indole-2-carboxamide trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-N-(4-cyano-benzyl)-1H-indole-2-carboxamide

[0138] A mixture of 275 mg (1 mmol) of 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2), 350 mg of diphenylphosphoryl azide, 200 mg of 4-cyano-benzylamine hydrochloride, 5 ml of dimethylformamide, and 0.4 ml of diisopropylethylamine was stirred at room temperature for 20 hours. The solvent was evaporated and the residue was dissolved in methylene chloride. The solution was washed with 1 N hydrochloric acid and 10 % aqueous sodium carbonate, dried, and evaporated. The residue was passed over 10 g of silica gel using methylene chloride for elution. Crystallization from methylene chloride/hexane gave 310 mg of colorless crystals with m.p. 160-162°C.

25 2.) 1-[3-Thiocarbamoyl-phenyl)methyl]-N-[4-(thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

[0139] A solution of 150 mg of the above 1-(3-cyano-benzyl)-N-(4-cyano-benzyl)-1H-indole-2-carboxamide in 4 ml of pyridine and 2 ml of triethylamine was cooled in ice water and saturated with hydrogen sulfide. After stirring in a sealed vessel for 18 hours at room temperature, the solvent was evaporated and the residue was crystallized from acetone/methylene chloride/ether to yield 180 mg of light yellow crystals with m.p. 225-230°C (dec.).

30 3.) 1-(3-Amidino-benzyl)-N-(4-amidino-benzyl)-1H-indole-2-carboxamide trifluoroacetic acid salt

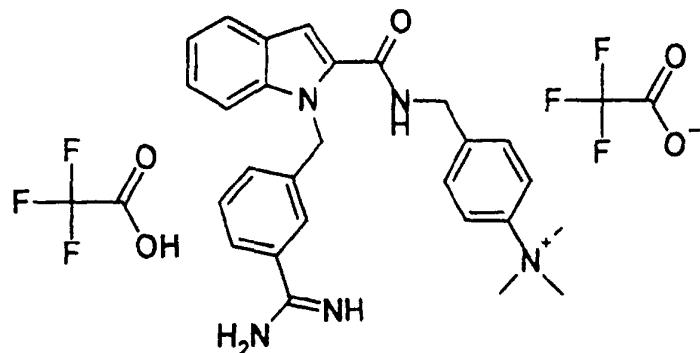
[0140] A mixture of 160 mg of 1-[3-thiocarbamoyl-phenyl)methyl]-N-[4-(thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide, 5 ml acetone, 1 ml of dimethylsulfoxide, and 0.4 ml of methyl iodide was stirred at room temperature for 18 hours. It was diluted with toluene and evaporated. The residue was stirred with acetone/ether and the solvent was decanted. The residue was dissolved in acetone/methanol and the product was precipitated by addition of ether. The solids were filtered off, dried, and dissolved in 20 ml of methanol. The solution was treated with 0.3 ml of acetic acid and 0.6 g of ammonium acetate and the mixture was heated in a sealed vial for 3 hours to 55°C. The solvent was evaporated and the bulk of ammonium acetate was removed under high vacuum. The residue was lyophilized from acetonitrile and water containing 1 % of trifluoroacetic acid. Purification by HPLC yielded the title compound with retention time of 17.46 min and the correct molecular weight.

40 Example 4:

[0141] [4-({[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

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1.) 1-[3-Cyano-benzyl]-N-[4-(dimethylaminophenyl)methyl]-1H-indole-2-carboxamide

[0142] A mixture of 275 mg (1 mmol) of 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2), 350 mg of diphenylphosphoryl azide, 250 mg of 4-(dimethylamino)benzylamine dihydrochloride, 5 ml of dimethylformamide, and 0.5 ml of diisopropylethylamine was stirred at room temperature for 20 hours. The solvent was evaporated and the residue was dissolved in methylene chloride. The solution was washed with 10 % aqueous sodium carbonate, dried, and evaporated. Crystallization of the residue from methylene chloride/ether/hexane gave 330 mg of colorless crystals with m.p. 153-155°C.

2.) N-[4-(Dimethylaminophenyl)methyl]-1-[{(3-thiocarbamoyl-phenyl)methyl}-1H-indole-2-carboxamide

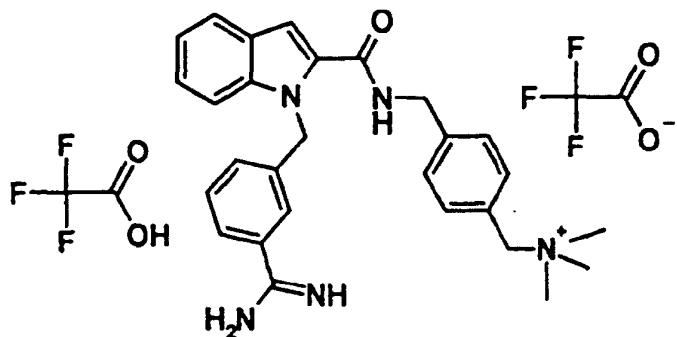
[0143] Hydrogen sulfide was introduced into an ice-water cooled solution of 200 mg of the above 1-(3-cyano-benzyl)-N-[4-(dimethylaminophenyl)methyl]-1H-indole-2-carboxamide in 5 ml of pyridine and 3 ml of triethylamine. The mixture was stored in a sealed vial in the refrigerator for 3 days. The solvents were evaporated and the residue was crystallized from methylene chloride/ether/hexane to leave 170 mg of yellowish product with m.p. 152-154°C.

3.) [4-{[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl]-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

[0144] A mixture of 160 mg of N-[4-(dimethylaminophenyl)methyl]-1-[{(3-thiocarbamoyl-phenyl)methyl}-1H-indole-2-carboxamide, 5 ml of acetone, and 0.4 ml of methyl iodide was stirred in a sealed vial for 18 hours at room temperature. The product was precipitated by addition of ether and collected by filtration. The solids were washed with acetone/ether and dried. This material was dissolved in 10 ml of methanol and the solution was treated with 0.25 ml of acetic acid and 0.5 g of ammonium acetate. The mixture was heated at 55°C for 3 hours in a sealed vial. The solvent was evaporated and the residue was lyophilized from acetonitrile and water containing 1 % of trifluoroacetic acid. Purification by HPLC gave the title compound with retention time of 17.38 min and correct molecular weight.

Example 6:

[0145] [4-{[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl]-benzyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt



15 1.) 1-(3-Cyano-benzyl)-N-[{4-(dimethylaminomethyl)phenyl]methyl]-1H-indole-2-carboxamide

[0146] A mixture of 275 mg (1 mmol) of 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2), 350 mg of diphenylphosphoryl azide, 250 mg of 4-(dimethylaminomethyl)benzylamine dihydrochloride, 5 ml of dimethylformamide, and 0.2 ml of diisopropylethylamine was stirred at room temperature for 3 days. The solvent was evaporated and the residue was partitioned between methylene chloride and 10 % aqueous sodium carbonate solution. The organic phase was dried and evaporated. The residue was stirred with ether/hexane to yield 240 mg of colorless crystals with m.p. 127-128°C.

20 2.) N-[{4-(Dimethylaminomethyl)phenyl]methyl]-1-[{3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

[0147] A solution of 240 mg of the above 1-(3-cyano-benzyl)-N-[{4-(dimethylaminomethyl)phenyl]-methyl]-1H-indole-2-carboxamide in 5 ml of pyridine and 3 ml of triethylamine was saturated with hydrogen sulfide while cooled in ice-water. The mixture was allowed to sit for 20 hours at room temperature in a sealed vial. The solvents were evaporated and the residue was stirred with ether to yield 200 mg of yellow crystals with m.p. 120-125°C.

25 3.) [4-{[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl]-benzyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

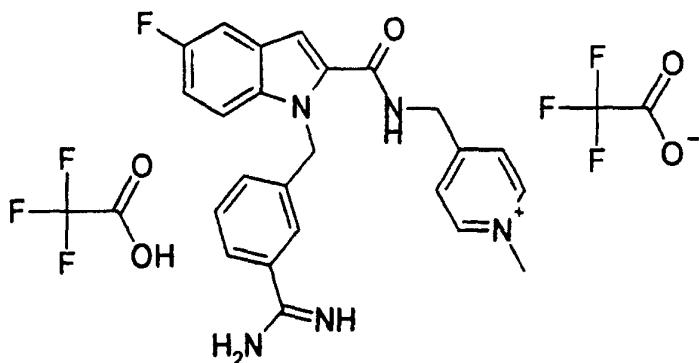
[0148] A mixture of 200 mg of N-[{4-(dimethylaminomethyl)phenyl]-methyl]-1-[{3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide, 6 ml of acetone, 1 ml of dimethylsulfoxide, and 0.8 ml of methyl iodide was stirred in a sealed vial for 20 hours. After evaporation the residue was dissolved in acetone and the product was precipitated with ether. The solids were reprecipitated from acetone with ether. After drying the product was dissolved in 20 ml of methanol. The solution was treated with 0.3 ml of acetic acid and 0.6 g of ammonium acetate and the mixture was heated at 55°C for 3 hours. The solvent was evaporated and the residue was lyophilized from acetonitrile/water containing 1 % of trifluoroacetic acid. The crude product was purified by HPLC to give the title compound with a retention time of 17.96 min and the correct molecular weight.

Example 7:

45 [0149] 4-{[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-1-methyl- pyridinium trifluoroacetate trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid methyl ester

[0150] A solution of 0.96 g (5 mmol) of 5-fluoro-1H-indole-2-carboxylic acid methyl ester in 20 ml of dimethylformamide was treated with 0.6 g (5.25 mmol) of potassium tert-butoxide. The mixture was stirred at room temperature for 10 minutes to give a clear solution. 3-Cyano-benzyl bromide, 1 g (5 mmol), was added and the mixture was slowly heated to 100°C, cooled, acidified with acetic acid and poured on ice-water. The precipitated product was filtered off and dissolved in methylene chloride. The solution was dried and evaporated and the residue was crystallized from methanol to give 1.3 g of colorless crystals with m.p. 148-148°C.

25 2.) 1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid

[0151] A mixture of 1 g of the above 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid methyl ester, 30 ml of methanol, 3 ml of water, and 0.5 g of sodium hydroxide was heated to reflux for 20 minutes. The solvent was partially evaporated and the residue was acidified with 2 N hydrochloric acid. The precipitated crystals were filtered off and dissolved in methylene chloride/2-propanol. The solution was dried and evaporated and the residue was crystallized from acetone/hexane to give 0.9 g of colorless crystals with m.p. 247-250°C (dec.).

35 3.) 1-(3-Cyano-benzyl)-5-fluoro-N-[(4-pyridyl)methyl]-1H-indole-2-carboxamide

[0152] This compound was prepared by converting the above carboxylic acid to the acid chloride and reacting it with 4-aminomethylpyridine as described for the desfluoro analog in example 1/3. It was crystallized from ethyl acetate/ether/hexane to yield colorless crystals with m.p. 160-162°C.

40 4.) 5-Fluoro-N-[(4-pyridyl)methyl]-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

[0153] This thioamide was obtained by reaction of the above nitrile with hydrogen sulfide as described in example 1/4 for the desfluoro analog. It was obtained as a yellow crystalline solid from acetone with m.p. 220-223°C.

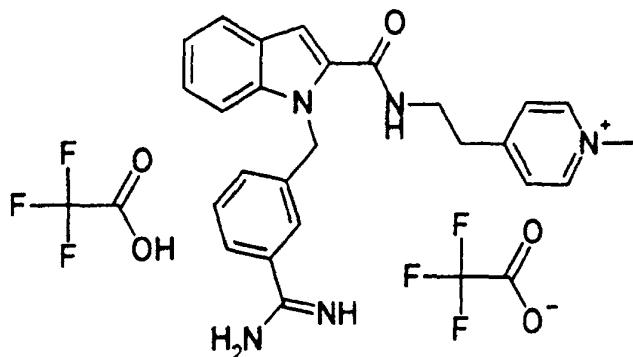
45 5.) 4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

[0154] This compound was similarly prepared by treatment of 5-fluoro-N-[(4-pyridyl)methyl]-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide with methyl iodide and subsequently with ammonium acetate as described in example 1/5. The product was purified by HPLC and had a retention time of 16.64 min and the correct molecular weight.

50 Example 8:

55 [0155] 4-(2-{[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-ethyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-N-[2-(4-pyridyl)ethyl]-1H-indole-2-carboxamide

[0156] 1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2), 280 mg, was converted to the acid chloride by means of thionyl chloride as described in example 1/3. This acid chloride was added to a mixture of 300 mg of 2-(4-pyridyl)ethylamine dihydrochloride and 0.4 ml of diisopropylethylamine in methylene chloride. After stirring for 10 minutes, the mixture was layered with 10 % aqueous sodium carbonate and stirred for additional 10 minutes. The organic layer was dried and evaporated and the residue was chromatographed over 12 g of silica gel using methylene chloride/acetone 1:1 to yield 280 mg of resinous product.

25 2.) N-[2-(4-Pyridyl)ethyl]-1-[{(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide}

[0157] The above 1-(3-cyano-benzyl)-N-[2-(4-pyridyl)ethyl]-1H-indole-2-carboxamide was reacted with hydrogen sulfide as described in example 1/4. Crystallization from acetone/hexane gave 290 mg of yellowish crystals with m.p. 208-210°C.

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3.) 4-(2-{[1-(3-Amidino-benzyl)-1H-indole-2-carbonyl]-amino}-ethyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

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[0158] A mixture of 250 mg of N-[2-(4-pyridyl)ethyl]-1-[{(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide, 2 ml of dimethylsulfoxide, 10 ml of acetone, and 1 ml of methyl iodide was stirred in a sealed vial for 20 hours. The reaction mixture was diluted with toluene and evaporated. The residue was dissolved in acetone and the product was precipitated with ether. The solvents were decanted and the residue was reprecipitated from methanol with ether. The solids were separated and dried in vacuum. This material was dissolved in 25 ml of methanol and the solution was treated with 0.4 ml of acetic acid and 0.8 g of ammonium acetate. The mixture was heated to 55-60°C for 2 hours in a sealed vial. The solvent was evaporated and the bulk of the ammonium acetate was removed under high vacuum. The residue was lyophilized from acetonitrile/water 1:1 containing 1 % of trifluoroacetic acid. Final purification by reverse phase HPLC gave the product with a retention time of 16.23 min and correct molecular weight.

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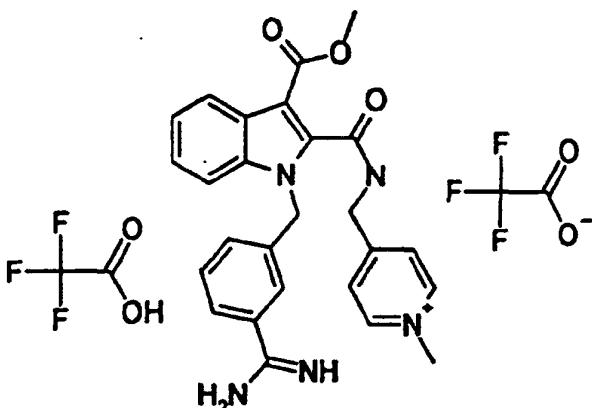
Example 11: (Reference)

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[0159] 4-(2-{[1-(3-Amidino-benzyl)-3-methoxycarbonyl-1H-indole-2-carbonyl]-amino}-methyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-1H-indole-2,3-dicarboxylic acid dimethyl ester

[0160] A solution of 0.47 g (2 mmol) of 1H-indole-2,3-dicarboxylic acid dimethyl ester in 10 ml of dimethylformamide was treated with 0.23 g (2 mmol) of potassium tert-butoxide. After stirring for 5 minutes, 0.4 g (2 mmol) of 3-cyano-benzyl bromide was added and the mixture was heated to 95°C. After cooling, the mixture was partitioned between methylene chloride/hexane and aqueous sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was chromatographed over 15 g of silica gel using 10 % ether in methylene chloride for elution. The clean fractions were combined and evaporated to leave 0.6 g of colorless resin.

25 2.) 1-(3-Cyano-benzyl)-3-methoxycarbonyl-1H-indole-2-carboxylic acid

[0161] A mixture of 0.4 g of the above 1-(3-cyano-benzyl)-1H-indole-2,3-dicarboxylic acid dimethyl ester, 20 ml of methanol, 2 ml of water, and 0.4 g of sodium hydroxide was heated to reflux for 5 minutes. The solvent was partially removed and the residue was diluted with water and acidified with 2 N hydrochloric acid. The precipitated acid was extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from methylene chloride/ether/hexane gave 370 mg of colorless crystals.

35 3.) 1-(3-Cyano-benzyl)-3-methoxycarbonyl-N-(4-pyridylmethyl)-1H-indole-2-carboxamide

[0162] A mixture of 200 mg of 1-(3-cyano-benzyl)-3-methoxycarbonyl-1H-indole-2-carboxylic acid, 110 mg of 4-aminomethylpyridine, 210 mg of diphenylphosphoryl azide, 4 ml of dimethylformamide, and 0.3 ml of diisopropylethylamine was allowed to sit at room temperature for 18 hours. The solvent was evaporated and the residue was partitioned between methylene chloride and 10 % aqueous sodium carbonate. The organic layer was dried and evaporated and the residue was chromatographed over 12 g silica gel using methylene chloride/ethyl acetate/acetone 2:2:1 for elution. Crystallization from ethyl acetate/ether/hexane gave 170 mg of colorless crystals with m.p. 152-154°C.

40 4.) 3-Methoxycarbonyl-N-[(4-pyridyl)methyl]-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

[0163] A solution of 150 mg of 1-(3-cyano-benzyl)-3-methoxycarbonyl-N-(4-pyridylmethyl)-1H-indole-2-carboxamide in 4 ml of pyridine and 2 ml of triethylamine was cooled in ice-water and saturated with hydrogen sulfide. After sitting in a sealed vial for 4 hours at room temperature, the solvents were evaporated, at the end azeotropically with ethyl acetate. The residue was crystallized from methylene chloride/ether/hexane to leave 160 mg of light yellow product which was used in the subsequent step.

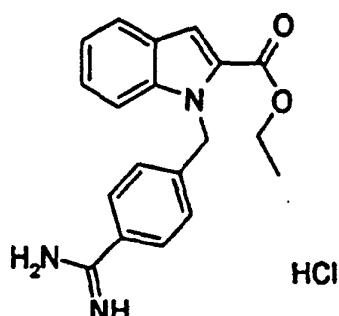
45 5.) 4-({[1-(3-Amidino-benzyl)-3-methoxycarbonyl-1H-indole-2-carbonyl]-amino}-methyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

[0164] A mixture of 150 mg of 3-methoxycarbonyl-N-(4-pyridylmethyl)-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide, 10 ml of acetone, 1 ml of dimethylsulfoxide, and 0.6 ml of methyl iodide was stirred at room temperature for 18 hours. It was then diluted with ethyl acetate and evaporated. The residue was stirred with ether and the solvent was decanted. The residue was precipitated from ethyl acetate with ether, collected and dried in vacuum. This material was dissolved in 15 ml of methanol, treated with 0.15 ml of acetic acid and 0.3 g of ammonium

acetate, and heated at 55°C for 2 hours. The solvent was evaporated and the residue was lyophilized from water containing 1 % of trifluoroacetic acid and acetonitrile (1:1). Purification by HPLC yielded the title compound with a retention time of 16.2 minutes and the correct molecular weight.

5 Example 13: (Reference)

[0165] 1-[4-Amidino-berizyl]-1H-indole-2-carboxylic acid ethyl ester hydrochloride



10 1.) 1-(4-Thiocarbamoyl-phenyl)methyl-1H-indole-2-carboxylic acid ethyl ester

15 [0166] A solution of 300 mg of 1-(4-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester in 8 ml of pyridine and 4 ml of triethylamine was saturated with hydrogensulfide while cooled in ice water. After sitting at room temperature over night in a sealed vial, the reaction mixture was partitioned between toluene and 10 % aqueous sodium carbonate. The organic phase was dried and evaporated. Crystallization of the residue from ether yielded 0.3 g of yellow crystals with m.p. 187-189°C;

20 2.) 1-[4-Amidino-benzyl]-1H-indole-2-carboxylic acid ethyl ester hydrochloride

25 [0167] A mixture of 250 mg of 1-(4-thiocarbamoyl-phenyl)methyl-1H-indole-2-carboxylic acid ethyl ester, 10 ml of acetone, and 1 ml of methyl iodide was stirred at room temperature for 20 hours. The precipitated crystals were filtered off, washed with ether, and dissolved in 10 ml of methanol. The solution was treated with 0.2 ml of acetic acid and 0.5 g of ammonium acetate and stirred at room temperature for 18 hours. The solvent was evaporated and the residue was partitioned between methylene chloride/2-propanol and 1 N sodium hydroxide solution. The organic phase was dried and evaporated. The residue was treated with hydrogen chloride in ether and crystallized from ethanol/ether to leave colorless crystals with m.p. 240-241°C.

30 Example 14: (Reference)

[0168] 1-[3-Amidino-benzyl]-1H-indole-2-carboxylic acid ethyl ester hydrochloride

35 1.) 1-(3-Thiocarbamoyl-phenyl)methyl-1H-indole-2-carboxylic acid ethyl ester

40 [0169] This compound was obtained by the standard reaction (see example 13/1) of 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester (example 1/1) with hydrogen sulfide. It was crystallized from ether/hexane to give yellow crystals with m.p. 124-126°C.

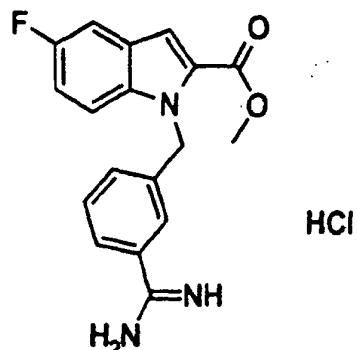
45 2.) 1-[3-Amidino-benzyl]-1H-indole-2-carboxylic acid ethyl ester hydrochloride

50 [0170] This compound was prepared similarly to example 13/2 by reaction of 1-(3-thiocarbamoyl-phenyl)methyl-1H-indole-2-carboxylic acid ethyl ester with methyl iodide and subsequently with ammonium acetate. The hydrochloride was crystallized from 2-propanol/ethyl acetate/ether to give colorless solvated crystals with m.p. 136-140°C (dec.). This compound had a HPLC retention time of 23.95 minutes and the correct molecular weight.

Example 15: (Reference)

[0171] 1-[3-Amidino-benzyl]-5-fluoro-1H-indole-2-carboxylic acid methyl ester hydrochloride

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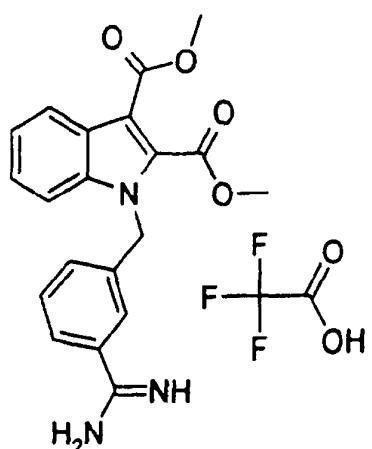
[0172] The starting material 5-fluoro-1-(3-thiocarbamoyl-phenyl)methyl-1H-indole-2-carboxylic acid methyl ester was similarly to example 13/1 obtained from the reaction of 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid methyl ester (example 7/1) with hydrogen sulfide. It was crystallized from ether/hexane to give a yellow crystalline powder which was directly converted to the amidine analogously to example 1/5.

[0173] The title compound was prepared analogously to example 1. The hydrochloride was crystallized from methanol/ether and gave colorless crystals with m.p. 235-237°C (dec.).

Example 16: (Reference)

[0174] 1-[3-Amidino-benzyl]-1H-indole-2,3-dicarboxylic acid dimethyl ester trifluoroacetic acid salt

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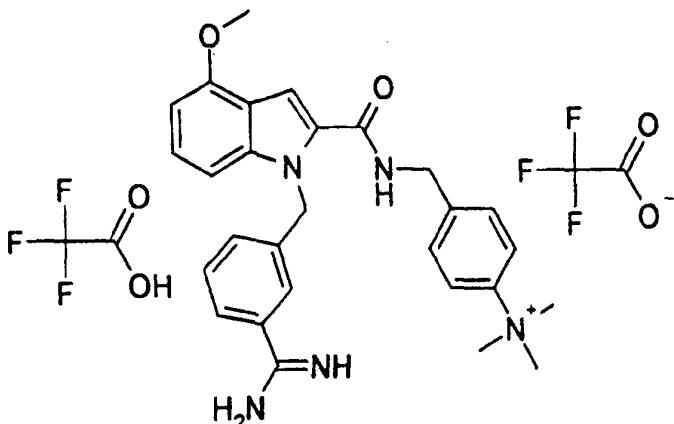
[0175] The starting material 1-(3-thiocarbamoylphenyl)methyl-1H-indole-2,3-dicarboxylic acid dimethyl ester was prepared analogously to example 13/1 by reacting 1-(3-cyano-benzyl)-1H-indole-2,3-dicarboxylic acid dimethyl ester (example 11/1) with hydrogen sulfide. It was crystallized from ether/hexane to give yellow crystals with m.p. 176-178°C.

[0176] The product was converted to the amidine analogously to example 1/5. The amidine was lyophilized from acetonitrile/water/trifluoroacetic acid and had a retention time on HPLC of 20.9 min and the correct molecular weight.

Example 17:

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[0177] [4-({[1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt



1.) 1-(3-Cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid methyl ester

20 [0178] A solution of 1.025 g (5 mmol) of 4-methoxy-1H-indole-2-carboxylic acid methyl ester in 20 ml of dimethylformamide was treated with 0.6 g (5.25 mmol) of potassium tert-butoxide. The mixture was stirred at room temperature for 10 minutes to give a clear solution. 1 g (5 mmol) of 3-cyano-benzyl bromide was added and the mixture was slowly heated to 90°C, cooled, acidified with acetic acid, and poured on ice-water and stirred to crystallize. The crystals were filtered off, washed with water and dissolved in methylene chloride. The solution was washed with saturated sodium bicarbonate solution, dried and evaporated and the residue was crystallized from methanol to give 1.3 g of colorless crystals with m.p. 135-136°C.

25 2.) 1-(3-Cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid

30 [0179] A mixture of 0.96 g (3 mmol) of the above 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid methyl ester, 20 ml of methanol, 2 ml of water, and 0.5 g of sodium hydroxide was heated to reflux for 40 minutes. The mixture was diluted with water and extracted with ether/hexane. The aqueous phase was acidified with 2 N hydrochloric acid and extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from methylene chloride/hexane gave 0.87 g of colorless crystals with m.p. 222-224°C (dec.).

35 3.) 1-(3-Cyano-benzyl)-4-methoxy-N-[(4-dimethylaminophenyl)methyl]-1H-indole-2-carboxamide

40 [0180] A mixture of 306 mg (1 mmol) of the above 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid, 250 mg (1.12 mmol) of 4-(dimethylamino)benzylamine dihydrochloride, 350 mg of diphenylphosphoryl azide, 0.5 ml of diisopropylethylamine, and 5 ml of dimethylformamide was stirred at room temperature over night. The solvent was evaporated and the residue was partitioned between methylene chloride and 10 % aqueous sodium carbonate solution. The organic layer was washed with dilute acetic acid and sodium bicarbonate, dried, and evaporated. The residue was passed over a plug of silica gel using 10 % of ethyl acetate in dichloromethane. Crystallization from ethyl acetate/hexane yielded 330 mg (75 %) of colorless crystals with m.p. 138-140°C.

45 4.) N-[(4-Dimethylaminophenyl)methyl]-4-methoxy-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

50 [0181] Hydrogen sulfide was introduced for 15 minutes into an ice-water cooled solution of 200 mg of the above 1-(3-cyano-benzyl)-4-methoxy-N-[(4-dimethylaminophenyl)methyl]-1H-indole-2-carboxamide in 65 ml of pyridine and 3 ml of triethylamine. The mixture was stirred at room temperature for 18 hours in a sealed vial and then evaporated. The residue was passed over 10 g of silica gel using 20 % of acetone in dichloromethane and crystallized from ethyl acetate/hexane to yield 150 mg (70 %) of light yellow crystals with m.p. 192-193°C.

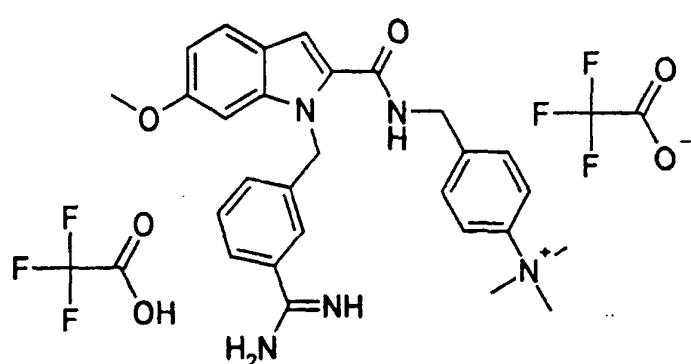
55 5.) [4-((1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carbonyl)-amino)-methyl]-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

[0182] A mixture of 125 mg of N-[4-(dimethylaminophenyl)methyl]-4-methoxy-1-[(3-thiocarbamoyl-phenyl)-methyl]-1H-indole-2-carboxamide, 10 ml of acetone, 1 ml of dimethylsulfoxide, and 0.6 ml of methyl iodide was stirred in a

sealed vial for 24 hours at room temperature. The mixture was diluted with ethyl acetate and evaporated. The residue was stirred with acetone/ether and the solvent was decanted. The residue was dissolved in a small amount of methanol and the product was precipitated with ether, collected, and dried. This material was dissolved in 15 ml of methanol and the solution was treated with 0.2 ml of acetic acid and 0.4 g of ammonium acetate. The mixture was heated at 55°C for 3 hours in a sealed vial. The solvent was evaporated and the residue was lyophilized from acetonitrile and water containing 1 % of trifluoroacetic acid. Purification by HPLC gave the title compound with retention time of 17.6 min and correct molecular weight.

Example 18:

[0183] [4-({[1-(3-Amidino-benzyl)-6-methoxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt



[0184] The starting material was prepared following the procedures described in Example 17.

1.) 1-(3-Cyano-benzyl)-6-methoxy-1H-indole-2-carboxylic acid methyl ester

[0185] This compound was obtained in 86 % yield by alkylation of 6-methoxy-1H-indole-2-carboxylic acid methyl ester with 3-cyano-benzyl bromide and had m.p. 152-153°C, crystallized from methanol.

2.) 1-(3-Cyano-benzyl)-6-methoxy-1H-indole-2-carboxylic acid

[0186] This compound was obtained in 91 % yield by alkaline hydrolysis of the above methyl ester and had m.p. 225-227°C (dec.), crystallized from dichloromethane/hexane.

3.) 1-(3-Cyano-benzyl)-N-[(4-dimethylaminophenyl)methyl]-6-methoxy-1H-indole-2-carboxamide

[0187] This compound was prepared in 78 % yield by coupling of the above acid with 4-dimethylaminobenzylamine using diphenylphosphoryl azide and had m.p. 156-158°C, crystallized from ethyl acetate/hexane.

4.) N-[(4-Dimethylaminophenyl)methyl]-6-methoxy-1-[(3-thiocarbamoyl-phenyl)methyl]-1H-indole-2-carboxamide

[0188] This compound was obtained in 93 % yield by reaction of the above nitrile with hydrogen sulfide. It was crystallized from ethyl acetate/hexane to give yellow crystals with m.p. 190-192°C.

5.) [4-({[1-(3-Amidino-benzyl)-6-methoxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

[0189] A mixture of 150 mg of N-[4-(dimethylaminophenyl)methyl]-6-methoxy-1-[(3-thiocarbamoyl-phenyl)-methyl]-1H-indole-2-carboxamide, 10 ml of acetone, 1 ml of dimethylsulfoxide, and 0.7 ml of methyl iodide was stirred in a sealed vial for 20 hours at room temperature. The mixture was diluted with ethyl acetate and evaporated. The residue was dissolved in acetone/ethyl acetate and precipitated with ether. The solvent was decanted and the residue was dissolved in a small amount of methanol and the product was precipitated with ether, collected, and dried. This material

was dissolved in 20 ml of methanol and the solution was treated with 0.2 ml of acetic acid and 0.4 g of ammonium acetate. The mixture was heated at 55°C for 2.5 hours in a sealed vial. The solvent was evaporated and the residue was lyophilized from acetonitrile and water containing 1 % of trifluoroacetic acid. Purification by HPLC gave the title compound with retention time of 17.5 min and correct molecular weight.

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Example 19: (Reference)

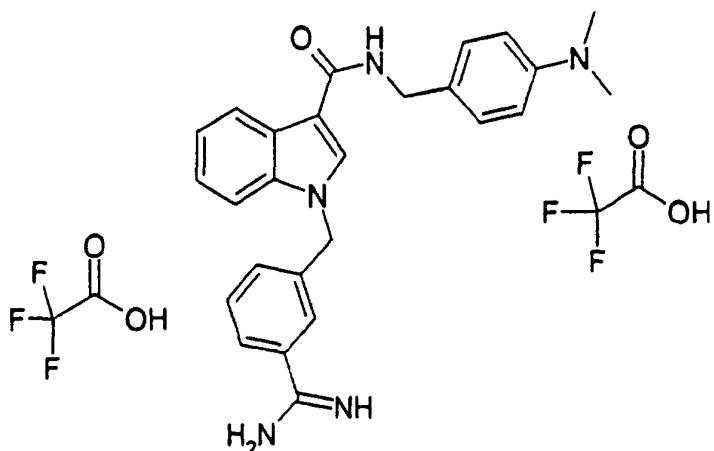
[0190] 1-(3-Amidino-benzyl)-1H-indole-3-carboxylic acid 4-(dimethylamino)-benzyl amide trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-1H-indole-3-carboxylic acid

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[0191] To a solution of 9 g (0.055 mol) 3-indole-carboxylic acid in 200 ml of tetrahydrofuran 3 g (0.122 mol) of sodium hydride was added at 0°C in portions. After 75 minutes at 0°C 10.7 g (0.055 mol) 3-cyano-benzyl bromide was added. After 16 h stirring at room temperature the precipitate was filtered off, dissolved in water, and precipitated by addition of hydrochloric acid to give 13 g (86 %) of the desired product. M.p. 226-228°C. MS: 277.2 (M+H⁺).

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2.) 1-(3-Cyano-benzyl)-1H-indole-3-carboxylic acid 4-(dimethylamino)-benzyl amide

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[0192] The compound was prepared from 1-(3-cyano-benzyl)-1H-indole-3-carboxylic acid, 4-dimethylaminobenzyl amine, diphenylphosphoryl azide and diisopropylethylamin as described in example 3/1. The crude material was purified by silica gel chromatography with toluene/ethyl acetate 5:1 to give the desired product in 32 % yield. M.p. 126-128°C. MS: 409.3 (M+H⁺).

3.) 1-(3-Amidino-benzyl)-1H-indole-3-carboxylic acid 4-(dimethylamino)-benzyl amide trifluoroacetic acid salt

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[0193] Into a solution of 250 mg (0.612 mmol) 1-(3-cyano-benzyl)-1H-indole-3-carboxylic acid 4-dimethylamino-benzyl amide in 10 ml of ethanol hydrogen chloride gas was bubbled in at 0°C for 4 hours. The mixture was warmed up to room temperature overnight and evaporated. The residue was dissolved in 10 ml ethanol and liquid ammonia was added. The mixture was allowed to warm up to room temperature with stirring and evaporated. The crude material was purified by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 6.5:3.5:0.1 to give 180 mg (36 %) of the desired product. M.p. 92-96°C. MS: 426.3 (M+H⁺).

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Example 20: (Reference)

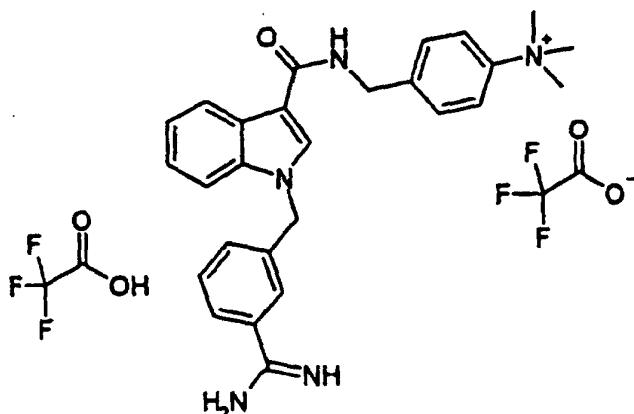
55

[0194] [4-({[1-(3-Amidino-benzyl)-1H-indole-3-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

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1.) [4-((1-(3-Cyano-benzyl)-1H-indole-3-carbonyl)-amino)-phenyl]-trimethyl-ammonium iodide

- 20 [0195] To a solution of 250 mg (0.611 mmol) 1-(3-cyano-benzyl)-1H-indole-3-carboxylic acid (4-dimethylaminobenzyl)-amide (example 19/2) in 20 ml of acetone 384 μl (6.11 mmol) of methyl iodide was added and it was stirred for 4 days at room temperature. The mixture was evaporated to give 350 mg (quantitative yield) of the desired product. MS: 423.2 (M^+).
- 25 2.) [4-((1-(3-Amidino-benzyl)-1H-indole-3-carbonyl)-amino)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

30 [0196] This compound was prepared from [4-((1-(3-cyano-benzyl)-1H-indole-3-carbonyl)-amino)-phenyl]-trimethyl-ammonium iodide by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 7:3:0.1 to give the desired product in 39 % yield. M.p. 177°C (dec.). MS: 440.3 (M^+).

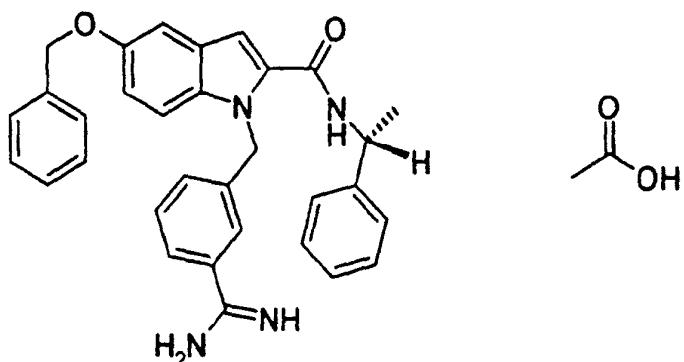
Example 21:

- 35 [0197] (R)-1-(3-Amidino-benzyl)-5-benzyloxy-1H-indole-2-carboxylic acid (1-phenyl-ethyl)-amide acetic acid salt

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1.) 5-Benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester

- 55 [0198] 10 g (0.034 mol) of 5-benzyloxy-1H-indole-2-carboxylic acid ethyl ester was dissolved in 100 ml dimethylformamide and 976 mg (0.04 mol) of sodium hydride was added portionwise. After 1 hour stirring at room temperature 797 mg (0.04 mol) of 3-cyano-benzyl bromide was added. The mixture was stirred at room temperature for 1.5 hours, neutralized with 2 N hydrochloric acid, and extracted with methyl tert-butyl ether. The organic phase was dried and evaporated. The crude material was purified by flash chromatography on silica gel with heptane/methyl tert-butyl ether

12.8 to give the desired product in 84 % yield. M.p. 98-102°C. MS: 411.2 (M+H⁺).

2.) 5-Benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid

5 [0199] This compound was prepared from 5-benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester and sodium hydroxide as described in example 1/2. The crude material was purified by flash chromatography on silica gel with dichloromethane/methanol 19:0.25 to give the desired product in 83 % yield. ¹H-NMR (DMSO-d₆, 200 MHz): δ = 5.11 (s, 2H, OCH₂); 5.88 (s, 2H, N-CH₂); 7.04 (dd, 1H, aromatic H); 7.20-7.60 (m, 11 H, aromatic H); 7.70 (d, 1H, aromatic H). MS: 383.2 (M+H⁺).

10 3.) (R)-5-Benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (1-phenyl-ethyl) amide

15 [0200] This compound was prepared from 5-benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid and (R)-1-phenyl-ethyl-amine by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with dichloromethane to give the desired product in 73 % yield. M.p. 169-170°C. MS: 486.3 (M+H⁺).

20 4.) (R)-5-Benzyl-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid (1-phenyl-ethyl) amide

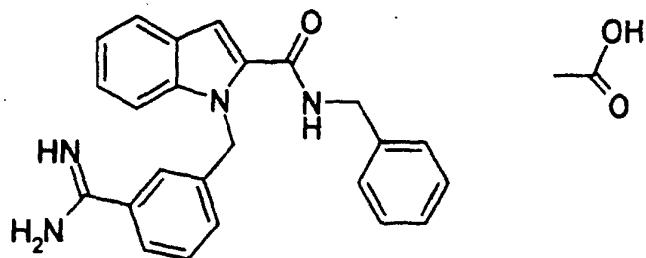
25 [0201] The compound was prepared from (R)-5-benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (1-phenyl-ethyl)-amide and hydrogen sulfide as described in example 1/4 to give the desired product in 55 % yield. M.p. 146-148°C. MS: 520.3 (M+H⁺).

30 5.) (R)-1-(3-Amidino-benzyl)-5-benzyl-1H-indole-2-carboxylic acid (1-phenyl-ethyl)-amide acetic acid salt

35 [0202] This compound was prepared from (R)-5-benzyl-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid (1-phenyl-ethyl)-amide, methyl iodide, and ammonium acetate as described in example 1/5, but for the methylation acetone was used as solvent and in the last step methanol and acetone were used as solvents. The crude material was purified by flash chromatography on silica gel with dichloromethane/methanol/acetic acid 9:0.25:0.5 to give the desired product in 28 % yield. M.p. 72°C (dec.). MS: 503.3 (M+H⁺).

Example 22:

[0203] 1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid benzyl amide acetic acid salt



40 1.) 1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid benzyl amide

45 [0204] This compound was prepared from 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2) and benzylamine by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with toluene/ethanol 19:0.5 to give the desired product in 97 % yield. M.p. 129-131°C. MS: 366.2 (M+H⁺).

50 2.) 1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid benzyl amide acetic acid salt

55 [0205] This compound was prepared from 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid benzyl amide by using hydrogen chloride and liquid ammonia as described in example 19/2. The crude material was purified by reversed

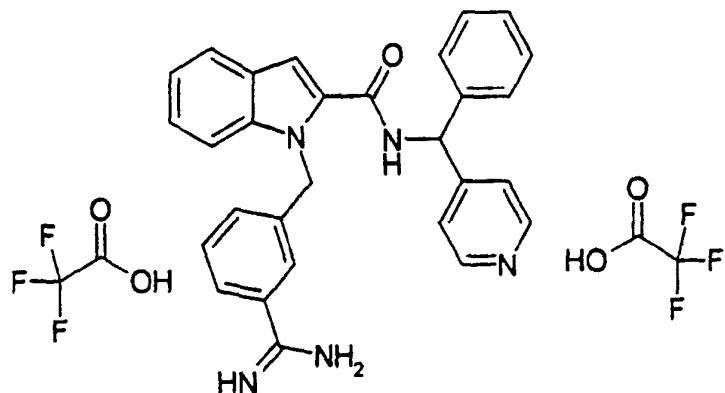
phase chromatography on RP₁₈ material with water/acetonitrile/ammonium acetate 6:4:0.1 to give the desired product in 40 % yield. M.p. 266-268°C (dec.). MS: 383.2 (M+H⁺).

Example 23:

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[0206] (RS)-1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid α -(4-pyridyl)-benzyl amide trifluoroacetic acid salt

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25 1.) (RS)-1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid α -(4-pyridyl)-benzyl amide

[0207] This compound was prepared from 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2) and (RS)- α -(4-pyridyl)-benzyl amine by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with dichloromethane/ethanol 19:0.25 to give 30 the desired product in 43 % yield. M.p. 90-110°C. MS: 443.2 (M+H⁺).

2.) (RS)-1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid α -(4-pyridyl)benzyl amide trifluoroacetic acid salt

[0208] This compound was prepared from (RS)-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid α -(4-pyridyl)-benzyl amide by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 7:3:0.1 to give 13 % of the desired product. M.p. 88-92°C. MS: 460.3 (M+H⁺).

Example 24:

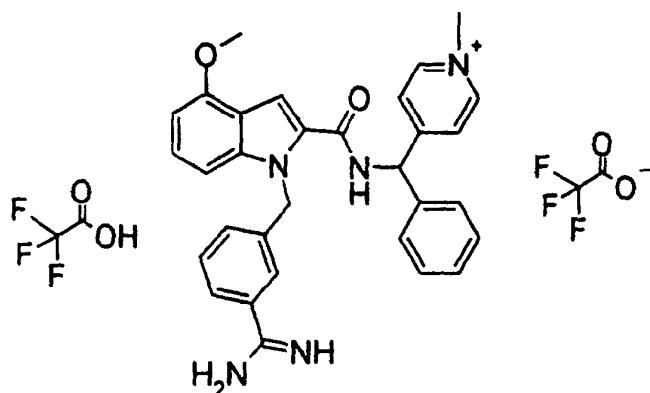
40

[0209] (RS)-4-({[1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carbonyl]-amino}-phenyl-methyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

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1.) (RS)-1-(3-Cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid α -(4-pyridyl)-benzyl amide

[0210] This compound was prepared from 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (example 17/2) and (RS)- α -(4-pyridyl)-benzyl amine by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with dichloromethane/methanol 19:0.3 to give the desired product in 18 % yield. MS: 473.2 ($M+H^+$).

2.) (RS)-4-Methoxy-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid α -(4-pyridyl)benzyl amide

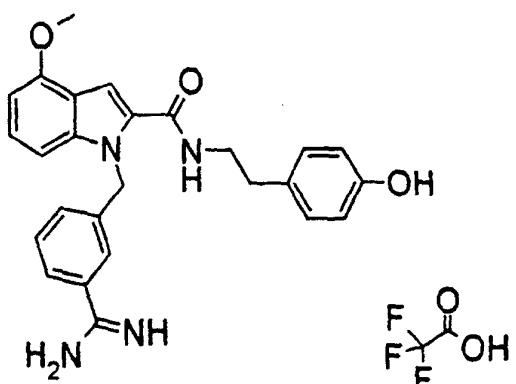
[0211] The compound was prepared from (RS)-1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid α -(4-pyridyl)-benzyl amide and hydrogen sulfide as described in example 1/4 to give the desired product in 78 % yield. MS: 507.1 ($M+H^+$).

5.) 4-({[1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carbonyl]-amino}-phenyl-methyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

[0212] This compound was prepared from (RS)-4-methoxy-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid α -(4-pyridyl)-benzyl amide, methyl iodide, and ammonium acetate as described in example 1/5. The crude material was purified by flash chromatography on silica gel first using dichloromethane/methanol/trifluoroacetic acid 9:1:0.2 to give a product described in example 54 and second 5:1:0.2 to give the desired product (20 % yield). M.p. 135°C. MS: 504.2 (M^+).

Example 25:

[0213] 1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (2-(4-hydroxyphenyl)-ethyl) amide trifluoroacetic acid salt



1.) 1-(3-Cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (2-(4-hydroxyphenyl)-ethyl) amide

[0214] This compound was prepared from 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (example 17/2) and 4-(2-aminoethyl)-phenol by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with dichloromethane/methanol 19:0.1 to give the desired product as an oil in 74 % yield. MS: 426 ($M+H^+$).

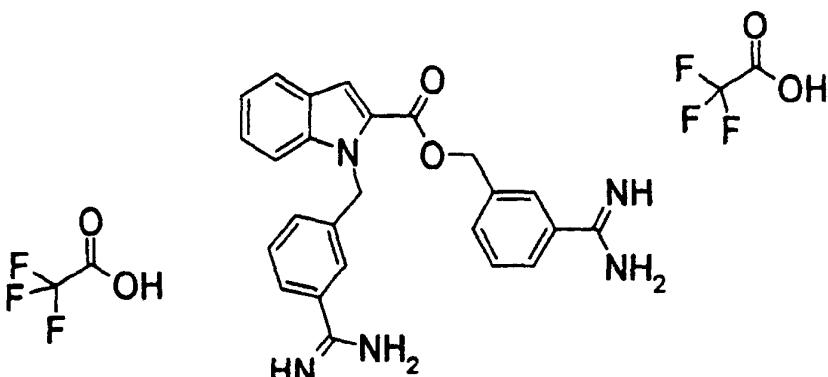
2.) 1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (2-(4-hydroxy-phenyl)-ethyl) amide trifluoroacetic acid salt

[0215] This compound was prepared from 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (2-(4-hydroxy-phenyl)-ethyl)-amide by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by reversed phase chromatography on RP₁₈ material with dichloromethane/methanol/trifluoroacetic acid 19:1.4:0.1 to give the desired product in 62 % yield. M.p. 140-142°C. MS: 443.3 ($M+H^+$).

Example 26: (Reference)

[0216] 1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid 3-amidino-benzyl ester trifluoroacetic acid salt

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20 1.) 1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid 3-cyano-benzyl ester

[0217] This compound was prepared from 1H-indole-2-carboxylic ethyl ester and 3-cyano-benzyl bromide by using sodium hydride as described in example 21/1, but it was done at 100°C instead of room temperature. The crude material was purified by flash chromatography on silica gel with heptane/ethylacetate 5:1 to give 67 % of 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester (fraction 1) and 10 % of the title compound (fraction 2). Yield: 10 %. M.p. 119-120°C. MS: 392.1 (M+H⁺).

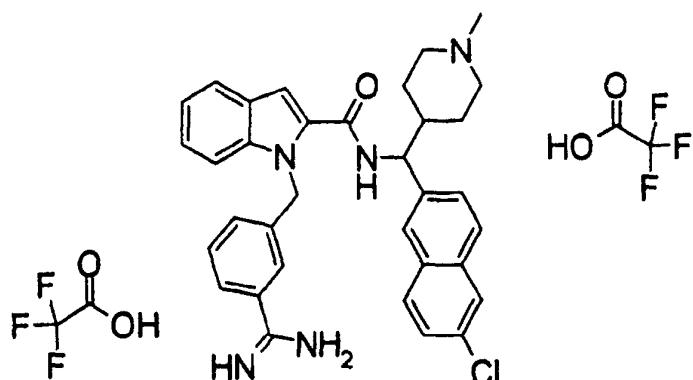
25 2.) 1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid 3-amidino-benzyl ester trifluoroacetic acid salt

30 [0218] This compound was prepared from 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 3-cyano-benzyl ester by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by MPLC on RP₁₈ material with water/ethanol/trifluoroacetic acid 7:3:0.1 to give the desired product in 12 % yield. M.p. 258°C. MS: 426.2 (M+H⁺).

35 Example 27:

[0219] (RS)-1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid ((6-chloro-2-naphthyl)-(1-methyl-piperidin-4-yl)-methyl) amide trifluoroacetic acid salt

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55 1.) (RS)-1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid ((6-chloro-2-naphthyl)-(1-methyl-piperidin-4-yl)-methyl) amide

[0220] This compound was prepared from 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2) and (RS)

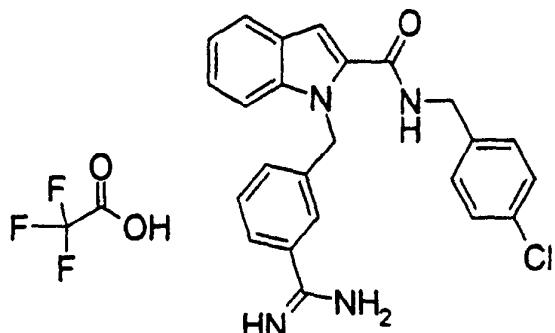
-(6-chloro-2-naphthyl)-(1-methyl-piperidin-4-yl)-methyl amine by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with dichloromethane/methanol 19:2 to give the desired product in 58 % yield. M.p. 141-145°C. MS: 547.2 (M+H⁺).

- 5 2.) (RS)-1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid ((6-chloro-2-naphthyl)-(1-methyl-piperidin-4-yl)-methyl) amide trifluoroacetic acid salt

[0221] This compound was prepared from (RS)-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ((6-chloro-2-naphthyl)-(1-methyl-piperidin-4-yl)-methyl) amide by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 5:5:0.1 to give the desired product in 31 % yield. M.p. 110-120°C. MS: 564.2 (M+H⁺).

Example 28:

- 15 [0222] 1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid 4-chloro-benzyl amide trifluoroacetic acid salt



- 1.) 1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid 4-chloro-benzyl amide

[0223] This compound was prepared from 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 1/2) and 4-chloro-benzyl amine by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with toluene/ethanol 19:0.065 to give the desired product in 80 % yield. M.p. 147-149°C. MS: 400.1 (M+H⁺).

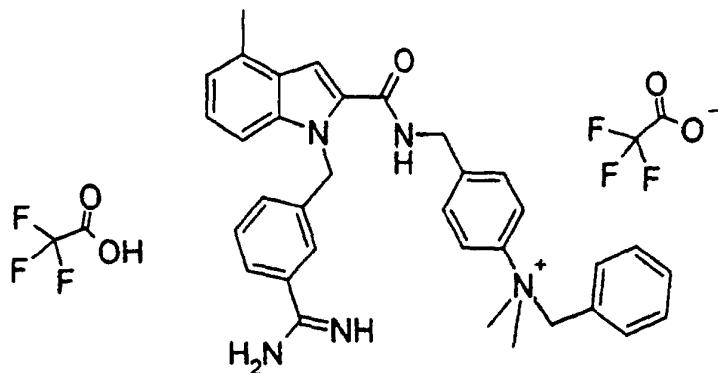
- 2.) 1-(3-Amidino-benzyl)-1H-indole-2-carboxylic acid 4-chloro-benzyl amide trifluoroacetic acid salt

[0224] This compound was prepared from 1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-chloro-benzyl amide by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 7:3:0.1 to the desired product in 74 % yield. M.p. 230°C (dec.). MS: 439.3 (M+H⁺).

Example 29:

- [0225] 4-({[1-(3-Amidino-benzyl)-4-methyl-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-benzyl-dimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid ethyl ester

[0226] This compound was prepared from 4-methyl-1H-indole-2-carboxylic acid ethyl ester and 3-cyano-benzyl bromide by using sodium hydride as described in example 21/1 to give the desired product in 70 % yield.

20 $^1\text{H-NMR}$ (DMSO-d_6 , 200 MHz): $\delta = 1.29$ (t, 3H, OCH_2CH_3); 2.52 (s, 3H, CH_3); 4.29 (q, 2H, OCH_2CH_3); 5.88 (s, 2H, N-CH_2); 6.97 (d, 1H, aromatic H); 7.12-7.32 (m, 2H, aromatic H); 7.34-7.55 (m, 4H, aromatic H); 7.69 (d, 1H, aromatic H).

25
2.) 1-(3-Cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid

25 **[0227]** This compound was prepared from 1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid ethyl ester and sodium hydroxide as described in example 1/2 to give the desired product in 99 % yield. M.p. 227-229°C. MS: 291.1 (M+H^+).

30
3.) 1-(3-Cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide

30 **[0228]** This compound was prepared from 1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid and 4-(dimethylamino)-benzylamine by using diphenylphosphoryl azide and diisopropylethylamine as described in example 3/1. The crude material was purified by flash chromatography on silica gel with dichloromethane/methanol 19:0.05 to give the desired product in 78 % yield. $^1\text{H-NMR}$ (DMSO-d_6 , 200 MHz): $\delta = 2.50$ (s, 3H, CH_3); 2.85 (s, 6H, $\text{N}(\text{CH}_3)_2$); 4.32 (d, 2H, NH-CH_2); 5.92 (s, 2H, N-CH_2); 6.68 (m, 2H, AA'BB'-System); 6.91 (d, 1H, aromatic H); 7.09 (m, 2H, AA'BB'-System); 7.15 (m, 2H, aromatic H); 7.27-7.40 (m, 3H, aromatic H); 7.48 (t, 1H, aromatic H); 7.50 (s, 1H, aromatic H); 7.69 (d, 1H, aromatic H); 9.01 (t, 1H, NH).

40
4.) Benzyl-[4-(1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carbonyl)-amino]-methyl]-phenyl]-dimethyl-ammonium bromide

45 **[0229]** This compound was prepared from 1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide and benzyl bromide as described in example 20/1 to give the desired product in 90 % yield. MS: 513.3 (M^+).

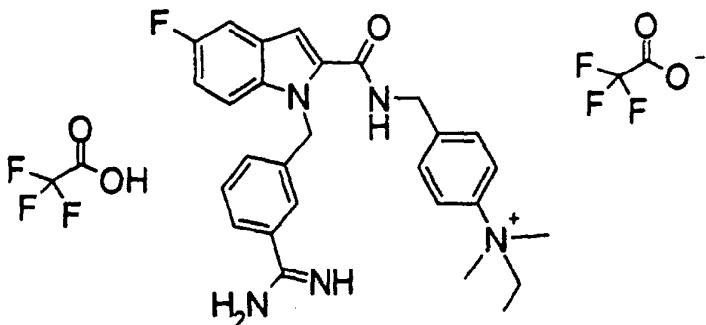
50
5.) 4-(1-(3-Amidino-benzyl)-4-methyl-1H-indole-2-carbonyl)-amino]-methyl]-phenyl]-benzyl-dimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

55 **[0230]** This compound was prepared from benzyl-[4-(1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carbonyl)-amino]-methyl]-phenyl]-dimethyl-ammonium bromide by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 7:3:0.1 to give the desired product in 60 % yield. M.p. 113°C (dec.). MS: 530.2 (M^+).

Example 30:

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[0231] [4-(1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl)-amino]-methyl]-phenyl]-ethyl-dimethyl-ammonium trifluoroacetate trifluoroacetic acid salt



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- 15 1.) 1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid ethyl ester

[0232] This compound was prepared from 5-fluoro-1H-indole-2-carboxylic acid ethyl ester (5 g, 24 mmol), sodium hydride (695 mg, 29 mmol), 3-cyano-benzyl bromide (5.678 g, 29 mmol), and N,N-dimethylformamide (50 ml). The indole was dissolved in N,N-dimethylformamide and sodium hydride was added in portions and the reaction mixture was stirred for 90 min. Then the nitrile was added. After stirring for 3 h and standing overnight the mixture was partitioned between sodium bicarbonate solution (5 % in water) and methyl tert-butyl ether. The organic layer was dried, evaporated, and purified by flash chromatography on silica gel with dichloromethane/heptane 1:1 to give 5.524 g (71 %) of the desired product. M.p. 94-96°C. MS: 323.1 (M+H⁺).

- 25 2.) 1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid

[0233] This compound was prepared from 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid ethyl ester (5.48 g, 17 mmol), sodium hydroxide (7.9 g, 198 mmol), methanol (600 ml), and water (33.4 ml) analogously to example 1/2. The crude material obtained after drying and evaporating the organic layer was purified by flash chromatography on silica gel with dichloromethane/methanol 19:1 to give 4.679 g (94 %) of the desired product. M.p. 253°C (dec.). MS: 295.0 (M+H⁺).

- 35 3.) 1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide

[0234] This compound was prepared from 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid (1.0 g, 3.4 mmol), diphenylphosphoryl azide (955 µl, 1.3 equivalents), N,N-diisopropylethylamine (2.02 ml, 3.5 equivalents), 4-(dimethylamino)-benzylamine dihydrochloride (849 mg, 1.1 equivalents), and N,N-dimethylformamide (40 ml) as described in example 3/1. Purification was done by flash chromatography on silica gel with dichloromethane/methanol 19:0.1. Yield: 1.22 g (84 %).

[0235] ¹H-NMR (DMSO-d₆, 200 MHz): δ = 2.85 (s, 6H, N(CH₃)₂); 4.32 (d, 2H, NH-CH₂); 5.91 (s, 2H, N-CH₂); 6.65 (m, 2H, AA'BB'-System); 7.13-7.00 (m, 2H, AA'BB'-System); 7.15 (d, 1H, aromatic H); 7.20 (s, 1H, aromatic H); 7.32 (d, 1H, aromatic H); 7.53-7.40 (m, 3H, aromatic H); 7.58 (m, 1H, aromatic H); 7.71 (m, 1H, aromatic H); 9.10 (t, 1H, NH).

- 45 4.) [4-({[1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-ethyl-dimethyl-ammonium iodide

[0236] This compound was prepared from 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide and ethyl iodide as described in example 20/1 to give the desired product in 74 % yield. MS: 455.3 (M⁺).

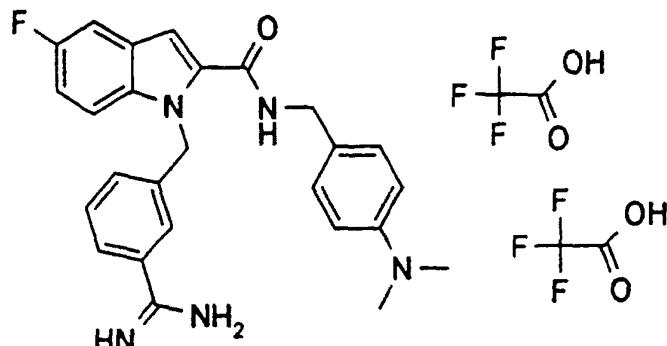
- 50 5.) [4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-ethyl-dimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

[0237] This compound was prepared from [4-({[1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-ethyl-dimethyl-ammonium iodide by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 7:3:0.1 to give the desired product in 28 % yield. M.p. 73-75°C (dec.). MS: 472.3 (M⁺).

Example 31:

[0238] 1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide trifluoroacetic acid salt

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[0239] This compound was prepared from 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid 4-(dimethylamino)-benzyl amide (example 30/3), hydrogen chloride, and liquid ammonia analogously to example 19/3. Yield: 59 %. M.p. 90°C (dec.). MS: 444.2 ($M+\text{H}^+$).

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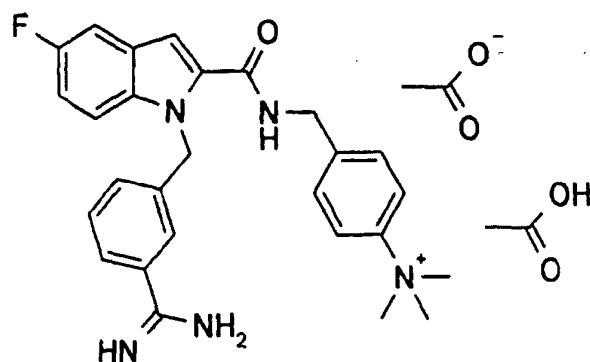
Example 32:

[0240] [4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium acetate acetic acid salt

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40



45

1.) [4-({[1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium iodide

[0241] Starting from 5-fluoro-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide (example 30/3) the compound was prepared by alkylation with methyl iodide analogously to example 20/1. Yield: 90 %. M.p. 203-205°C. MS: 441.2 (M^+).

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2.) [4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium acetate acetic acid salt

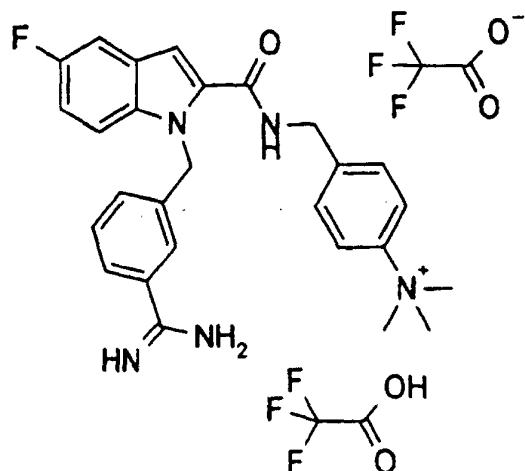
55

[0242] This compound was prepared from [4-({[1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium iodide, hydrogen chloride, and liquid ammonia analogously to example 19/3. Instead of trifluoroacetic acid acetic acid was used for chromatography. Yield: 74 %. M.p. 172°C (dec.). MS: 458.2 (M^+).

Example 33:

[0243] [4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

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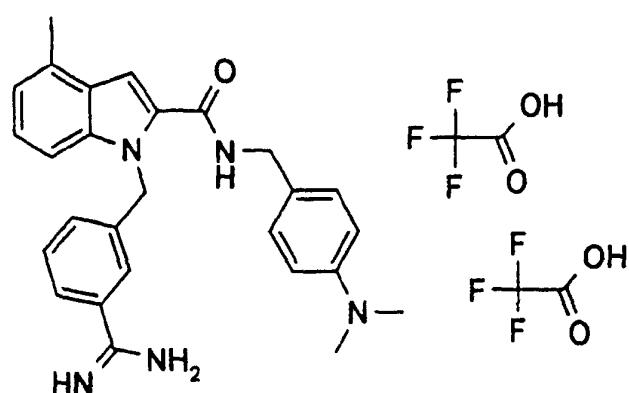
45

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[0244] [4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium acetate acetic acid salt (32/2) was dissolved in water/ethanol/trifluoroacetic acid 1:1:0.1. The product was separated by flash chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 1:1:0.1 to give the trifluoroacetic acid salt in 100 % yield. M.p.120-124°C. MS: 458.2 (M⁺).

Example 34:

[0245] 1-(3-(Amidino-benzyl)-4-methyl-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide trifluoroacetic acid salt

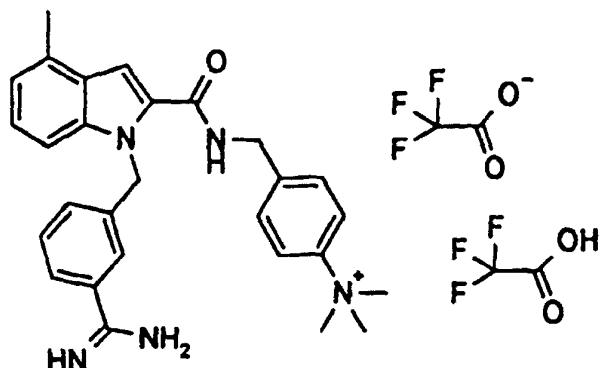


[0246] The starting material 1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid (4-dimethylamino)-benzylamide (example 29/3) was treated analogously to example 19/3. Yield: 46 %. M.p. 106°C (dec.). MS: 440.3 (M+H⁺).

Example 35:

[0247] [4-({[1-(3-Amidino-benzyl)-4-methyl-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

5



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[0248] The starting material was 1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide (example 29/3). All steps were prepared analogously to example 20/1 and 1913. Yield (last step): 45 %. M.p. 81°C (dec.).
MS: 454.3 (M^+).

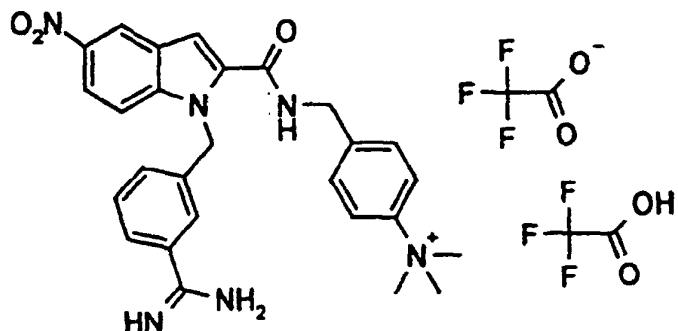
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Example 36: (Reference)

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[0249] [4-({[1-(3-Amidino-benzyl)-5-nitro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

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[0250] The starting material was 5-nitro-1H-indole-2-carboxylic acid ethyl ester. All steps were prepared analogously to examples 21/1, 1/2, 3/1, 20/1 and 19/3. Yield (last step): 52 %. M.p. 120°C (dec.). MS: 485.3 (M^+).

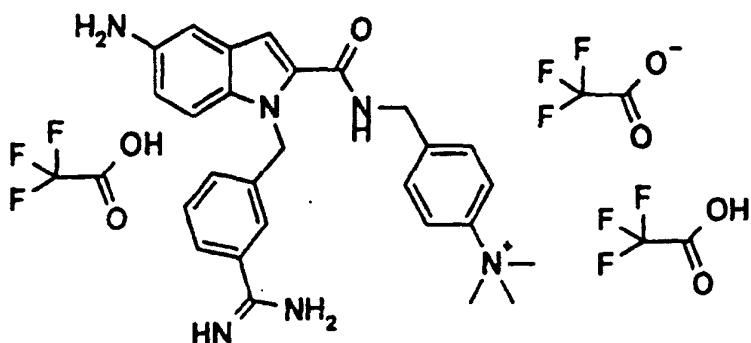
Example 37:

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[0251] [4-({[1-(3-Amidino-benzyl)-5-amino-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

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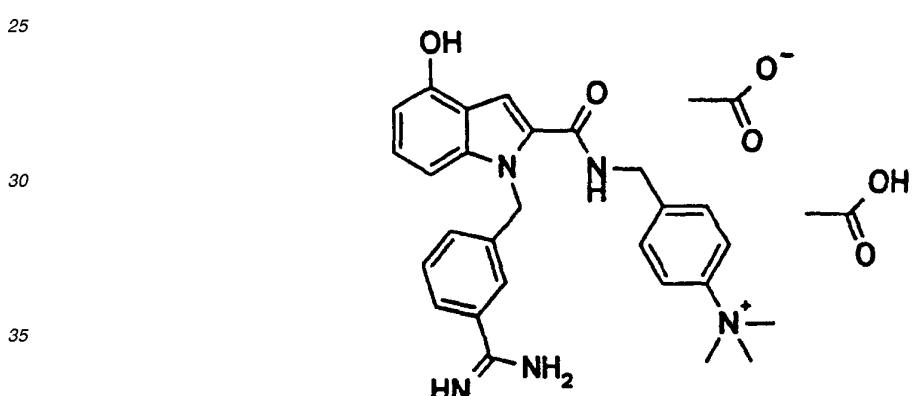
55



15 [0252] This compound was prepared from [4-({[1-(3-amidino-benzyl)-5-nitro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt (example 36) by hydrogenation in ethanol with 3 equivalents of acetic acid, catalyzed by Pd/C (10 %). Yield: 70 %. M.p. 114°C (dec.). MS: 455.3 (M^+).

Example 39:

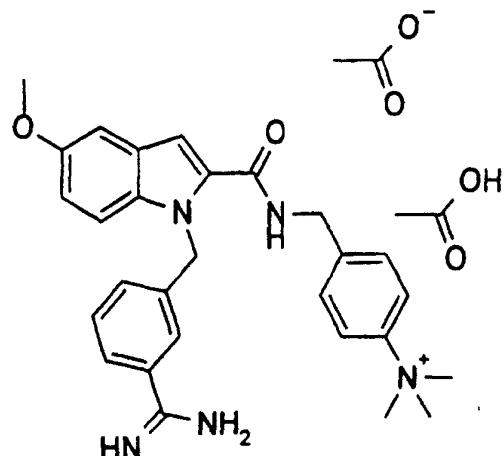
20 [0253] [4-({[1-(3-Amidino-benzyl)-4-hydroxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium acetate acetic acid salt



40 [0254] The starting material was 4-benzyloxy-1H-indole-2-carboxylic acid ethyl ester. All intermediates were prepared analogously to examples 21/1, 1/2, 3/1 and 20/1. In the last step hydrogen chloride gas was bubbled into a solution of 4-benzyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester and ethanol for 4 hours at 0°C. The mixture was warmed up to room temperature overnight and evaporated. The residue was dissolved in 10 ml ethanol and liquid ammonia was added. The mixture was allowed to warm up to room temperature during stirring and concentrated. The crude material was purified by flash chromatography on RP₁₈ material with water/ethanol/acetic acid 7:3:0.1. Yield (last step): 57 %. M.p. 113°C (dec.). MS: 456.3 (M^+).

Example 40:

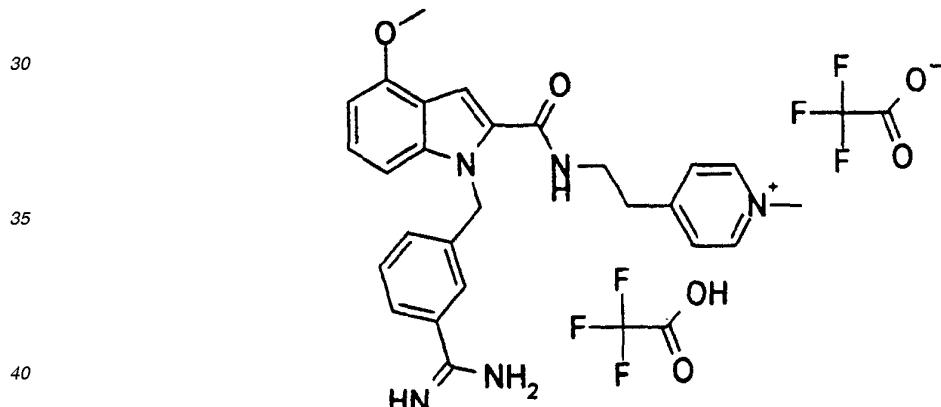
50 [0255] [4-({[1-(3-Amidino-benzyl)-5-methoxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium acetate acetic acid salt



20 [0256] The starting material was 5-methoxy-1H-indole-2-carboxylic acid ethyl ester. All steps were prepared analogously to examples 21/1, 1/2, 3/1, 2011 and 19/3. Yield (last step): 74 %. M.p. 94°C (dec.). MS: 470 (M⁺).

Example 41:

25 [0257] 4-(2-{{[1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carbonyl]-amino}-ethyl}-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

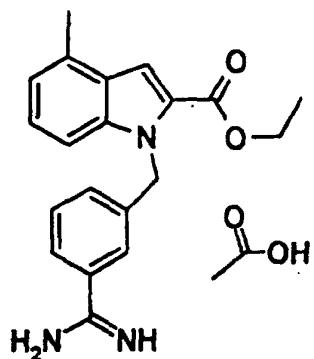


45 [0258] The starting material was 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (example 17/2). All steps were prepared analogously to examples 3/1, 20/1 and 19/3, but the amine in step 3/1 was 4-(2-aminoethyl)-pyridine instead of 4-(dimethylamino)-benzylamine dihydrochloride and to the solvent in step 20/1 dimethylsulfoxide was added. Yield (last step): 83 %.
M.p. 164°C (dec.). MS: 442.3 (M⁺).

50 Example 42: (Reference)

[0259] 1-(3-Amidino-benzyl)-4-methyl-1H-indole-2-carboxylic acid ethylester acetic acid salt

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- 1.) 4-Methyl-1H-indole-2-carboxylic acid 3-cyano-benzyl ester

[0260] The starting material was 4-methyl-1H-indole-2-carboxylic acid. Alkylation with 3-cyano-benzylbromide (analogously to example 19/1, but the solvent was dimethylformamide instead of tetrahydrofuran) gave 4-methyl-1H-indole-2-carboxylic acid 3-cyano-benzyl ester. Yield: 75 %. MS: 291.1 ($M+H^+$).

- 2.) 1-(3-Cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid 3-cyano-benzyl ester

[0261] The alkylation of 4-methyl-1H-indole-2-carboxylic acid 3-cyano-benzyl ester with 3-cyano-benzyl bromide was done analogously to example 21/1. Yield: 90 %.
MS: 406.1 ($M+H^+$).

- 3.) 1-(3-Amidino-benzyl)-4-methyl-1H-indole-2-carboxylic acid ethyl ester acetic acid salt.

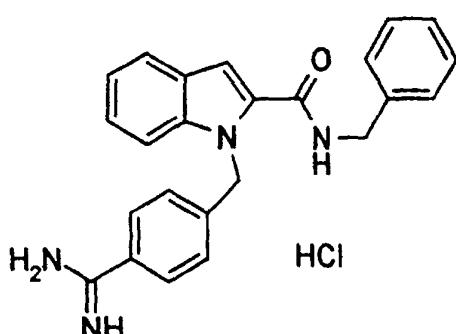
[0262] This compound was prepared from 1-(3-cyano-benzyl)-4-methyl-1H-indole-2-carboxylic acid 3-cyano-benzyl ester by using hydrogen chloride and liquid ammonia as described in example 19/3. The crude material was purified by flash chromatography on RP₁₈ material with water/ethanol/acetic acid 4:1:0.2 to give a fraction containing in a yield of 7 % the compound described in example 63 and a fraction containing in a yield of 16 % the title compound of this example. M.p. 187°C (dec.). MS: 336.2 ($M+H^+$).

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Example 43:

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[0264] A solution of 10 g (53 mmol) 1H-indole-2-carboxylic acid ethyl ester in 80 ml of dimethylformamide was treated with 10.95 g (79 mmol) of potassium carbonate. The mixture was stirred at room temperature for 10 minutes. 3-Cyano-benzyl bromide, 15.47 g (79 mmol), was added and the mixture was heated to 100°C. After 4 hours at that temperature, it was cooled to room temperature, acidified with acetic acid (pH 5-6) and poured on ice-water. The product was ex-

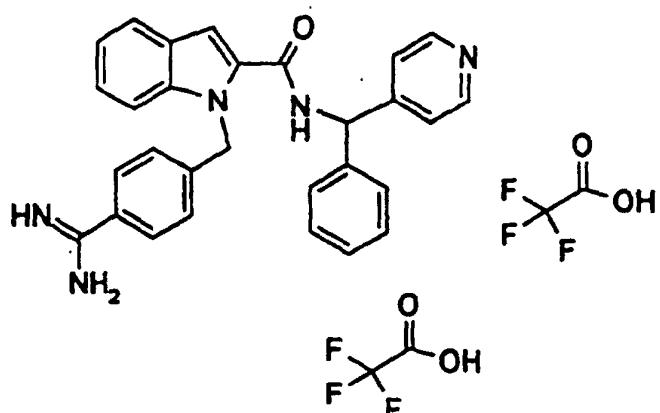
tracted with methylene chloride. The organic layer was dried and evaporated. The residue was crystallized from 2-propanol to give 9.8 g of the desired product. Yield 61 %. M.p. 214°C. MS: 305.1 (M+H⁺)

[0265] The following steps were prepared analogously to examples 1/2, 3/1 and 19/3, but the amino in step 3/1 was benzylamine instead of 4-(dimethylamino)-benzylamine dihydrochloride. Yield (last step): 35 %. M.p. 266-268°C (dec.).

5 MS: 383.2
(M+H⁺).

Example 44:

10 [0266] (RS)-1-(4-Amidino-benzyl)-1H-indole-2-carboxylic acid α -(4-pyridyl)-benzyl amide trifluoroacetic acid salt

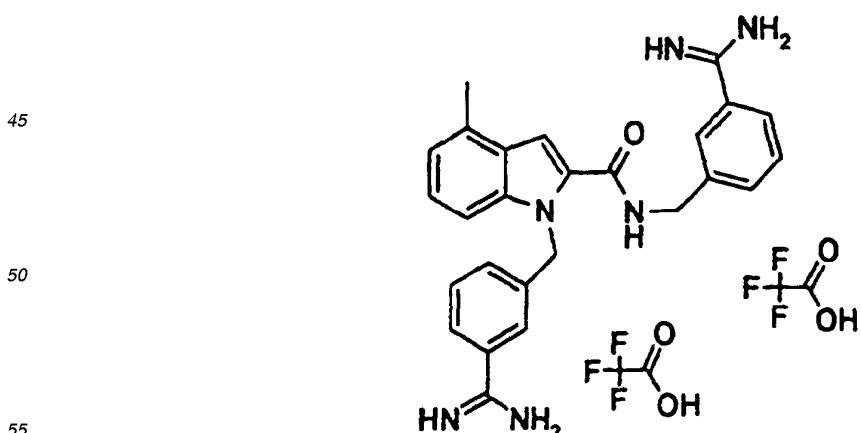


30 [0267] This compound was prepared from 1H-indole-2-carboxylic acid ethyl ester analogously to example 43. All steps were prepared analogously to examples 1/2, 3/1 and 19/3, but the amine in step 3/1 was (RS)- α -(4-pyridyl)-benzylamine dihydrochloride instead of 4-(dimethylamino)-benzylamine dihydrochloride. Yield (last step): 70 %. M.p. 150°C. MS: 460.3 (M+H⁺).

35 Example 47:

[0268] 1-(3-Amidino-benzyl)-4-methyl-1H-indole-2-carboxylic acid 3-amidino-benzyl amide trifluoroacetic acid salt

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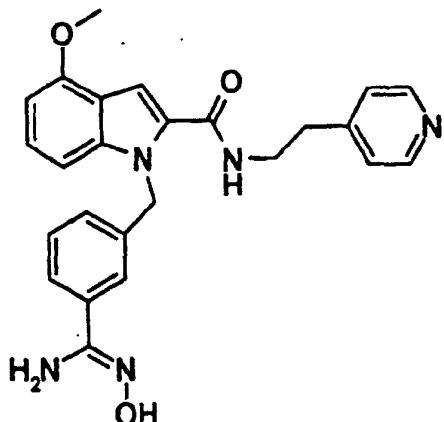
[0269] This compound was prepared from 1-(3-cyano benzyl)-4-methyl-1H-indole-2-carboxylic acid (example 29/2)

analogously to examples 3/1 and 19/3, but the amine in step 3/1 was 3-cyano-benzylamine hydrobromide instead of 4-(dimethylamino)-benzylamine dihydrochloride. Yield (last step): 25 %.
M.p. 242-243°C. MS: 439.3 (M+H⁺).

5 Example 49: (Reference)

[0270] 1-(3-Hydroxyamidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 2-(4-pyridyl)-ethyl amide

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[0271] The starting material 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 2-(4-pyridyl)-ethyl amide (example 41) was dissolved in ethanol, 2.4 equivalents of hydroxylamine hydrochloride and 2.4 equivalents of triethylamine were added and the mixture was refluxed for 6.5 h. The precipitate was filtered off to give 54 % of the desired product. M.p. 220-222°C. MS: 444.3 (M+H⁺).

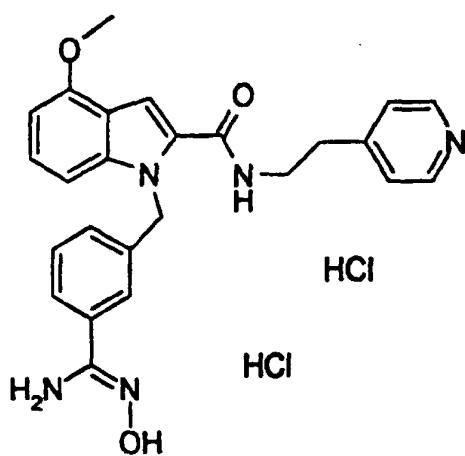
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Example 50: (Reference)

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[0272] 1-(3-Hydroxyamidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid-2-(4-pyridyl)-ethyl amide bishydrochloride

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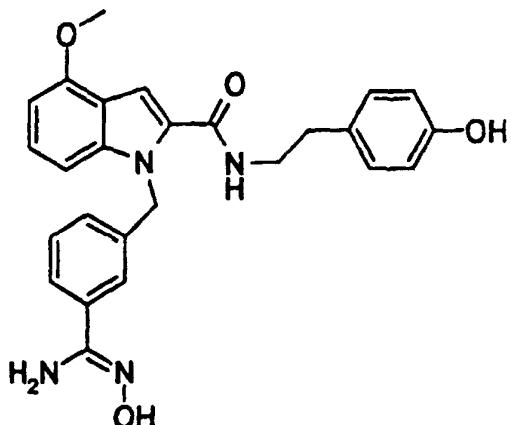
55

[0273] The starting material, 1-(3-hydroxyamidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 2-(4-pyridyl)-ethyl amide (example 49), was dissolved in 0.1 N hydrochloric acid, concentrated in vacuo, dissolved in water again and lyophilized. Yield: 66 %. M.p. 215-217°C. MS: 444.3 (M+H⁺).

Example 51: (Reference)

[0274] 1-(3-Hydroxyamidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 2-(4-hydroxy-phenyl)-ethyl amide

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[0275] The starting material 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 2-(4-hydroxyphenyl)-ethyl amide (example 25/1) was dissolved in ethanol and hydroxylamine hydrochloride and triethylamine were added. After reflux for 5 h the reaction mixture was concentrated in vacuo and partitioned between dichloromethane and water. The organic layer was separated, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with dichloromethane/methanol 19:1 to give 63 % of the desired product, which solidified underwater. M.p. 173-175°C (dec.). MS: 459.3 (M+H⁺).

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Example 52: (Reference)

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[0276] 1-(3-Hydroxyamidino-benzyl)-5-chloro-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide

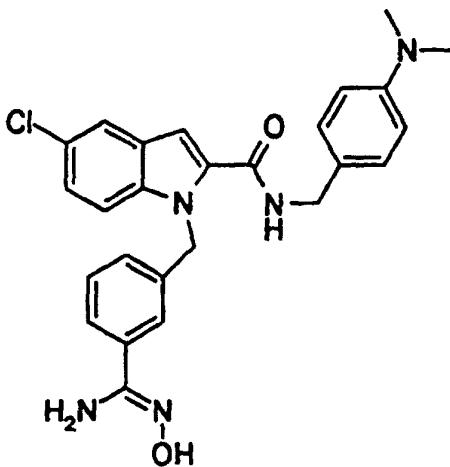
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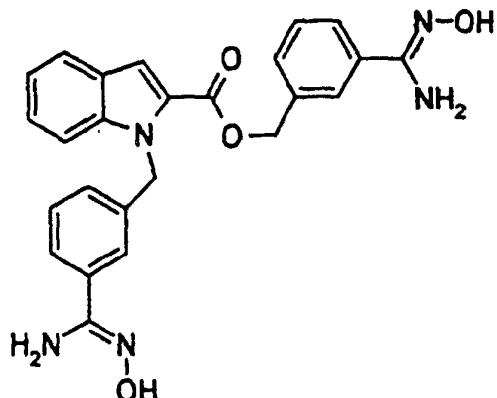
[0277] The starting material, 5-chloro-1H-indole-2-carboxylic acid ethyl ester, was treated analogously to example 21/1. All intermediates were prepared analogously to example 1/2 and 3/1. The title compound was prepared analogously to example 49. Purification by flash chromatography on silica gel with dichloromethane/methanol 19:0.6 gave a mixture of two compounds, the title compound and an unknown compound which were separated by HPLC. Yield (last step): 6 %. M.p. 200°C (dec.). MS: 476.1 (M+H⁺).

Example 53: (Reference)

[0278] 1-(3-Hydroxyamidino-benzyl)-1H-indole-2-carboxylic acid (3-hydroxyamidino-benzyl)ester

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[0279] 1-(3-Cyano-benzyl)-1H-indole-2-carboxylic acid 3-cyano-benzyl ester (example 26/1) was dissolved in ethanol, 3 equivalents of hydroxylamine were added, and the mixture was refluxed for 3 h. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and concentrated in vacuo. The compound was purified by flash chromatography on silica gel with dichloromethane/methanol 20:1 to give 76 % of the desired product. M.p. 114-116°C. MS: 458.2 ($M+H^+$).

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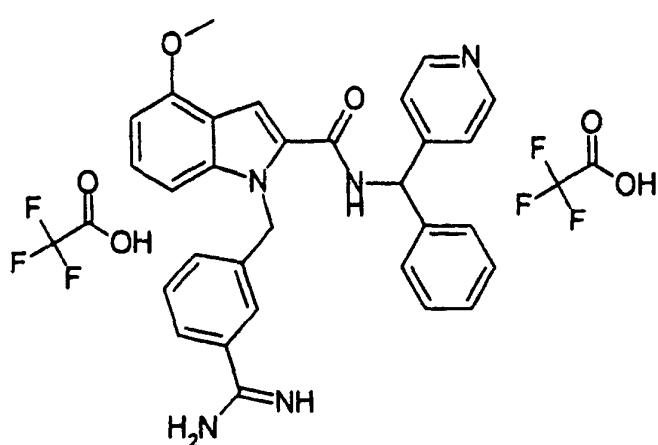
Example 54:

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[0280] (RS)-1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid α -(4-pyridyl-benzyl) amide trifluoroacetic acid salt

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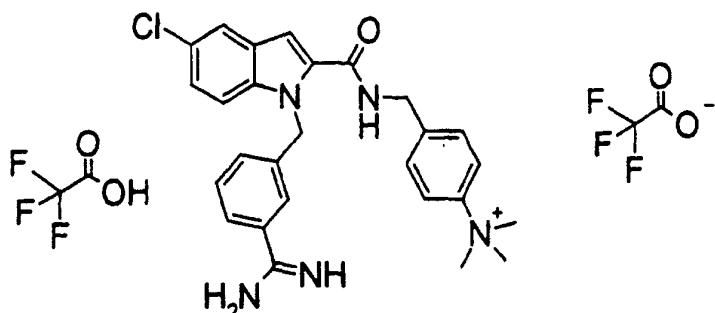
[0281] This compound was a by-product of the reactions described in example 24. Purification by flash chromatography on silica gel with dichloromethane/methanol/trifluoroacetic acid 9:1:0.2 gave 3 % of the title compound. M.p. 105°C. MS: 490.2 ($M+H^+$).

Example 55:

[0282] [4-({[1-(3-Amidino-benzyl)-5-chloro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trif-

luoroacetate trifluoroacetic acid salt

5



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[0283] The starting material, 5-chloro-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (4-dimethylaminobenzyl)amide (example 52) was reacted analogously to example 1/4 and 1/5. Yield (last 2 steps): 8 %. M.p. 112°C (dec.). MS: 474.2 (M⁺).

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Example 56:

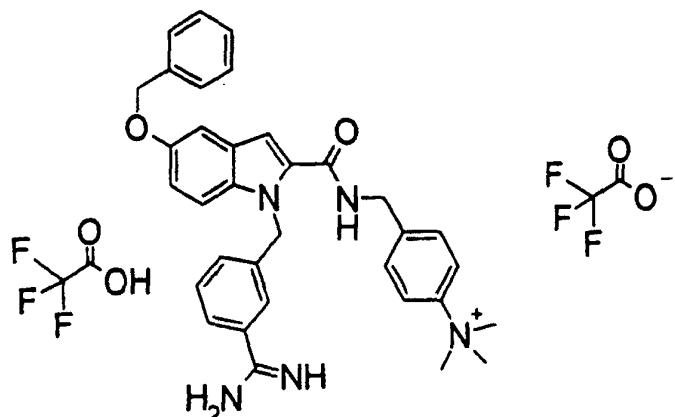
[0284] [4-({[5-Benzyl-1-(3-amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

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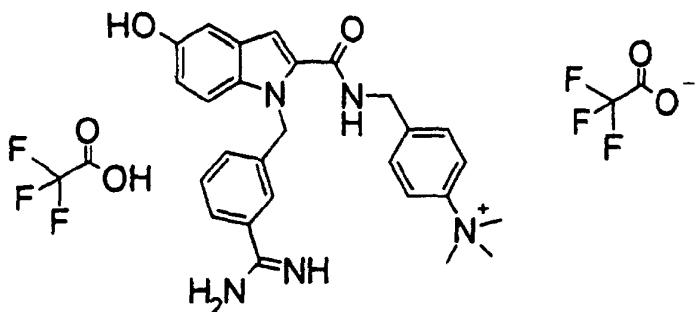
[0285] This compound was prepared from 5-benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (example 21/2), 4-(dimethylamino)-benzylamine dihydrochloride, diphenylphosphoryl azide, and diisopropylethylamine analogously to example 3/1, hydrogen sulfide analogously to example 1/4, and methyl iodide in acetone analogously to example 1/5. Yield (last step): 52 %. M.p. 60°C (dec.). MS: 546.3 (M⁺).

Example 57:

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[0286] [4-({[1-(3-Amidino-benzyl)-5-hydroxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt

55



15 [0287] The starting material, [4-({[5-benzyloxy-1-(3-amidino-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt (example 56), was dissolved in ethanol, 2 equivalents of trifluoroacetic acid and Pd/C (10 %) were added and the mixture was hydrogenated. The reaction mixture was concentrated and purified by flash-chromatography on silica gel with dichloromethane/methanol/trifluoroacetic acid 9:1: 0.1. The product was concentrated and lyophilized to give 53 % of the desired product. M.p. 78°C (dec.). MS: 456.4 (M⁺).

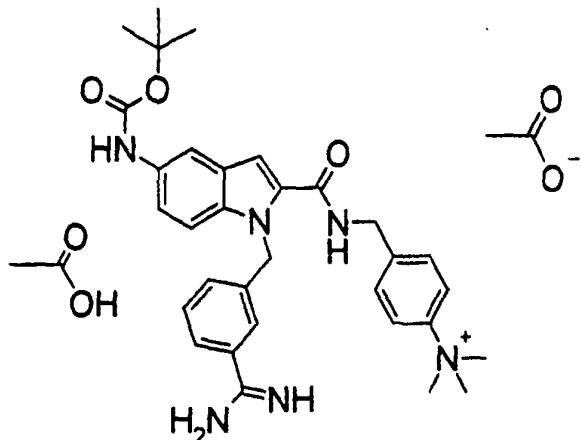
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Example 58:

[0288] [4-({[1-(3-Amidino-benzyl)-5-tert-butoxycarbonylamino-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium acetate acetic acid salt

25

30



45 1.) 5-(tert-Butoxycarbonylamino)-1-(3-thiocarbamoyl)-benzyl)-1H-indole-2-carboxylic acid 4-(dimethylamino)-benzyl amide

50 [0289] The starting material, 1-(3-cyano-benzyl)-5-nitro-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide (example 36), was treated with hydrogen sulfide gas analogously to example 1/4. The resulting compound was dissolved in ethanol, 2 equivalents of di-tert-butyl-dicarbonate, and 3 equivalents of sodium bicarbonate were added and the mixture was stirred at room temperature for 10 h. The reaction mixture was concentrated and then partitioned between dichloromethane and citric acid (0.1 % in water). The organic layer was dried over magnesium sulfate concentrated, and purified by flash chromatography on silica gel with dichloromethane/methanol 20:0.2 to give 43 % of the desired product. MS: 558.4 (M+H⁺).

55 2.) [4-({[1-(3-Amidino-benzyl)-5-tert-butoxycarbonylamino-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium acetate acetic acid salt

[0290] This compound was prepared analogously to example 1/5 but the solvent for the methylation was pure ace-

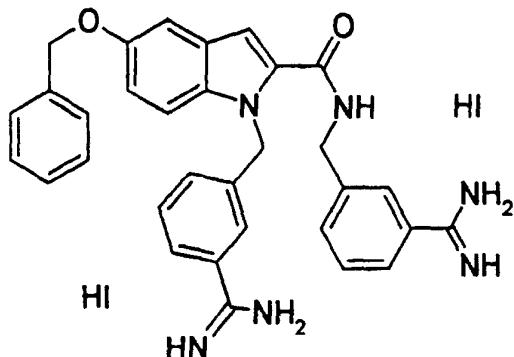
tone. The crude product was purified by flash chromatography on RP₁₈-material with ethanol/water/trifluoroacetic acid 1:1:0.1 to give 55 % of the desired product. M.p. 146°C (dec.). MS: 555 (M⁺).

Example 59:

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[0291] 1-(3-Amidino-benzyl)-5-benzyloxy-1H-indole-2-carboxylic acid 3-amidino-benzylamide dihydroiodide

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1.) 5-Benzylbenzylamido-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid

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[0292] This compound was prepared from 5-benzyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (500 mg, 1.3 mmol, example 21/2), diphenylphosphoryl azide (370 µl, 1.7 mmol), N,N-diisopropylethylamine (440 µl, 2.6 mmol), and 3-cyano-benzyl amine hydrobromide (312 mg, 1.5 mmol) in N, N-dimethylformamide (10 ml) as described in example 3/1. The purification by flash chromatography on silica gel was done with dichloromethane to give 451 mg (69 %) of the desired product.

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2.) 5-Benzylbenzylamido-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 3-thiocarbamoyl-benzylamide

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[0293] This compound was prepared from 5-benzyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 3-cyano-benzylamide (451 mg, 0.9 mmol), pyridine (6.67 ml, 83 mmol), triethylamine (5.41 ml, 39 mmol), and hydrogen sulfide as described in example 1/4. The purification by flash chromatography on silica gel was done with dichloromethane/methanol 19:0.15 to give 138 mg (27 %) of the desired product.

40

3.) 1-(3-Amidino-benzyl)-5-benzyloxy-1H-indole-2-carboxylic acid 3-amidino-benzylamide dihydroiodide

45

[0294] 5-Benzylbenzylamido-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 3-thiocarbamoyl-benzylamide (138 mg, 0.24 mmol) was dissolved in 5 ml of acetone in a vial, the vial was sealed and methyl iodide (0.4 ml, 26 equivalents) was added via a syringe. The reaction mixture was stirred at room temperature. 4 days later the yellow precipitate was collected by filtration and washed with diethylether. The precipitate (188 mg, 0.22 mmol), acetic acid (0.15 ml, 12 equivalents), ammonium acetate (307 mg, 18 equivalents), and methanol (6 ml) were treated as described in example 1/5. The crude material was purified by flash chromatography on RP₁₈ material with ethanol/water/trifluoroacetic acid 1:1:0.1 to give 157 mg of the desired compound (90 %) after lyophilization. M.p. 138°C (dec.). MS: 531.3 (M+H⁺).

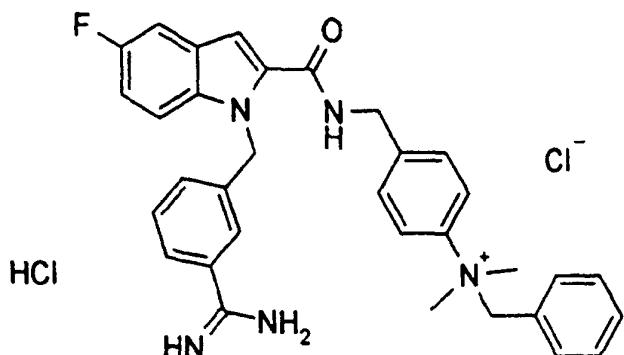
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Example 60:

[0295] [4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-benzyl-dimethyl-ammonium chloride hydrochloride

55

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10

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1.) Benzyl-[4-({[1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-dimethyl-ammonium bromide

20

[0296] This compound was prepared from 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide (840 mg, 1.97 mmol, example 30/3), benzyl bromide (237 µl, 1 equivalent), and acetone (8 ml) analogously to example 20/1, but the reaction temperature was kept at 50°C. The precipitate was filtered off to give 1.02 g of the desired product (87 %).

25

2.) [4-({[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-benzyl-dimethyl-ammonium chloride hydrochloride

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[0297] This compound was prepared from benzyl-[4-({[1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-dimethyl-ammonium bromide (200 mg, 0.335 mmol), ethanol, hydrogen chloride, and liquid ammonia analogously to example 19/3. Purification by reversed phase chromatography on RP₁₈ material (water/ethanol/acetic acid 7:3:0.1) followed by lyophilization gave 156 mg of the desired product (77 %). M.p. 136°C. MS: 534.4 (4 %, M⁺).

Example 61:

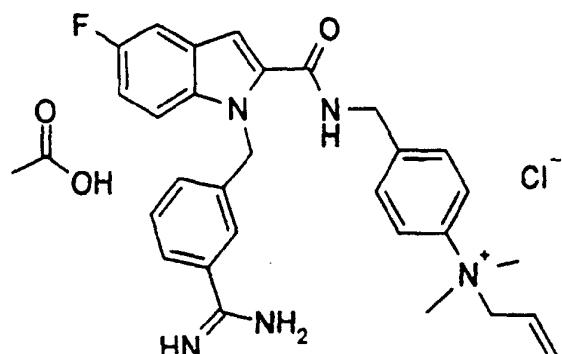
35

[0298] Allyl-[4-({[1-(3-amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-dimethyl-ammonium chloride acetic acid salt

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1.) Allyl-[4-({[1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-dimethyl-ammonium bromide

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[0299] This compound was prepared from 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid (4-dimethylamino)-benzyl amide (200 mg, 0.47 mmol, example 30/3), allyl bromide (81 µl, 2 equivalents), and acetone (3.5 ml). The reaction partners were mixed, the flask was closed and heated to 55°C. After 6 h the heating was stopped. Four weeks later another 1.06 ml allyl bromide were added, the flask was closed, and it was heated to 55°C again. After 3 weeks

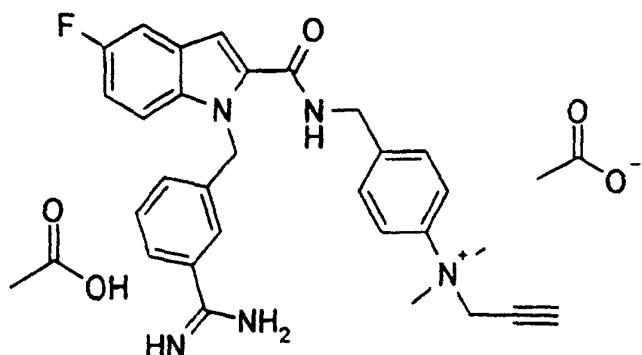
a white precipitate was filtered off, washed with diethylether, and dried in vacuo to give 222 mg of the desired product (86 %). M.p. 163-165°C.

2.) Allyl-[4-([[1-(3-amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino]-methyl)-phenyl]-dimethyl-ammonium
5 chloride acetic acid salt

[0300] This compound was prepared from allyl-[4-([[1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino]-me-
10 thyl)-phenyl]-dimethyl-ammonium bromide (222 mg, 0.406 mmol), ethanol (12 ml), hydrogen chloride, and liquid am-
monia analogously to example 19/3. The crude product was purified by chromatography on silica gel with dichlorometh-
15 ane/methanol/acetic acid 3:2:0.05 to 1:4:0.05. Lyophilization gave 131 mg of the desired product (56 %). M.p. 133°C
(dec.). MS: 484.3 (M⁺).

Example 62:

15 [0301] [4-([[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino]-methyl)-phenyl]-dimethyl-2-propynyl-am-
monium acetate acetic acid salt



1.) [4-([[1-(3-Cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino]-methyl)-phenyl]-dimethyl-2-propynyl-ammonium
35 bromide

[0302] This compound was prepared from 1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carboxylic acid (4-dimethylami-
no)-benzyl amide (200 mg, 0.47 mmol, example 30/3), propargylbromide (140 mg, 2 equivalents, 80 % in toluene),
40 and acetone (5 ml). The reaction partners were mixed, the flask was closed and heated to 50°C. After 5 h the heating
was stopped. After two days the mixture was concentrated in vacuo and the desired product was precipitated with
diethylether to yield 220 mg of a white solid (86 %).

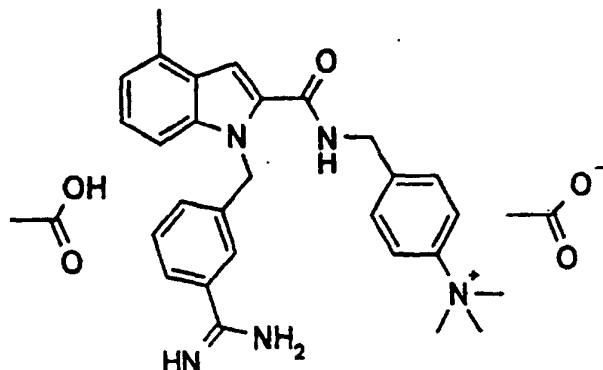
2.) [4-([[1-(3-Amidino-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino]-methyl)-phenyl]-dimethyl-2-propynyl-ammonium
acetate acetic acid salt

[0303] This compound was prepared from [4-([[1-(3-cyano-benzyl)-5-fluoro-1H-indole-2-carbonyl]-amino]-methyl)-
45 phenyl]-dimethyl-2-propynyl-ammonium bromide (220 mg, 0.406 mmol), ethanol (12 ml), hydrogen chloride, and liquid
ammonia analogously to example 19/3. The crude product was purified by chromatography on silica gel with dichlo-
romethane/methanol/acetic acid 3:2:0.05 to 1:4:0.05. Lyophilization gave 131 mg of the desired product (56 %). M.p.
109°C (dec.). MS: 482.3 (M⁺).

50 Example 64:

[0304] [4-([[1-(3-Amidino-benzyl)-4-methyl-1H-indole-2-carbonyl]-amino]-methyl)-phenyl]-trimethyl-ammonium ac-
55 etate acetic acid salt

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[0305] 10 g of ion exchange resin AG 1-X8 (Bio-Rad) were filled into a column, rinsed first with water, then with 1 N sodium acetate solution, and again with water. [4-([[1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid]-amino]-methyl)-phenyl]-trimethyl-ammonium trifluoroacetate trifluoroacetic acid salt (example 35) was dissolved in water and passed through the ion exchange column. After rinsing with 150 ml water, the solution was concentrated in vacuo to 25 ml, which were lyophilized to give 79 mg of the desired product (100 %). M.p. 89°C (dec.). MS: 454.3 (M^+).

20

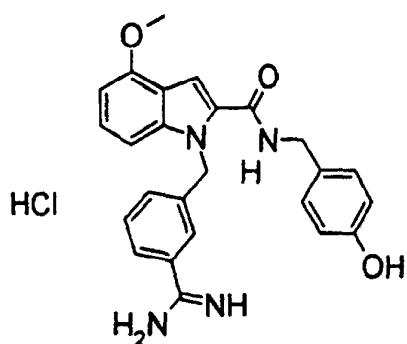
Example 65:

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[0306] 1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-hydroxy-benzyl amide hydrochloride

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1.) 1-(3-Cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-hydroxy-benzyl amide

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[0307] The title compound was prepared using 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (400 mg, 1.31 mmol; example 24/2), diphenylphosphoryl azide (365 μ l, 1.3 equivalents), N,N-diisopropylethylamine (850 μ l, 3.75 equivalents), and 4-aminomethyl-phenol (560 mg, 2.1 equivalents) in N,N-dimethylformamide (10 ml) as described in example 3/1.

45

2.) 1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-hydroxy-benzyl amide hydrochloride

50

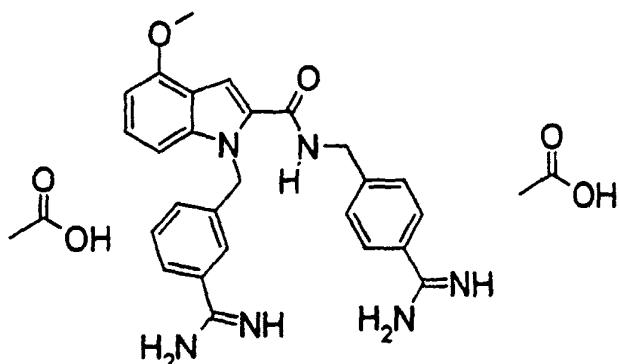
[0308] This compound was prepared from 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-hydroxy-benzyl amide (200 mg, 0.49 mmol), hydrogen chloride, and liquid ammonia analogously to example 19/3. Purification by reversed phase chromatography on RP₁₈ material with water/ethanol/acetic acid 7:3:0.1 and lyophilization gave 179 mg of the desired product (79 %). M.p. 202°C (dec.). MS: 429.2 (100 %; $M+H^+$).

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Example 66:

[0309] 1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-amidino-benzyl amide acetic acid salt

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1.) 1-(3-Cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-cyano-benzyl amide

[0310] The title compound was prepared using 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid (400 mg, 1.31 mmol; example 24/2), diphenylphosphoryl azide (365 µL, 1.3 equivalents), N,N-diisopropylethylamine (850 µL, 3.75 equivalents), and 4-aminomethyl-benzonitrile (585 mg, 2.1 equivalents) in N,N-dimethylformamide (10 mL) as described in example 3/1.

2.) 1-(3-Amidino-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-amidino-benzyl amide acetic acid salt

[0311] This compound was prepared from 1-(3-cyano-benzyl)-4-methoxy-1H-indole-2-carboxylic acid 4-cyano-benzyl amide (200 mg, 0.48 mmol), hydrogen chloride, and liquid ammonia analogously to example 19/3. Purification by reversed phase chromatography on RP₁₈ material with water/ethanol/acetic acid 1:1:0.1 followed by lyophilization gave 68 mg of the desired product (25 %). M.p. 186°C (dec.). MS: 228.1 ((M+2H⁺)/2).

30 Example 68:

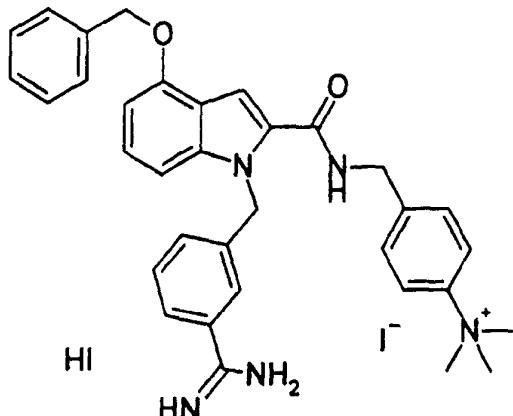
[0312] [4-({[1-(3-Amidino-benzyl)-4-benzyloxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium iodide hydroiodide

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1.) 4-Benzyl-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester

[0313] This compound was prepared from 4-benzyloxy-1H-indole-2-carboxylic acid ethyl ester (3 g, 10 mmol), sodium hydride (294 mg, 12 mmol), 3-cyano-benzyl bromide (2.4 g, 12 mmol), and N,N-dimethylformamide (20 mL) analogously to example 21/1. The reaction mixture was neutralized with 2 N hydrochloric acid and partitioned between water and methyl tert-butyl ether. The organic layer was dried, concentrated in vacuo, and purified by flash chromatography with dichloromethane/heptane 7:3 to give 2.914 g (71 %) of the desired product.

2.) 4-Benzylxyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid

[0314] This compound was prepared from 4-benzylxyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester (2.914 g, 7.1 mmol), sodium hydroxide (2.13 g, 53 mmol), methanol (175 ml), and water (8.95 ml) analogously to example 1/2. The reaction mixture was neutralized with 4 N hydrochloric acid. The white precipitate was collected by filtration, washed with water, and purified by flash chromatography on silica gel with dichloromethane/methanol 19:1 to give 2.147 g (79 %) of the desired product.

3.) 4-Benzylxyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-(dimethylamino)-benzylamide

[0315] This compound was prepared from 4-benzylxyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (400 mg, 1.05 mmol), diphenylphosphoryl azide (290 µl, 1.36 mmol), N,N-diisopropylethylamine (360 µl, 2.1 mmol), and 4-(dimethylamino)-benzylamine dihydrochloride (261 mg, 1.2 mmol) in N,N-dimethylformamide (10 ml) as described in example 3/1. The purification by flash chromatography on silica gel was done with dichloromethane/methanol 20:0.05 to give 347 mg (64 %) of the desired product.

4.) 4-Benzylxyloxy-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 4-(dimethylamino)-benzylamide

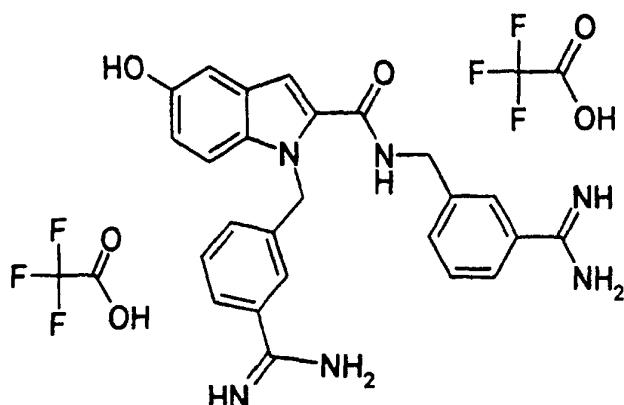
[0316] This compound was prepared from 4-benzylxyloxy-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-(dimethylamino)-benzylamide (347 mg, 0.67 mmol) and hydrogen sulfide as described in example 1/4. The purification by flash chromatography on silica gel was done with dichloromethane/methanol 19:1 to give 342 mg (92 %) of the desired product.

5.) [4-({[1-(3-Amidino-benzyl)-4-benzylxyloxy-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium iodide hydroiodide

[0317] This compound was prepared from 4-benzylxyloxy-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 4-(dimethylamino)-benzylamide (342 mg, 0.62 mmol), acetone (15 ml), methyl iodide (0.98 ml, 15 mmol), acetic acid (0.4 m, 0.7 mmol), ammonium acetate (809 mg, 10 mmol), and methanol (7 ml) as described in example 1/5 but the solvent for the methylation was pure acetone. The crude material was purified by flash chromatography on RP₁₈ material with ethanol/water/acetic acid 1:1:0.1 to give 374 mg of the desired compound (80 %). M.p. 158°C (dec.). MS: 546.2 (M⁺).

Example 69:

[0318] 1-(3-Amidino-benzyl)-5-hydroxy-1H-indole-2-carboxylic acid 3-amidino-benzylamide; trifluoroacetic acid salt



[0319] 1-(3-Amidino-benzyl)-5-benzylxyloxy-1H-indole-2-carboxylic acid 3-amidino-benzylamide dihydroiodide (74 mg, 0.09 mmol; example 59) was dissolved in ethanol (9 ml). Hydrogen chloride gas was bubbled through the solution for 5 h. After standing for about 3 days the mixture was evaporated and purified by flash chromatography on RP₁₈ material

with ethanol/water/trifluoroacetic acid 1:1:0.1 to give 51 mg of the desired product containing an unknown impurity. Preparative HPLC of 44 mg of this mixture gave 6.7 mg of the pure desired compound (10 %). M.p. 125°C (dec.). MS: 441.3 (M+H⁺).

5 Example 70:

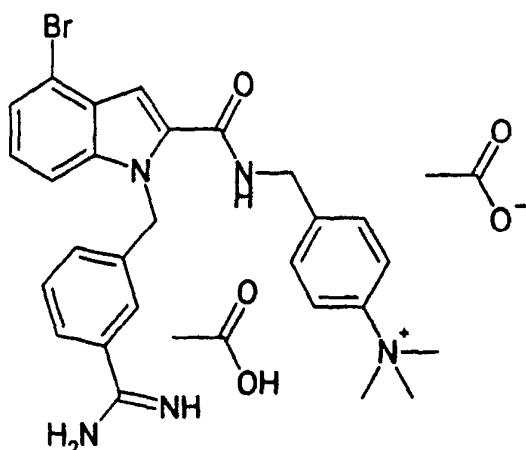
[0320] [4-({[1-(3-Amidino-benzyl)-4-bromo-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium acetate acetic acid salt

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1.) 4-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester

30 [0321] The compound was prepared from 4-bromo-1H-indole-2-carboxylic acid ethyl ester (5 g, 19 mmol), sodium hydride (537 mg, 22 mmol), 3-cyano-benzyl bromide (4.39 g, 22 mmol), and N,N-dimethylformamide (50 ml) analogously to example 21/1. The crude material was purified by crystallization from methanol to give 6.093 g (84 %) of the desired product. M.p. 163-165°C (dec.).

35 2.) 4-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid

[0322] This compound was prepared from 4-bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester (6.093 g, 16 mmol), sodium hydroxide (4.77 g, 120 mmol), methanol (800 ml), and water (20.2 ml) analogously to example 1/2. The precipitated product was washed and dried. Yield: 5.562 g (98 %). M.p. 236-238°C.

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3.) 4-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-dimethylamino-benzylamide

45 [0323] This compound was prepared from 4-bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (1 g, 2.8 mmol), diphenylphosphoryl azide (790 µl, 3.66 mmol), N,N-diisopropylethylamine (960 µl, 5.6 mmol), and 4-(dimethylamino)-benzylamine dihydrochloride (703 mg, 3.1 mmol) in N,N-dimethylformamide (40 ml) as described in example 3/1. The purification by flash chromatography on silica gel was done with dichloromethane/methanol 20:0.05 to give 818 mg (60 %) of the desired product. M.p. 110-112°C.

50 4.) [4-({[4-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium iodide

[0324] This compound was prepared from 4-bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-dimethylamino-benzylamide (818 mg, 1.68 mmol), methyl iodide (2.27 ml, 44 mmol), and acetone (8 ml) analogously to example 20/1. Yield: 927 mg (88 %). M.p. 219-224°C.

55 5.) [4-({[1-(3-Amidino-benzyl)-4-bromo-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium acetate acetic acid salt

[0325] This compound was prepared from [4-({[4-bromo-1-(3-cyano-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-

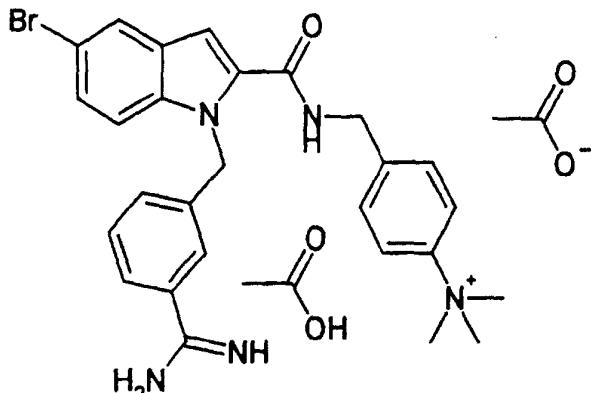
phenyl]-trimethyl-ammonium iodide (200mg, 0.32mmol), ethanol (13 ml), hydrogen chloride, and liquid ammonia analogously to example 19/3. Purification by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 1:1:0.1 gave 249 mg of the desired product as trifluoroacetic acid salt. This compound was converted into the acetic acid salt by ion exchanger chromatography analogously to example 64. Yield: 150 mg (74 %). M.p. 145°C (dec.). MS: 518.2 (M⁺; ⁷⁹Br).

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Example 71:

10 [0326] [4-({[1-(3-Amidino-benzyl)-5-bromo-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium acetate acetic acid salt

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1.) 5-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester

30 [0327] The compound was prepared from 5-bromo-1H-indole-2-carboxylic acid ethyl ester (6 g, 22 mmol), sodium hydride (645 mg, 27 mmol), 3-cyano-benzyl bromide (5.26 g, 27 mmol), and N,N-dimethylformamide (50 ml) analogously to example 21/1. The crude material was purified by crystallization from methanol to give 8.07 g (96 %) of the desired product. M.p. 124-128°C (dec.).

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2.) 5-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid

40

[0328] This compound was prepared from 5-bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester (8.07 g, 21 mmol), sodium hydroxide (6.32 g, 160 mmol), methanol (360 ml), and water (26.8 ml) analogously to example 1/2. The precipitate was washed and dried. It was used in the next step without further purification. Yield: 6.63 g (89 %). M.p. 230-233°C.

3.) 5-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-dimethylamino-benzylamide

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[0329] This compound was prepared from 5-bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (1 g, 2.8 mmol), diphenylphosphoryl azide (790 µl, 3.66 mmol), N,N-diisopropylethylamine (960 µl, 5.6 mmol), and 4-(dimethylamino)-benzylamine dihydrochloride (703 mg, 3.1 mmol) in N,N-dimethylformamide (40 ml) as described in example 3/1. The purification by flash chromatography on silica gel was done with dichloromethane/methanol 20:0.05 to give 949 mg (69 %) of the desired product. M.p. 145-146°C.

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4.) [4-({[5-Bromo-1-(3-cyano-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium iodide

[0330] This compound was prepared from 5-bromo-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-dimethylamino-benzylamide (890 mg, 1.83 mmol), methyl iodide (2.95 ml, 47 mmol), and acetone (8 ml) analogously to example 20/1. Yield: 1.289 g. M.p. 145-148°C. The compound was used for the next steps without further purification.

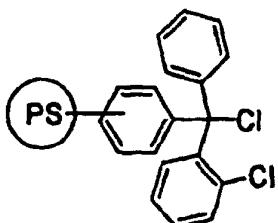
55

5.) [4-({[1-(3-Amidino-benzyl)-5-bromo-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]- trimethyl-ammonium acetate acetic acid salt

[0331] This compound was prepared from [4-({[5-bromo-1-(3-cyano-benzyl)-1H-indole-2-carbonyl]-amino}-methyl)-phenyl]-trimethyl-ammonium iodide (200 mg, 0.32 mmol), ethanol, hydrogen chloride, and liquid ammonia analogously to example 19/3. Purification by reversed phase chromatography on RP₁₈ material with water/ethanol/trifluoroacetic acid 1:1:0.1 gave 199 mg of the desired product as trifluoroacetic acid salt. This compound was converted into the acetic acid salt by ion exchange chromatography analogously to example 64. Yield: 130 mg (64 %). M.p. 86°C (dec.). MS: 520.2 (M⁺, ⁸¹Br).

[0332] Examples 74-78 were synthesized on solid phase using a polystyrene (PS) resin with a 2-chlorotriptylchloride linker (L) (substitution 1.05 mmol/g and 0.67 mmol/g, respectively; Novabiochem).

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Linker L

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[0333] The general procedures applied in examples 74 to 78 are as follows.

Linking:

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[0334] The indole derivatives were dissolved in dichloromethane or dichloromethane tetrahydrofuran mixtures. N, N-diisopropylethylamine was added and the mixture was sucked into a syringe fitted with a polyethylene sheet and containing the resin. After shaking for 2 hours at room temperature the mixture was removed and the resin was washed with dichloromethane. A mixture of methanol, N,N-diisopropylethylamine, and dichloromethane was added and the syringe was shaken at room temperature. After 1.5 hours the mixture was removed and the resin was washed with N, N-dimethylformamide (1x), dichloromethane (3x), and methanol (3x).

Cleaving:

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[0335] The compounds were cleaved from the resin by treating the resin with a mixture of dichloromethane, trifluoroacetic acid, and water (60:40:0.1). After 15 minutes the cleavage mixture was transferred into a flask and the resin was washed with methanol (3x). The methanol washes were added to the cleavage mixture and the resulting solution was evaporated in vacuo. The residue was dissolved in an appropriate acetonitrile-water mixture and characterized by HPLC and MS (Beckman HPLC used with the following columns: A: YMC ODS-AM 4.6 mm x 250 mm; B: VYDAC RP-18, 90 Å, 4.6 mm x 250 mm; C: YMC basic, 4.6 mm x 250 mm; Thermo Separation Products HPLC used with column D: Macherey-Nagel ET 250/8/4 Nucleosil 7 C₁₈).

Purification:

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[0336] The final products were purified by preparative HPLC using the following conditions:

System 1 used for examples 74-78: Beckman HPLC, column: VYDAC Protein & Peptide, C₁₈, 10 µm, 22 x 250 mm; flow 8 ml/min, acetonitrile/water-gradient, wavelength 324 nm, or

55

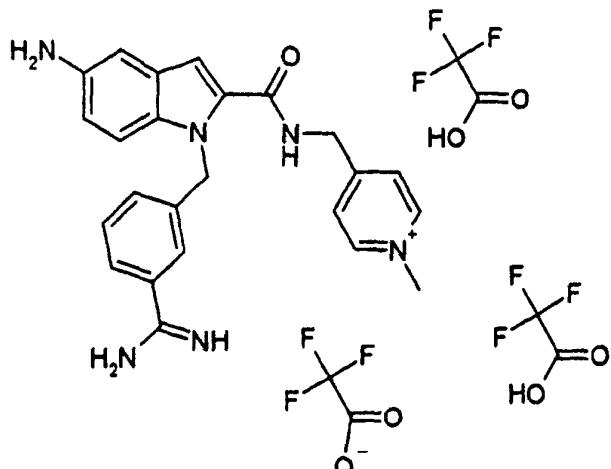
System 2 used for all other compounds synthesized on solid phase: Thermo Separation Products HPLC, column: Macherey-Nagel 100 7 C₁₈, 20 mm x 250 mm; flow 5-6 ml/min, appropriate mixtures of water (70-60 %) and acetonitrile (30-40 %), wavelength 236-242 nm.

Example 74:

[0337] 4-(((1-(3-Amidino-benzyl)-5-amino-1H-indole-2-carbonyl)-amino)-methyl)-1-methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

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25 1.) 5-Amino-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid ethyl ester trifluoroacetic acid salt

[0338] 5-Amino-1H-indole-2-carboxylic acid ethyl ester (343 mg, 1.68 mmol) was coupled to the resin (529 mg, 0.56 mmol) as described above. The dry indole-coupled resin was shaken in dry N,N-dimethylformamide for 5 min. After removal of the N,N-dimethylformamide a mixture of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (405 µl; 1.4 mmol) and N,N-dimethylformamide (5 ml) was added followed by a solution of 3-cyano-benzyl bromide (220 mg, 1.12 mmol) in N,N-dimethylformamide after 1 hour. 3 hours later the mixture was removed, the resin was washed with N,N-dimethylformamide (5x) and methanol (5x) and dried in vacuo. A sample was taken and cleaved as described above. The compound obtained was characterized by HPLC and MS.

HPLC: column B, 0-60 % acetonitrile in water, 30 min, 324 nm, retention time: 16.88 min. MS: 320.1 (M+H⁺).

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2.) 5-Amino-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid trifluoroacetic acid salt

[0339] The resin from step 1 (331 mg) was shaken for 5 minutes with N,N-dimethylformamide (8 ml). After the removal of the N,N-dimethylformamide a mixture of benzyl-trimethyl-ammonium hydroxide (40 % in methanol; 2.8 mmol, 1.27 ml) and N,N-dimethylformamide (10 ml) was sucked in and shaken for 4 h 40 min. After removal of the mixture the resin was washed with N,N-dimethylformamide (5x) and dichloromethane (3x) and dried in vacuo. A sample was taken and cleaved.

HPLC: column B, 0-60 % acetonitrile in water, 30 min, 324 nm, retention time: 11.72 min. MS: 292.1 (M+H⁺).

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3.) 5-Amino-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid (4-pyridylmethyl)-amide trifluoroacetic acid salt

[0340] The resin from step 2 (105 mg) was shaken for 5 minutes with N,N-dimethylformamide, before the reagent mixture consisting of 4-(aminomethyl)pyridine (34 µl, 0.33 mmol), N,N'-diisopropylcarbodiimide (49 mg, 0.39 mmol), and 1-hydroxybenzotriazole hydrate (53 mg, 0.39 mmol) in N,N-dimethylformamide (4 ml) was added. After 22 hours the reaction mixture was removed and the resin was washed with N,N-dimethylformamide, methanol, and dichloromethane and dried in vacuo. A sample was taken and cleaved.

HPLC: column B, 0-60 % acetonitrile in water, 30 min, 324 nm, retention time: 9.73 min. MS: 382.1 (M+H⁺).

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4.) 5-Amino-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid (4-pyridyl-methyl)-amide trifluoroacetic acid salt

[0341] The resin from step 3 (45 mg) was shaken in 2 ml pyridine/triethylamine (2:1) for 15 minutes. The solution was removed, a saturated solution of hydrogen sulfide in pyridine/triethylamine (2:1) (1 ml) was added and the mixture was shaken overnight.

The next day the hydrogen sulfide solution was removed. The resin was washed with acetone and dried in vacuo. A sample was taken and cleaved.

HPLC: column C, 0-60 % acetonitrile in water, 30 min, 324 nm, retention time: 14.30 min. MS: 416.0 (M+H⁺).

- 5 5.) 4-(((1-(3-Amidino-benzyl)-5-amino-1H-indole-2-carbonyl)-amino)-methyl)-1- methyl-pyridinium trifluoroacetate trifluoroacetic acid salt

[0342] 5.1) To 10 mg of the resin from step 4 a solution of methyl iodide (100 µl) in acetone (0.4 ml) was added. After shaking overnight the reaction mixture was removed and the resin was washed with acetone (7x) and methanol. A solution of ammonium acetate (31 mg), acetic acid (15 µl), and methanol (300 µl) was added. The syringe was closed and heated in a water bath at 50°C for 3 hours. After this conversion the solution was removed and the resin was washed with methanol, N,N-dimethylformamide, and dichloromethane.

[0343] 5.2) To 10 mg of the resin from step 4 a solution of N,N-dimethylformamide (0.4 ml) and methyl iodide (100 µl) was added. After shaking overnight the reaction mixture was removed and the resin was washed with acetone (7x) and methanol. A solution of ammonium acetate (31 mg), acetic acid (15 µl), and methanol (300 µl) was added. The syringe was closed and heated in a water bath at 50°C for 3 hours. After this conversion the solution was removed and the resin was washed with methanol, N,N-dimethylformamide, and dichloromethane.

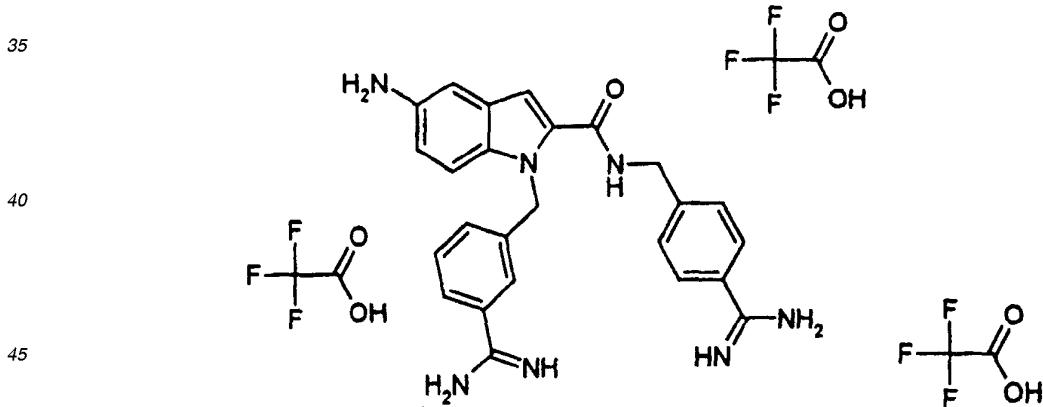
[0344] 5.3) The resin from step 4 (25 mg) was shaken with acetone for 5 minutes. The acetone was replaced by a solution of methyl iodide (0.3 ml) in acetone (1.2 ml) and the syringe was shaken overnight. The next day the methyl iodide solution was removed and the resin washed with acetone and methanol. A solution of ammonium acetate (92 mg), acetic acid (45 µl), and methanol (300 µl) was added and the syringe heated at 50°C for 3 hours. The solution was removed and the resin washed with methanol, N,N-dimethylformamide, and dichloromethane.

[0345] The resins obtained in steps 5.1 - 5.3 were pooled. The combined material was cleaved and then purified by preparative HPLC. After lyophilization 8 mg of a solid material was obtained. M.p. 115°C.

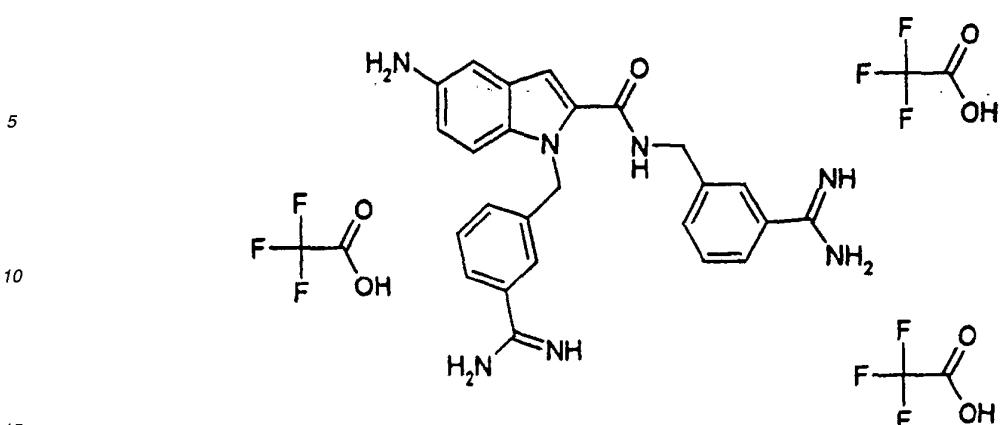
25 HPLC:column C, 0-40 % acetonitrile in water, 20 min, 230 nm, retention time: 11.05 min. MS: 413.0 (M⁺).

Examples 75 and 76:

- 30 [0346] 1-(3-Amidino-benzyl)-5-amino-1H-indole-2-carboxylic acid 4-amidino-benzylamide trifluoroacetic acid salt (example 75)



- 50 and
1-(3-Amidino-benzyl)-5-amino-1H-indole-2-carboxylic acid 3-amidino-benzylamide trifluoroacetic acid salt (example 76)



1.) 5-Amino-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 4-cyano-benzylamide trifluoroacetic acid salt and 5-Amino-1-(3-cyano-benzyl)-1H-indole-2-carboxylic acid 3-cyano-benzylamide trifluoroacetic acid salt

[0347] 1.1) The resin from example 74 step, 2 (130 mg, 0.11 mmol) was shaken with N,N-dimethylformamide for 5 minutes. After removal of the N,N-dimethylformamide a solution of diphenylphosphoryl azide (36 µl, 0.165 mmol), N,N-disopropylethylamine (172 µl; 0.99 mmol), and 4-aminomethyl-benzonitrile hydrobromide (70 mg, 0.33 mmol) in N,N-dimethylformamide (4 ml) was added and the syringe was shaken overnight. After 16 h the reaction mixture was removed, the resin washed with N,N-dimethylformamide, methanol, and dichloromethane and dried. After drying a sample was taken and cleaved. HPLC analysis showed a conversion of 50 %.

[0348] 1.2) The resin from step 1.1 was shaken with N,N-dimethylformamide for 5 minutes. The removal of N,N-dimethylformamide was followed by the addition of the reagent mixture consisting of 3-aminomethyl-benzonitrile (22 mg, 0.165 mmol), 1-hydroxybenzotriazole (30 mg; 0.22 mmol), N,N'-diisopropylcarbodiimide (24 mg; 0.193 mmol), and N,N-dimethylformamide (2 ml). After shaking for 16 hours the reagent mixture was removed, the resin washed with N,N-dimethylformamide, methanol, and dichloromethane and dried.

A sample was taken and cleaved.

HPLC: column C, 0-60% acetonitrile in water, 30 min, 324 nm, retention time: 23.70 min (peak showed a shoulder).

35 2.) 5-Amino-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 4-thiocarbamoyl-benzylamide trifluoroacetic acid salt and 5-Amino-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 3-thiocarbamoyl-benzylamide trifluoroacetic acid salt

[0349] The resin obtained in step 1.2 was treated with hydrogen sulfide, pyridine, and triethylamine as described in example 74/4. Due to the fact that there still was some starting material present it was treated once again with hydrogen sulfide, pyridine, and triethylamine to get complete conversion. After cleavage of a small sample the compounds obtained were characterized by HPLC analysis.

HPLC: column C, 60–60 % acetonitrile in water, 30 min, 324 nm, retention time: 20.17 min (53 %), 20.52 min (32 %).

45 3.) 1-(3-Amidino-benzyl)-5-amino-1H-indole-2-carboxylic acid 4-amidino-benzylamide trifluoroacetic acid salt and
1-(3-Amidino-benzyl)-5-amino-1H-indole-2-carboxylic acid 3-amidino-benzylamide trifluoroacetic acid salt

[0350] The resin from step 2 was treated with methyl iodide (250 µl, 4 mmol), acetone (2 ml), ammonium acetate (210 mg, 2.7 mmol), acetic acid (100 µl), and methanol (2 ml) analogously to example (74/5.3). The compounds were cleaved from the resin. After evaporation the residue was dissolved in acetonitrile/water 15:85 (400 µl). Preparative HPLC of the residue resulted in two main fractions. Fraction I contained meta-para-amidine with an impurity of bis-meta-amidine, Fraction II contained bis-meta-amidine with an impurity of meta-para-amidine.

[0351] A second preparative HPLC of fraction I gave 10.2 mg of the meta-para-amidine (example 75) as a white solid. M.p. 146°C (dec.).

[0352] A second preparative HPLC of fraction II gave 12.5 mg of the bis-meta-amidine (example 76). M.p. 125°C

(dec.).

Example 77:

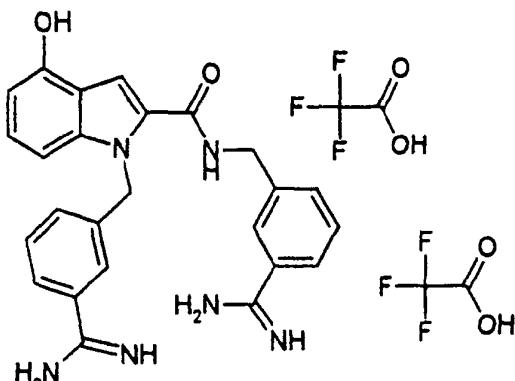
[0353] 1-(3-Amidino-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid 3-amidino-benzylamide trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid ethyl ester

[0354] 4-Hydroxy-1H-indole-2-carboxylic acid ethyl ester (345 mg, 1.69 mmol) was coupled to the resin (535 mg, 0.56 mmol). Then the resin was shaken in dry N,N-dimethylformamide for 5 minutes, washed with N,N-dimethylformamide and a mixture of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (405 µl, 1.4 mmol) and N,N-dimethylformamide (5 ml) was added to the resin. After shaking for 1 hour 3-cyano-benzyl bromide (220 mg, 1.12 mmol) was added. 3 hours later the mixture was removed, the resin was washed with N,N-dimethylformamide (5x) and methanol (5x) and dried in vacuo. After cleavage of a small sample the product was characterized by HPLC. HPLC: column B, 0-80 % acetonitrile in water, 40 min, 324 nm, retention time: 25.53 min.

35

2.) 1-(3-Cyano-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid

[0355] The resin obtained in step 1 was treated with benzyl-trimethyl-ammonium hydroxide (40 % in methanol, 2.5 ml, 5.6 mmol) in N,N-dimethylformamide (15 ml) analogously to the resin in example 74/2. A sample was taken and cleaved. HPLC: column B, 0-60 % acetonitrile in water, 30 min, 324 nm, retention time: 20.98 min.

40 3.) 1-(3-Cyano-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid 3-cyano-benzylamide
[0356] The resin obtained in step 2 (98 mg, 0.1 mmol) was reacted with a mixture of 3-aminomethyl-benzonitrile hydrobromide (64 mg; 0.3 mmol), N,N-diisopropylethylamine (70 µl, 0.4 mmol), 1-hydroxybenzotriazole (54 mg, 0.4 mmol), and N,N'-diisopropylcarbodiimide (44 mg, 0.35 mmol) analogously to examples 75 and 76, step 1.2.

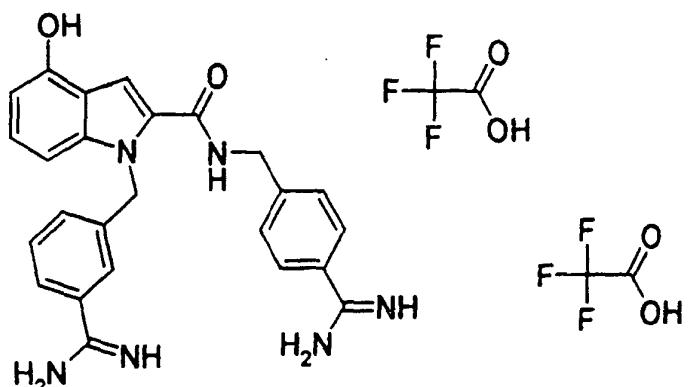
45 4.) 4-Hydroxy-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 3-thiocarbamoyl-benzylamide
[0357] The resin obtained in step 3 was treated with hydrogen sulfide, pyridine, and triethylamine as described in example 74.4.

50 5.) 1-(3-Amidino-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid 3-amidino-benzylamide trifluoroacetic acid salt
[0358] The resin obtained in step 4 was treated with methyl iodide (250 µl, 4 mmol), acetone (2 ml), ammonium acetate (210 mg, 2.7 mmol), acetic acid (100 µl), and methanol (2 ml) analogously to example 74, step 5.3. Preparative HPLC after cleavage: The residue was dissolved in water and acetonitrile to give 900 µl of volume. This solution was split in two parts and each part was separated by HPLC to yield a total amount of 11 mg of a white solid. M.p. 128-131 °C. HPLC: column B, 0-40 % acetonitrile in water, 20 min, 230 nm, retention time: 11.97 min. MS: 441.0 (M+H⁺).

Example 78:

[0359] 1-(3-Amidino-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid 4-amidino-benzylamide trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid 4-cyano-benzylamide

[0360] 50 mg (0.05 mmol) of the resin obtained in example 77/2 was reacted with a mixture of 4-aminomethyl-benzonitrile hydrobromide (32 mg, 0.15 mmol), N,N-diisopropylethylamine (35 µl, 0.2 mmol), 1-hydroxybenzotriazole (27 mg, 0.2 mmol), and N,N'-diisopropylcarbodiimide (22 mg; 0.175 mmol), analogously to example 74/3.

25

2.) 4-Hydroxy-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid 4-thiocarbamoyl-benzylamide

[0361] The resin obtained in step 1 was treated with hydrogen sulfide, pyridine, and triethylamine as described in example 74/4.

30

3.) 1-(3-Amidino-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid 4-amidino-benzyl amide trifluoroacetic acid salt

[0362] The resin obtained in step 2 was treated with methyl iodide (125 µl, 2 mmol), acetone (1 ml), ammonium acetate (105 mg, 1.35 mmol), acetic acid (50 µl), and methanol (1 ml) analogously to example 75/5.3.

35

Preparative HPLC after cleavage: The residue was dissolved in water and acetonitrile and purified to yield 7 mg of a white solid. M.p. 155-157°C.

HPLC: column B, 0-40 % acetonitrile in water, 20 min, 324 nm, retention time: 11.77 min. MS: 441.0 ($\text{M}+\text{H}^+$).

40

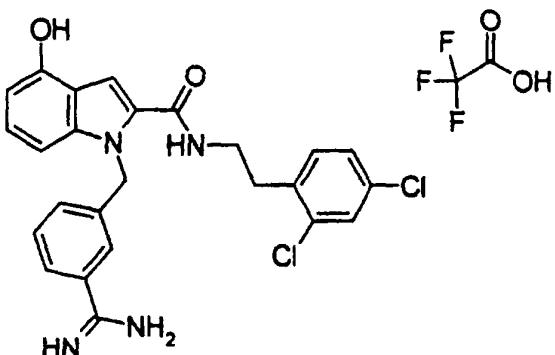
Example 79:

[0363] 1-(3-Amidino-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide trifluoroacetic acid salt

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1.) 1-(3-Cyano-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide

[0364] This compound was synthesized using a substituted resin like the one described in example 77/2 but with a lower substitution (the 2-chlorotriptylchloride resin used in the linking step only had a substitution of 0.67 mmol/g). This resin (300 mg, 0.201 mmol) carrying 1-(3-cyano-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid was treated with N,N-dimethylformamide for five minutes. After removal of the N,N-dimethylformamide a mixture of 2-(2,4-dichloro-phenyl)-ethylamine (0.51 ml, 3.35 mmol), N,N-diisopropylethylamine (0.57 ml, 3.35 mmol), diphenylphosphoryl azide (0.72 ml, 3.35 mmol), and N,N-dimethylformamide (6 ml) was added. After shaking overnight the reaction mixture was removed and the resin washed with N,N-dimethylformamide (5x) and methanol (5x). After drying in vacuo a sample was taken and cleaved.

HPLC: column D; water/acetonitrile 90:10 to 10:90, 30 min, 324 nm, retention time: 23.10 min.

2.) 4-Hydroxy-1-(3-thiocarbamoyl-benzyl)-1H-indole-2-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide

[0365] The resin from example 79/1 was similarly treated as described in example 74/4. HPLC: column D, water/acetonitrile 90:10 to 10:90, 30 min, 324 nm, retention time: 20.74 min.

3.) 1-(3-Amidino-benzyl)-4-hydroxy-1H-indole-2-carboxylic acid [2-(2,4-dichloro-phenyl)-ethyl]-amide trifluoroacetic acid salt

[0366] The resin from example 79/2 was similarly treated as described in example 74/5.3. Preparative HPLC after cleavage gave 20 mg of a white solid. M.p. 144°C. HPLC: column D, water/acetonitrile 45:55, 30 min, 236 nm, retention time 9.43 min. MS: 481.2 ($M+H^+$; $2x^{35}Cl$).

[0367] Analogously to the above-described compounds the following example compounds of the formula Ib were prepared which are listed in Table 2. Unless indicated otherwise in Table 2 the compounds of examples 85 to 165 were obtained as trifluoroacetic acid salts.

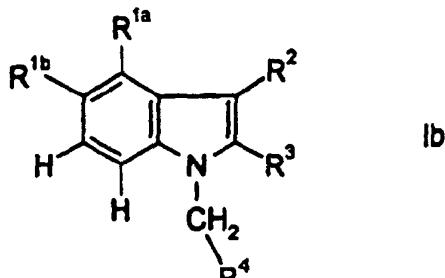
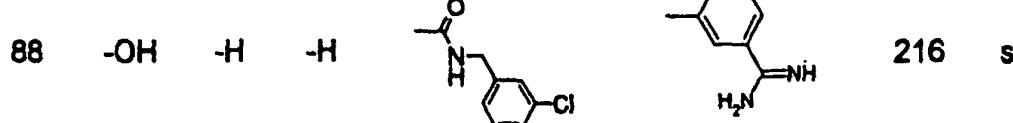


Table 2: Example compounds of the formula Ib

Example no.	$-R^{1a}$	$-R^{1b}$	$-R^2$	$-R^3$	$-R^4$	M.p. (°C)	(a)
-------------	-----------	-----------	--------	--------	--------	--------------	-----



Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)
5 91	-H	-H	-H			nd	c
10 92	-H	-H	-H			140 -150	c
15 93	-H	-H	-H			104	c
20 94 (b)	-H	-H	-H			106	c
25 95 (R)	-H	-OH	-H	-COOH		119	c
30							
35							
40							
45							
50							
55							

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)
5							
10	96	-OH	-H	-H		144	s
15	97	-OH	-H	-H		163	s
20	98	-OH	-H	-H		130	s
25	99	-OH	-H	-H		172	s
30	100	-OH	-H	-H		196	s
35	102	-OH	-H	-H		200	s
40	103	-OH	-H	-H		nd	s
45							
50							
55							

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)
5							
10	104	-OH	-H	-H		264	s
15	106	-H	-H	-Cl		57	c
20							
25	107	-CH ₃	-H	-H		120	c
30	108	-CH ₃	-H	-H		252	c
35	109	-OH	-H	-H		nd	s
40							
45	110	-OH	-H	-H		nd	s
50							
55							

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)	
5								
10	111	-OH	-H	-H			122	s
15	112	-OH	-H	-H			126	s
20	113	-H	-H	-Cl			252	c
25	114	-CH ₃	-H	-H			113	c
30	115	-H	-H	-Cl			227	c
35	116	-CH ₃	-H	-H			100	c
40	117	-CH ₃	-H	-H			210	c
45								
50								
55								

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)
5							
10	118	-OH	-H	-H		nd	s
15	119	-OH	-H	-H		nd	s
20	120	-OH	-H	-H		117	s
25	121	-OH	-H	-H		184	s
30	122	-OH	-H	-H		89	s
35	123	-H	-H	-Br		166	c
40	124	-CH ₃	-H	-H		220	c
45							
50							
55							

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)
5							
10	125 -CH ₃	-H	-H			236	c
15	126 -OH	-H	-H			117	s
20							
25	127 -CH ₃	-H	-Br			260	c
30							
35	128 -OH	-H	-H			107	s
40							
45	129 -OH	-H	-H			75	s
50							
55	130 -OH	-H	-H			82	s
	131 -OH	-H	-H			109	s

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)
5							
10	132	-OH	-H	-H		95	s
15	133	-OH	-H	-H		nd	s
20	134	-OH	-H	-H		nd	s
25	135 (c)	-OH	-H	-H		230	c
30	137	-OH	-H	-H		nd	s
35	138	-OH	-H	-H		nd	s
40							
45							
50							

Exam- ple no.	$-R^{1a}$	$-R^{1b}$	$-R^2$	$-R^3$	$-R^4$	M.p. (°C)	(a)
5 10 15 20 25 30 35 40 45 50 55	139 -OH	-H	-H			197	s
	140 -OH	-H	-H			90	s
	141 -OH	-H	-H			200	s
	142 (c) -OH	-H	-H			207	s
	143 -OH	-H	-H			210	s
	144 -CH ₃	-H	-H			249	c
	145 -H	-H	-Br			236	c

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)
5							
10	146	-H	-H	-Br		224	c
15	147	-OH	-H	-H		227	s
20	148	-CH ₃	-H	-H		201	c
25	149	-OH	-H	-H		nd	s
30	151 (c) (R)	-H		-H		166	c
35	152 (c) (R)	-OCH ₃	-H	-H		170	c
40	153 (d) (R)	-OCH ₃	-H	-H		160	c
45							
50							

Exam- ple no.	$-R^{1a}$	$-R^{1b}$	$-R^2$	$-R^3$	$-R^4$	M.p. (°C)	(a)	
5								
10								
154 (c) (R)	-H		-H			169	c	
15								
155 (c) (R)	-H		-H			87	c	
20								
158 (d) (R)	-H	-NH ₂	-H			170	c	
25								
30								
35	159 (c) (R)	-OCH ₃	-H	-H			128	c
40								
45								
50								
55								

Example no.	-R ^{1a}	-R ^{1b}	-R ²	-R ³	-R ⁴	M.p. (°C)	(a)	
5								
10	161	-OH	-H	-H			233	s
15	162	-OH	-H	-H			166	s
20	163	-OH	-H	-H			128	s
25	164	-OH	-H	-H			177	s
30	165	-OH	-H	-H			165	s
35								

40 nd = not determined

(a) way of preparation: c = classical synthesis, s = solid phase chemistry

(b) Obtained as acetic acid salt instead of trifluoroacetic acid salt

45 (c) Not obtained as trifluoroacetic acid salt but as the free compound (which
in the case of example 135 is a betain)

(d) Obtained as hydrochloride instead of as trifluoroacetic acid salt

(R) Reference

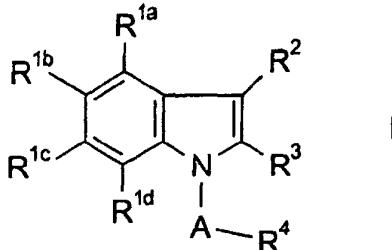
55 [0368] The disclosure of all publications mentioned above is expressly incorporated herein by reference in their entireties to the same extent as if each publication were incorporated by reference individually.

Claims

1. A compound of the formula I,

5

10



15

wherein

two of the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} independent of one another are hydrogen, F, Cl, Br, I, methyl, (C₁-C₄)-alkoxy, phenyl-(C₁-C₄)-alkoxy-, OH or NR^{5a}R^{5b}, and are identical or different, and the other two of the residues R^{1a}, R^{1b}, R^{1c} and R^{1d} are hydrogen;

R^{5a} is hydrogen or ((C₁-C₄)-alkoxy)carbonyl-;

R^{5b} is hydrogen;

R² is hydrogen, Cl or Br;

R³ is -CO-NHR¹⁰;

R⁷ is hydroxy, (C₁-C₄)-alkoxy, phenyl-(C₁-C₄)-alkoxy- or -NR^{5a}R^{5b};

R¹⁰ is (C₁-C₁₀)-alkyl-, phenyl-(C₁-C₄)-alkyl- or naphthyl-(C₁-C₄)-alkyl-, where the (C₁-C₁₀)-alkyl- residue, the phenyl residue and the naphthyl residue are unsubstituted or substituted by one, two or three identical or different residues R¹¹;

R¹¹ is -N(R¹²)₂, -OR¹², -CO-N(R¹³)₂, -CO-R⁷, R^{15b}, (C₁-C₁₄)-alkyl, phenyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b}, naphthyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b} and/or substituted at the nitrogen atom by R¹⁴, isoquinolinyl which is unsubstituted or substituted by one, two or three identical or different residues R^{15b} and/or substituted at the nitrogen atom by R¹⁴, pyridyl which is unsubstituted or substituted at the nitrogen atom by R¹⁴, or Het which is unsubstituted or substituted by R^{15a}, where residues R¹¹ if present more than one time in the molecule, are independent of each other and can be identical or different;

Het is the residue of a 5-membered or 6-membered saturated heterocyclic ring containing 1 or 2 identical or different ring heteroatoms selected from the series consisting of nitrogen, oxygen and sulfur;

each residue R¹² independent of the denotation of another residue R¹² is hydrogen, (C₁-C₄)-alkyl, phenyl, phenyl-(C₁-C₄)-alkyl-, naphthyl, naphthyl-(C₁-C₄)-alkyl-, pyrrolidinyl, piperidinyl, pyrrolidinyl-(C₁-C₄)-alkyl- or piperidinyl-(C₁-C₄)-alkyl-, where each pyrrolidinyl residue and each piperidinyl residue is unsubstituted or substituted at the nitrogen atom by phenyl-(C₁-C₄)-alkyl- or R^{15a};

each residue R¹³ independent of the denotation of another residue R¹³ is hydrogen, (C₁-C₄)-alkyl, phenyl, phenyl-(C₁-C₄)-alkyl-, naphthyl or naphthyl-(C₁-C₄)-alkyl-, or the two residues R¹³ together with the nitrogen atom to which they are bonded form a 5-membered or 6-membered saturated heterocyclic ring which can contain an additional nitrogen atom or oxygen atom in the ring where the additional nitrogen atom in the ring is unsubstituted or substituted by (C₁-C₄)-alkyl or phenyl-(C₁-C₄)-alkyl-;

R¹⁴ is (C₁-C₆)-alkyl, (C₁-C₆)-alkenyl, (C₁-C₆)-alkynyl, phenyl-(C₁-C₆)-alkyl- or ((C₁-C₆)-alkoxy)carbonyl-(C₁-C₆)-alkyl-, where phenyl present in R¹⁴ denotes an unsubstituted phenyl residue, the substitution by these residues at the nitrogen atom of the heterocyclic residue leading to a positively charged group having X⁻ as the counterion; or R¹⁴ is oxido this substitution at the nitrogen atom of the heterocyclic residue leading to an N-oxide; and where residues R¹⁴ if present more than one time in the molecule, are independent of each other and can be identical or different;

R^{15a} is (C₁-C₆)-alkyl, ((C₁-C₆)-alkyl)-C(=NH)-, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N<sup>+(R^{16a})₂(-O⁻), -(CH₂)_t-N<sup>+(R^{16a})₃ X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ or -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷, where ((C₁-C₆)-alkyl)-C(=NH)- is bonded to a ring nitrogen atom, and where residues R^{15a} if present more than one time in the molecule, are independent of each other and can be identical or different;

R^{15b} is (C₁-C₆)-alkyl, hydroxy, (C₁-C₄)-alkoxy, F, Cl, Br, I, NO₂, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N<sup>+(R^{16a})₂(-O⁻), -(CH₂)_t-N<sup>+

$(R^{16a})_3 X^-$, $-(CH_2)_t-NHR^{17}$, $-(CH_2)_t-CO-OR^{18}$, $-(CH_2)_t-CO-O(N(R^{18}))_2$, $-(CH_2)_t-CN$, $-(CH_2)_t-CS-N(R^{18})_2$, $-(CH_2)_t-C(=NR^{17})-NHR^{17}$ or $-(CH_2)_t-NH-C(=NR^{17})-NHR^{17}$, where alkyl can be substituted 1, 2, 3, 4, 5, 6, or 7 times by fluoro, and where residues R^{15b} if present more than one time in the molecule, are independent of each other and can be identical or different;

5 t is 0, 1, 2 or 3, where numbers t, if present more than one time in the molecule, are independent of each other and can be identical or different;

each residue R^{16} independent of the denotations of another residue R^{16} is hydrogen, (C_1-C_6) -alkyl, (C_1-C_6) -alkenyl, (C_1-C_6) -alkynyl, phenyl- (C_1-C_6) -alkyl- or $((C_1-C_6)$ -alkoxy)carbonyl- (C_1-C_6) -alkyl-, where phenyl present in R^{16} denotes an unsubstituted phenyl residue, and where groups containing residues R^{16} if present more than one time in the molecule, are independent of each other and can be identical or different;

10 each residue R^{16a} independent of the denotations of another residue R^{16a} is (C_1-C_6) -alkyl, (C_1-C_6) -alkenyl, (C_1-C_6) -alkynyl, phenyl- (C_1-C_6) -alkyl- or $((C_1-C_6)$ -alkoxy)carbonyl- (C_1-C_6) -alkyl-, where phenyl present in R^{16a} denotes an unsubstituted phenyl residue, and where groups containing residues R^{16a} if present more than one time in the molecule, are independent of each other and can be identical or different;

15 each residue R^{17} independent of the denotation of another residue R^{17} is hydrogen, (C_1-C_6) -alkyl, (C_1-C_6) -alkyl-carbonyl-, (C_1-C_6) -alkoxycarbonyl-, (C_1-C_6) -alkylcarbonyloxy- (C_1-C_6) -alkoxycarbonyl-, phenylcarbonyl-, phenoxycarbonyl-, phenyl- (C_1-C_6) -alkoxycarbonyl-, hydroxy, (C_1-C_6) -alkoxy, phenyl- (C_1-C_6) -alkoxy- or amino, and additionally in the groups $-(CH_2)_t-C(=NR^{17})-NHR^{17}$ and $-(CH_2)_t-NH-C(=NR^{17})-NHR^{17}$ the two residues R^{17} together with the $C(=N)-NH$ group to which they are bonded, can form a 5-membered or 6-membered heterocyclic ring, and where phenyl present in R^{17} denotes an unsubstituted phenyl residue, and where groups containing residues R^{17} if present more than one time in the molecule, are independent of each other and can be identical or different;

20 each residue R^{18} independent of the denotation of another residue R^{18} is hydrogen or (C_1-C_4) -alkyl; A is a methylene residue $-CH_2-$;

25 R^4 is phenyl which is substituted by one residue R^{15c} in the meta position;

R^{15c} is $-C(=NR^{17})-NHR^{17}$ wherein the residues R^{17} are hydrogen;

X^- is a physiologically acceptable anion;

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

2. A compound of the formula I as claimed in claim 1, wherein the residues R^{1c} and R^{1d} are hydrogen, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically acceptable salts.

3. A compound of the formula I as claimed in claims 1 and/or 2, wherein one of the residues R^{1a} and R^{1b} is hydrogen and the other is selected from the series consisting of hydrogen, methyl, F, Cl, Br, I, hydroxy, (C_1-C_4) -alkoxy, phenyl- (C_1-C_4) -alkoxy- and $-NHR^{5a}$, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically acceptable salts.

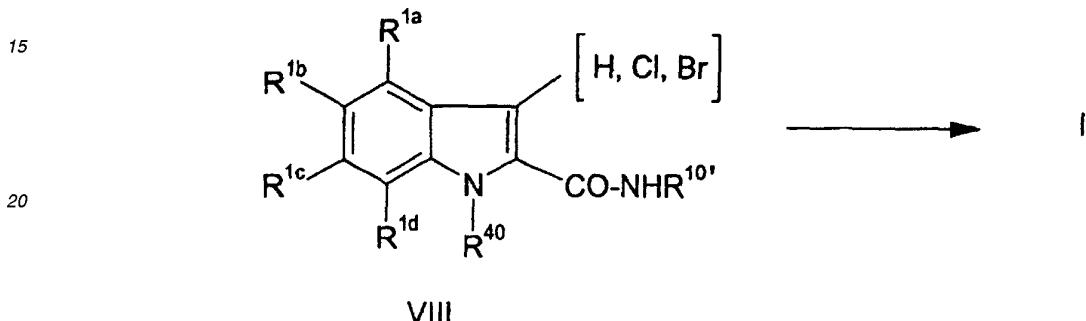
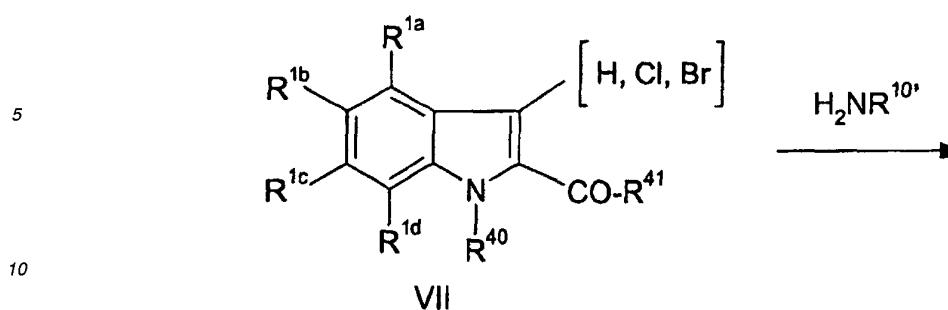
4. A compound of the formula I as claimed in one or more of claims 1 to 3, wherein the residue R^2 is hydrogen, in all its stereoisomeric forms and mixtures thereof in any ratio, and its physiologically acceptable salts.

40 5. A process for the preparation of a compound of the formula I as claimed in one or more of claims 1 to 4, comprising condensing a compound of the formula VII with a compound of the formula $H_2NR^{10'}$ to give a compound of the formula VIII, and converting the compound of the formula VIII into a compound of the formula I,

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25 where the residue R¹⁰ can have the denotations of R¹⁰ indicated in claims 1 to 4, but where in R¹⁰ functional groups can also be present in the form of groups that are subsequently transformed into the final functional groups present in R¹⁰, and where the residue R⁴⁰ can denote the group -A-R⁴ or can denote a group which is subsequently transformed into the group -A-R⁴, and where the group -COR⁴¹ can be a carboxylic acid group or derivative thereof, and where the groups R^{1a}, R^{1b}, R^{1c} and R^{1d} are defined as in claims 1 to 4 or functional groups in them can also be present in protected form or in the form of precursor groups.

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6. A pharmaceutical composition, comprising one or more compounds of the formula I as claimed in one or more of claims 1 to 4 and/or their physiologically acceptable salts together with a pharmaceutically acceptable carrier.

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 7. A compound of the formula I as claimed in one or more of claims 1 to 4 and/or its physiologically acceptable salts, for use as a pharmaceutical.

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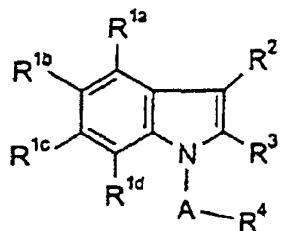
 8. A compound of the formula I as claimed in one or more of claims 1 to 4 and/or its physiologically acceptable salts, for use as an inhibitor of factor Xa.
 9. A compound of the formula I as claimed in one or more of claims 1 to 4 and/or its physiologically acceptable salts, for use as an inhibitor of blood clotting.

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 10. A compound of the formula I as claimed in one or more of claims 1 to 4 and/or its physiologically acceptable salts, for use in the treatment or prophylaxis of cardiovascular disorders or thromboembolic conditions.
 11. A compound of the formula I as claimed in one or more of claims 1 to 4 and/or its physiologically acceptable salts for use in the treatment or prophylaxis of thromboses, cardiac infarction, angina pectoris, restenoses or reocclusion.
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Patentansprüche

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1. Verbindung der Formel I



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worin

zwei von den Resten R^{1a}, R^{1b}, R^{1c} und R^{1d} unabhängig voneinander Wasserstoff, F, Cl, Br, I, Methyl, (C₁-C₄)-Alkoxy, Phenyl-(C₁-C₄)-alkoxy-, OH oder NR^{5a}R^{5b} darstellen und gleich oder verschieden sind, und die anderen zwei der Reste R^{1a}, R^{1b}, R^{1c} und R^{1d} Wasserstoff darstellen;

R^{5a} Wasserstoff oder ((C₁-C₄)-Alkoxy) carbonyldarstellt;

R^{5b} Wasserstoff darstellt;

R² Wasserstoff, Cl oder Br darstellt;

R³ -CO-NHR¹⁰ darstellt;

R⁷ Hydroxy, (C₁-C₄)-Alkoxy, Phenyl-(C₁-C₄)-alkoxy- oder -NR^{5a}R^{5b} darstellt;

R¹⁰ (C₁-C₁₀)-Alkyl-, Phenyl-(C₁-C₄)-alkyl- oder Naphthyl-(C₁-C₄)-alkyl- darstellt, wobei der (C₁-C₁₀)-Alkyl-Rest, der Phenyl-Rest und der Naphthyl-Rest unsubstituiert oder mit einem, zwei oder drei gleichen oder verschiedenen Resten R¹¹ substituiert sind;

R¹¹ -N(R¹²)₂, -OR¹², -CO-N(R¹³)₂, -CO-R⁷, R^{15b}, (C₁-C₁₄)-Alkyl, Phenyl, das unsubstituiert oder mit einem, zwei oder drei gleichen oder verschiedenen Resten R^{15b} substituiert ist, Naphthyl, das unsubstituiert oder mit einem, zwei oder drei gleichen oder verschiedenen Resten R^{15b} substituiert ist, Chinolinyl, das unsubstituiert oder mit einem, zwei oder drei gleichen oder verschiedenen Resten R^{15b} substituiert ist und/oder an dem Stickstoffatom mit R¹⁴ substituiert ist, Isochinolinyl, das unsubstituiert oder mit einem, zwei oder drei gleichen oder verschiedenen Resten R^{15b} substituiert ist und/oder an dem Stickstoffatom mit R¹⁴ substituiert ist, Pyridyl, das unsubstituiert oder an dem Stickstoffatom mit R¹⁴ substituiert ist, oder Het, das unsubstituiert oder mit R^{15a} substituiert ist, darstellt, wobei Reste R¹¹, falls mehr als einmal in dem Molekül vorliegend, unabhängig voneinander sind und gleich oder verschieden sein können;

Het den Rest eines 5-gliedrigen oder 6-gliedrigen gesättigten heterocyclischen Rings, enthaltend 1 oder 2 gleiche oder verschiedene Ringheteroatome, ausgewählt aus der Reihe bestehend aus Stickstoff, Sauerstoff und Schwefel, darstellt;

jeder Rest R¹² unabhängig von der Bedeutung von einem weiteren Rest R¹² Wasserstoff, (C₁-C₄)-Alkyl, Phenyl, Phenyl-(C₁-C₄)-alkyl-, Naphthyl, Naphthyl-(C₁-C₄)-alkyl-, Pyrrolidinyl, Piperidinyl, Pyrrolidinyl-(C₁-C₄)-alkyl- oder Piperidinyl-(C₁-C₄)-alkyl- darstellt, wobei jeder Pyrrolidinyl-Rest und jeder Piperidinyl-Rest unsubstituiert oder an dem Stickstoffatom mit Phenyl-(C₁-C₄)-alkyl- oder R^{15a} substituiert ist;

jeder Rest R¹³ unabhängig von der Bedeutung von einem weiteren Rest R¹³ Wasserstoff, (C₁-C₄)-Alkyl, Phenyl, Phenyl-(C₁-C₄)-alkyl-, Naphthyl oder Naphthyl-(C₁-C₄)-alkyl- darstellt oder die zwei Reste R¹³ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 5-gliedrigen oder 6-gliedrigen gesättigten heterocyclischen Ring bilden, der ein weiteres Stickstoffatom oder Sauerstoffatom in dem Ring enthalten kann, wobei das weitere Stickstoffatom in dem Ring unsubstituiert oder mit (C₁-C₄)-Alkyl oder Phenyl-(C₁-C₄)-alkyl- substituiert ist;

R¹⁴ (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkinyl, Phenyl- (C₁-C₆)-alkyl- oder ((C₁-C₆)-Alkoxy) carbonyl-(C₁-C₆)-alkyl- darstellt, wobei in R¹⁴ vorliegendes Phenyl einen unsubstituierten Phenyl-Rest darstellt, wobei die Substitution durch diese Reste an dem Stickstoffatom des heterocyclischen Rests zu einer positiv geladenen Gruppe mit X⁻ als Gegenion führt; oder R¹⁴ Oxido darstellt, wobei diese Substitution an dem Stickstoffatom des heterocyclischen Rests zu einem N-Oxid führt; und wobei Reste R¹⁴, falls mehr als einmal in dem Molekül vorliegend, unabhängig voneinander sind und gleich oder verschieden sein können;

R^{15a} (C₁-C₆)-Alkyl, ((C₁-C₆)-Alkyl)-C(=NH)-, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N^{+(R^{16a})₂(-O⁻), -(CH₂)_t-N^{+(R^{16a})₃X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ oder -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷ darstellt, wobei ((C₁-C₆)-Alkyl)-C(=NH)- an ein Ringstickstoffatom gebunden ist, und wobei Reste R^{15a}, falls mehr als einmal in dem Molekül vorliegend, unabhängig voneinander sind und gleich oder verschieden sein können;}}

R^{15b} (C₁-C₆)-Alkyl, Hydroxy, (C₁-C₄)-Alkoxy, F, Cl, Br, I, NO₂, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N^{+(R^{16a})₂(-O⁻), -(CH₂)_t-N^{+(R^{16a})₃X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CO-OR¹⁸, -(CH₂)_t-CO-N(R¹⁸)₂, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ oder -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷ darstellt, wobei Alkyl 1-, 2-, 3-, 4-, 5-, 6- oder 7-fach mit Fluor substituiert sein kann, und wobei Reste R^{15b}, falls mehr als einmal in dem Molekül vorliegend, unabhängig}}

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voneinander sind und gleich oder verschieden sein können;

t 0, 1, 2 oder 3 ist, wobei Zahlen t, falls mehr als einmal in dem Molekül vorliegend, unabhängig voneinander sind und gleich oder verschieden sein können;

5 jeder Rest R¹⁶ unabhängig von den Bedeutungen von einem weiteren Rest R¹⁶ Wasserstoff, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkinyl, Phenyl-(C₁-C₆)-alkyl- oder ((C₁-C₆)-Alkoxy)carbonyl-(C₁-C₆)-alkyl- darstellt, wobei in R¹⁶ vorliegendes Phenyl einen unsubstituierten Phenyl-Rest bedeutet und wobei Reste R¹⁶ enthaltende Gruppen, falls mehr als einmal in dem Molekül vorliegend, unabhängig voneinander sind und gleich oder verschieden sein können;

10 jeder Rest R^{16a} unabhängig von den Bedeutungen von einem weiteren Rest R^{16a} (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkinyl, Phenyl-(C₁-C₆)-alkyl- oder ((C₁-C₆)-Alkoxy)carbonyl-(C₁-C₆)-alkyl- darstellt, wobei in R^{16a} vorliegendes Phenyl einen unsubstituierten Phenyl-Rest bedeutet und wobei Reste R^{16a} enthaltende Gruppen, falls mehr als einmal in dem Molekül vorliegend, unabhängig voneinander sind und gleich oder verschieden sein können;

15 jeder Rest R¹⁷ unabhängig von der Bedeutung von einem weiteren Rest R¹⁷ Wasserstoff, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkylcarbonyl-, (C₁-C₆)-Alkoxycarbonyl-, (C₁-C₆)-Alkylcarbonyloxy- (C₁-C₆)-alkoxycarbonyl-, Phenylcarbonyl-, Phenoxy carbonyl-, Phenyl-(C₁-C₆)-alkoxycarbonyl-, Hydroxy, (C₁-C₆)-Alkoxy, Phenyl-(C₁-C₆)-alkoxy- oder Amino darstellt und zusätzlich in den Gruppen - (CH₂)_t-C(=NR¹⁷)-NHR¹⁷ und - (CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷ die zwei Reste R¹⁷ zusammen mit der Gruppe C(=N)-NH, an die sie gebunden sind, einen 5-gliedrigen oder 6-gliedrigen heterocyclischen Ring bilden können, und wobei in R¹⁷ vorliegendes Phenyl einen unsubstituierten Phenyl-Rest bedeutet und wobei Reste R¹⁷ enthaltende Gruppen, falls mehr als einmal in dem Molekül vorliegend, unabhängig voneinander sind und gleich oder verschieden sein können;

20 jeder Rest R¹⁸ unabhängig von der Bedeutung von einem weiteren Rest R¹⁸ Wasserstoff oder (C₁-C₄)-Alkyl darstellt;

A einen Methylen-Rest -CH₂- darstellt;

25 R⁴ Phenyl darstellt, das in der Metaposition mit einem Rest R^{15c} substituiert ist;

R^{15c} -C(=NR¹⁷)-NHR¹⁷ darstellt, worin die Reste R¹⁷ Wasserstoff darstellen;

X⁻ ein physiologisch verträgliches Anion darstellt;

in allen ihren stereoisomeren Formen und Gemische davon in einem beliebigen Verhältnis, und ihre physiologisch verträglichen Salze.

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2. Verbindung der Formel I nach Anspruch 1, worin die Reste R^{1c} und R^{1d} Wasserstoff darstellen, in allen ihren stereoisomeren Formen und Gemische davon in beliebigem Verhältnis und ihre physiologisch verträglichen Salze.

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3. Verbindung der Formel I nach Ansprüchen 1 und/oder 2, worin einer der Reste R^{1a} und R^{1b} Wasserstoff darstellt und der andere ausgewählt ist aus der Reihe bestehend aus Wasserstoff, Methyl, F, Cl, Br, I, Hydroxy, (C₁-C₄)-Alkoxy, Phenyl-(C₁-C₄)-alkoxy- und -NHR^{5a}, in allen ihren stereoisomeren Formen und Gemische davon in beliebigem Verhältnis und ihre physiologisch verträglichen Salze.

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4. Verbindung der Formel I nach einem oder mehreren der Ansprüche 1 bis 3, worin der Rest R² Wasserstoff darstellt, in allen ihren stereoisomeren Formen und Gemische davon in beliebigem Verhältnis und ihre physiologisch verträglichen Salze.

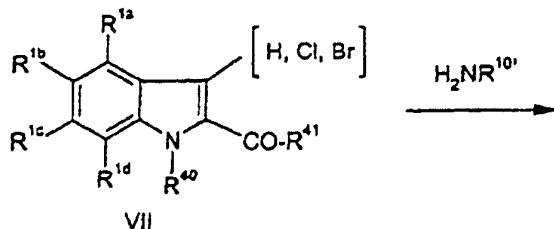
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5. Verfahren zur Herstellung einer Verbindung der Formel I nach einem oder mehreren der Ansprüche 1 bis 4, umfassend das Kondensieren einer Verbindung der Formel VII mit einer Verbindung der Formel H₂NR^{10'} zu einer Verbindung der Formel VIII und das Umwandeln der Verbindung der Formel VIII in eine Verbindung der Formel I,

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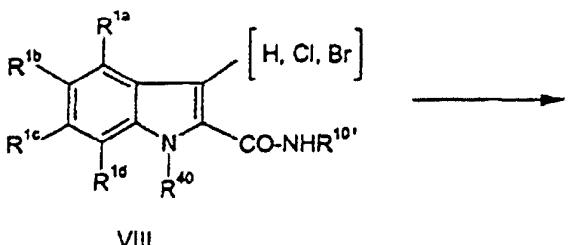
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wobei der Rest R^{10'} die Bedeutungen von R¹⁰, die in Ansprüchen 1 bis 4 ausgewiesen sind, aufweisen kann, wobei jedoch in R^{10'} funktionelle Gruppen ebenfalls in Form von Gruppen vorliegen können, die anschließend in die in R¹⁰ vorliegenden endgültigen funktionellen Gruppen überführt werden, und wobei der Rest R⁴⁰ die Gruppe -A-R⁴ bedeuten kann oder eine Gruppe bedeuten kann, die anschließend in die Gruppe -A-R⁴ überführt wird, und wobei die Gruppe -COR⁴¹ eine Carbonsäure-Gruppe oder ein Derivat davon sein kann, und worin die Gruppen R^{1a}, R^{1b}, R^{1c} und R^{1d} wie in Ansprüchen 1 bis 4 definiert sind oder funktionelle Gruppen in ihnen auch in geschützter Form oder in Form von Vorstufengruppen vorliegen können.

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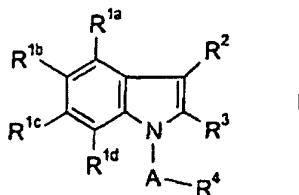
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6. Pharmazeutische Zusammensetzung, enthaltend eine oder mehrere Verbindungen der Formel I nach einem oder mehreren der Ansprüche 1 bis 4 und/oder deren physiologisch verträgliche Salze zusammen mit einem pharmazeutisch verträglichen Träger.
7. Verbindung der Formel I nach einem oder mehreren der Ansprüche 1 bis 4 und/oder ihre physiologisch verträglichen Salze zur Verwendung als Arzneimittel.
8. Verbindung der Formel I nach einem oder mehreren der Ansprüche 1 bis 4 und/oder ihre physiologisch verträglichen Salze zur Verwendung als Inhibitor von Faktor Xa.
9. Verbindung der Formel I nach einem oder mehreren der Ansprüche 1 bis 4 und/oder ihre physiologisch verträglichen Salze zur Verwendung als Inhibitor der Blutgerinnung.
10. Verbindung der Formel I nach einem oder mehreren der Ansprüche 1 bis 4 und/oder ihre physiologisch verträglichen Salze zur Verwendung bei der Behandlung oder Prophylaxe von cardiovaskulären Störungen oder thromboembolischen Zuständen.
11. Verbindung der Formel I nach einem oder mehreren der Ansprüche 1 bis 4 und/oder ihre physiologisch verträglichen Salze zur Verwendung bei der Behandlung oder Prophylaxe von Thrombosen, Herzinfarkt, Angina Pectoris, Restenosen oder Wiederverschluss.

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Revendications

1. Composé de formule I



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dans laquelle

deux des résidus R^{1a}, R^{1b}, R^{1c} et R^{1d}, indépendamment les uns des autres, sont des atomes d'hydrogène, F, Cl, Br, I, ou des groupes méthyle, alcoxy en C₁-C₄, phényl-alcoxy(en C₁-C₄), OH ou NR^{5a}R^{5b}, et sont identiques ou différents, et les deux autres des résidus R^{1a}, R^{1b}, R^{1c} et R^{1d} sont des atomes d'hydrogène ;

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R^{5a} est un atome d'hydrogène ou un groupe alcoxy(en C₁-C₄)carbonyle ;

R^{5b} est un atome d'hydrogène ;

R² est un atome d'hydrogène, Cl ou Br ;

R³ est un groupe -CO-NHR¹⁰ ;

R⁷ est un groupe hydroxy, alcoxy en C₁-C₄, phényl-alcoxy (en C₁-C₄) ou NR^{5a}R^{5b} ;

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R¹⁰ est un groupe alkyle en C₁-C₁₀, phényl-alkyle(en C₁-C₄) ou naphtyle(alkyle en C₁-C₄), le résidu alkyle en C₁-C₁₀, le résidu phényle et le résidu naphtyle sont non substitués ou substitués par un, deux ou trois résidus R¹¹ identiques ou différents ;

25

R¹¹ est un groupe -N(R¹²)₂, -OR¹², -CO-N(R¹³)₂, -CO-R⁷, R^{15b}, alkyle en C₁-C₁₄, phényle qui est non substitué ou substitué par un, deux ou trois résidus R^{15b} identiques ou différents, naphtyle qui est non substitué ou substitué par un, deux ou trois résidus R^{15b} identiques ou différents, quinoléinyle qui est non substitué ou substitué par un, deux ou trois résidus R^{15b} identiques ou différents et/ou substitué sur l'atome d'azote par R¹⁴, isoquinoléinyle qui est non substitué ou substitué par un, deux ou trois résidus R^{15b} identiques ou différents et/ou substitué sur l'atome d'azote par R¹⁴, pyridyle qui est non substitué ou substitué sur l'atome d'azote par R¹⁴, ou Het qui est non substitué ou substitué par R^{15a}, les résidus R¹¹, s'ils sont présents plus d'une fois dans la molécule, étant indépendants les uns des autres et pouvant être identiques ou différents ;

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Het est le résidu d'un noyau hétérocyclique saturé à 5 chaînons ou à 6 chaînons contenant 1 ou 2 hétéroatomes dans le noyau, identiques ou différents, choisis dans la série constituée par l'azote, l'oxygène et le soufre ; chaque résidu R¹², indépendamment de la désignation d'un autre résidu R¹², est un atome d'hydrogène ou un groupe alkyle en C₁-C₄, phényle, phényl-alkyle(en C₁-C₄), naphtyle, naphtyl-alkyle(en C₁-C₄), pyrrolidinyle, pipéridinyle, pyrrolidinyl-alkyle(en C₁-C₄) ou pipéridinyl-alkyle(en C₁-C₄), où chaque résidu pyrrolidinyle et chaque résidu pipéridinyle est non substitué ou substitué sur l'atome d'azote par un groupe phényl-alkyle(en C₁-C₄) ou R^{15a} ;

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chaque résidu R¹³, indépendamment de la désignation d'un autre résidu R¹³, est un atome d'hydrogène ou un groupe alkyle en C₁-C₄, phényle, phényl-alkyle(en C₁-C₄), naphtyle, ou naphtyl-alkyle (en C₁-C₄), ou les deux résidus R¹³, conjointement avec l'atome d'azote auquel ils sont fixés, forment un noyau hétérocyclique saturé à 5 chaînons ou à 6 chaînons qui peut contenir un atome d'azote ou un atome d'oxygène supplémentaire dans le noyau, l'atome d'azote supplémentaire dans le noyau étant non substitué ou substitué par un groupe alkyle en C₁-C₄ ou phényl-alkyle(en C₁-C₄) ;

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R¹⁴ est un groupe alkyle en C₁-C₆, alcényle en C₁-C₆, alcynyle en C₁-C₆, phényl-alkyle(en C₁-C₆) ou alcoxy(en C₁-C₆)carbonyl-alkyle(en C₁-C₆), où le groupe phényle présent dans R¹⁴ désigne un résidu phényle non substitué, la substitution par ces résidus sur l'atome d'azote du résidu hétérocyclique conduisant à un groupe de charge positive possédant un contre-ion X⁻; ou bien R¹⁴ est un groupe oxydo, cette substitution sur l'atome d'azote du résidu hétérocyclique conduisant à un N-oxyde ; et où les résidus R¹⁴, s'ils sont présents plus d'une fois dans la molécule, sont indépendants les uns des autres et peuvent être identiques ou différents ;

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R^{15a} est un groupe alkyle en C₁-C₆, alkyl(en C₁-C₆)-C(=NH)-, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N<sup>+(R^{16a})₂(-O⁻), -(CH₂)_t-N<sup>+(R^{16a})₃X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ ou -(CH₂)_t-NH-C(=NR¹⁷) ; où le groupe alkyl(en C₁-C₆)-C(=NH)- est fixé à un atome d'azote du noyau, et où les résidus R^{15a}, s'ils sont présents plus d'une fois dans la molécule, sont indépendants les uns des autres et peuvent être identiques ou différents ;

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R^{15b} est un groupe alkyle en C₁-C₆, hydroxy, alcoxy en C₁-C₄, F, Cl, Br, I, NO₂, -(CH₂)_t-N(R¹⁶)₂, -(CH₂)_t-N<sup>+(R^{16a})₂(-O⁻), -(CH₂)_t-N<sup>+(R^{16a})₃X⁻, -(CH₂)_t-NHR¹⁷, -(CH₂)_t-CO-OR¹⁸, -(CH₂)_t-CO-N(R¹⁸)₂, -(CH₂)_t-CN, -(CH₂)_t-CS-N(R¹⁸)₂, -(CH₂)_t-C(=NR¹⁷)-NHR¹⁷ ou -(CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷, où le groupe alkyle peut être substitué 1, 2, 3, 4, 5, 6 ou 7 fois par un groupe fluoro, et où les résidus R^{15b}, s'ils sont présents plus d'une fois dans la molécule,

sont indépendants les uns des autres et peuvent être identiques ou différents ; t vaut 0, 1, 2 ou 3, les nombres t, s'ils sont présents plus d'une fois dans la molécule, étant indépendants les uns des autres et pouvant être identiques ou différents ;

5 chaque résidu R¹⁶, indépendamment des désignations d'un autre résidu R¹⁶, est un atome d'hydrogène ou un groupe alkyle en C₁-C₆, alcényle en C₁-C₆, alcynyle en C₁-C₆, phényl-alkyle (en C₁-C₆) ou alcoxy(en C₁-C₆)carbonyl-alkyle(en C₁-C₆), où le groupe phényle présent dans R¹⁶ désigne un résidu phényle non substitué, et où les groupes contenant des résidus R¹⁶, s'ils sont présents plus d'une fois dans la molécule, sont indépendants les uns des autres et peuvent être identiques ou différents ;

10 chaque résidu R^{16a}, indépendamment des désignations d'un autre résidu R^{16a}, est un groupe alkyle en C₁-C₆, alcényle en C₁-C₆, alcynyle en C₁-C₆, phényl-alkyle(en C₁-C₆) ou alcoxy(en C₁-C₆) carbonyl-alkyle (en C₁-C₆), où le groupe phényle présent dans R^{16a} désigne un résidu phényle non substitué, et où les groupes contenant des résidus R^{16a}, s'ils sont présents plus d'une fois dans la molécule, sont indépendants les uns des autres et peuvent être identiques ou différents ;

15 chaque résidu R¹⁷, indépendamment de la désignation d'un autre résidu R¹⁷, est un atome d'hydrogène ou un groupe alkyle en C₁-C₆, alkyl(en C₁-C₆)carbonyle, alcoxy(en C₁-C₆)carbonyle, alkyl(en C₁-C₆)carbonyloxy-alcoxy (en C₁-C₆)carbonyle, phénylcarbonyle, phénoxycarbonyle, phényl-alcoxy(en C₁-C₆)carbonyle, hydroxy, alcoxy en C₁-C₆, phényl-alcoxy(en C₁-C₆) ou amino, et de plus, dans les groupes -(CH₂)_tC(=NR¹⁷)-NHR¹⁷ et - (CH₂)_t-NH-C(=NR¹⁷)-NHR¹⁷, les deux résidus R¹⁷, conjointement avec le groupe C(=N)-NH auquel ils sont fixés, peuvent former un noyau hétérocyclique à 5 chaînons ou à 6 chaînons, et où le groupe phényle présent dans R¹⁷ désigne un résidu phényle non substitué, et où les groupes contenant des résidus R¹⁷, s'ils sont présents plus d'une fois dans la molécule, sont indépendants les uns des autres et peuvent être identiques ou différents ;

20 chaque résidu R¹⁸, indépendamment de la désignation d'un autre résidu R¹⁸, est un atome d'hydrogène ou un groupe alkyle en C₁-C₄ ;

A est un résidu méthylène -CH₂- ;

25 R⁴ est un groupe phényle, qui est substitué par un résidu R^{15c} en position méta ;

R^{15c} est un groupe -C(=NR¹⁷)-NHR¹⁷ dans lequel les résidus R¹⁷ sont des atomes d'hydrogène ;

X⁻ est un anion acceptable sur le plan physiologique ;

sous toutes ses formes stéréoisomères et leurs mélanges en toutes proportions, et ses sels acceptables sur le plan physiologique.

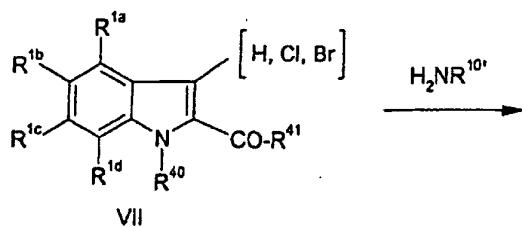
30 2. Composé de formule I selon la revendication 1, dans lequel les résidus R^{1c} et R^{1d} sont des atomes d'hydrogène, sous toutes ses formes stéréoisomères et leurs mélanges en toutes proportions, et ses sels acceptables sur le plan physiologique.

35 3. Composé de formule I selon les revendications 1 et/ou 2, dans lequel un des résidus R^{1a} et R^{1b} est un atome d'hydrogène et l'autre est choisi dans la série constituée de l'hydrogène et des groupes méthyle, F, Cl, Br, I, hydroxy, alcoxy en C₁-C₄, phényl-alcoxy(en C₁-C₄) et -NHR^{5a}, sous toutes ses formes stéréoisomères et leurs mélanges en toutes proportions, et ses sels acceptables sur le plan physiologique.

40 4. Composé de formule I selon une ou plusieurs des revendications 1 à 3, dans lequel le résidu R² est un atome d'hydrogène, sous toutes ses formes stéréoisomères et leurs mélanges en toutes proportions, et ses sels acceptables sur le plan physiologique.

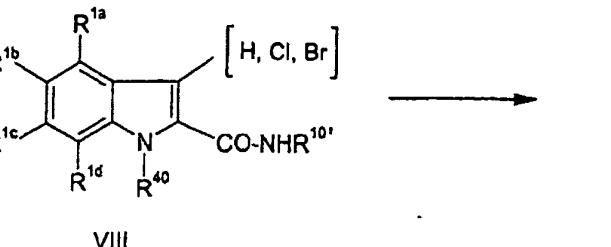
45 5. Procédé de préparation d'un composé de formule I selon une ou plusieurs des revendications 1 à 4, comprenant la condensation d'un composé de formule VII avec un composé de formule H₂NR¹⁰, pour obtenir un composé de formule VIII, et la transformation du composé de formule VIII en composé de formule I,

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où le résidu R^{10'} peut avoir les définitions de R¹⁰ indiquées dans les revendications 1 à 4, mais où, dans R^{10'}, des groupes fonctionnels peuvent aussi être présents sous forme de groupes qui sont ensuite transformés en groupes fonctionnels finals présents dans R¹⁰, et où le résidu R⁴⁰ peut désigner le groupe -A-R⁴ ou peut désigner un groupe qui est ensuite transformé en groupe -A-R⁴, et où le groupe -COR⁴¹ peut être un groupe acide carboxylique ou un de ses dérivés, et où les groupes R^{1a}, R^{1b}, R^{1c} et R^{1d} sont définis comme dans les revendications 1 à 4 ou bien les groupes fonctionnels qu'ils contiennent peuvent aussi être présents sous forme protégée ou sous forme de groupes précurseurs.

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6. Composition pharmaceutique comprenant un ou plusieurs composés de formule I selon une ou plusieurs des revendications 1 à 4 et/ou leurs sels acceptables sur le plan physiologique, avec un véhicule pharmaceutiquement acceptable.
7. Composé de formule I selon une ou plusieurs des revendications 1 à 4 et/ou ses sels acceptables sur le plan physiologique, à utiliser comme produit pharmaceutique.
8. Composé de formule I selon une ou plusieurs des revendications 1 à 4 et/ou ses sels acceptables sur le plan physiologique, à utiliser comme inhibiteur du facteur Xa.
9. Composé de formule I selon une ou plusieurs des revendications 1 à 4 et/ou ses sels acceptables sur le plan physiologique, à utiliser comme inhibiteur de la coagulation sanguine.
10. Composé de formule I selon une ou plusieurs des revendications 1 à 4 et/ou ses sels acceptables sur le plan physiologique, à utiliser dans le traitement ou la prophylaxie de troubles cardio-vasculaires ou de pathologies thromboemboliques.
11. Composé de formule I selon une ou plusieurs des revendications 1 à 4 et/ou ses sels acceptables sur le plan physiologique, à utiliser dans le traitement ou la prophylaxie de thromboses, d'infarctus du myocarde, d'angine de poitrine, de resténoses ou de réocclusion.

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