SUBSTITUTED N-(AMINOIMINOMETHYL OR AMINOMETHYL)PHENYL PROPYL AMIDES
SUBSTITUIERTE N-(AMINOIMINOMETHYL ODER AMINOMETHYL)PHENYL PROPYLAMIDE
N- AMINOIMINOMETHYL OU AMINOMETHYL)PHENYL PROPYLAMIDES SUBSTITUES

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The file contains technical information submitted after the application was filed and not included in this specification

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Field of the Invention

[0001] The compounds of formula I exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, they are Factor Xa inhibitors. The present invention is directed to compounds of formula I, compositions containing compounds of formula I, and their use for the manufacture of a medicament for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa.

[0002] Factor Xa is the penultimate enzyme in the coagulation cascade. Both free factor Xa and factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited by compounds of formula I. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the factor Xa induced formation of thrombin from prothrombin.

[0003] Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients.

With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening clots throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

Some substituted N-[(Aminiminomethyl or Aminomethyl)phenyl]propyl amides Factor Xa inhibitors are disclosed in International Patent Application Number WO 97/24118.

SUMMARY OF THE INVENTION

[0004] This invention is directed to a compound of formula I:

\[
\begin{array}{c}
\text{R1} \quad \text{R2} \\
\text{H2N} \\
\text{R3} \\
\text{NR6COR6} \\
\end{array}
\]

which is:
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DETAILED DESCRIPTION OF THE INVENTION

Species according to the invention are selected from the following:

or a pharmaceutically acceptable salt thereof or a solvate thereof.

or a pharmaceutically acceptable salt thereof or a solvate thereof.
Compounds of Formula I may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, or by methods according to this invention herein.

Scheme A exemplifies a general method for preparing intermediates for use in preparing compounds of formula I according to the invention.
Scheme B exemplifies a general method for converting the intermediates prepared according to Scheme A to compounds of formula I according to the invention.

Scheme C exemplifies a general method for effecting interconversions between compounds of formula I according to the invention.
In addition, the compounds of formula 1 wherein R₃ is hydroxymethyl may be converted to the corresponding thiomethyl compounds by treating the alcohol with an alkyl or aryl sulfonyl halide and displacing the alkyl or aryl sulfonate with NaSH, the thiomethyl compounds may then be alkylated or acylated to give other compounds within the scope of the invention.

[0009] Scheme D exemplifies a general method for converting a nitrile intermediate to a compound of formula I and
additional general methods for effecting interconversions between compounds of formula I according to the invention.

Scheme E exemplifies an additional general method for effecting interconversions between compounds of formula I according to the invention.
Scheme F exemplifies a general method for preparing compounds according to the present invention wherein $R_4$ of formula I is optionally substituted phenethyl.
Scheme G exemplifies a general method for preparing compounds according to the present invention wherein $R_4$ of formula I is methyl.
Scheme H exemplifies a general method for preparing compounds according to the present invention.

[0011] Scheme H exemplifies a general method for preparing compounds according to the present invention.

[0012] Scheme H exemplifies a general method for preparing compounds according to the present invention.
Scheme I exemplifies a general method for preparing compounds according to the present invention.
[0014] It will be apparent to those skilled in the art that certain compounds of formula I can exhibit isomerism, for example geometrical isomerism, e.g., E or Z isomerism, and optical isomerism, e.g., R or S configurations. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl moieties. Individual geometrical isomers and stereoisomers within formula I, and their mixtures, are within the scope of the invention.

[0015] Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

[0016] The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

[0017] Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification,
and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylenebis-B-hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

According to a further feature of the invention, acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution. Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on Factor Xa inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of the compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an alpha-OH ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an alkali, e.g. hydrochloric acid.

Pharmaceutically acceptable salts also include quaternary lower alkyl ammonium salts. The quaternary salts are prepared by the exhaustive alkylation of basic nitrogen atoms in compounds, including nonaromatic and aromatic basic nitrogen atoms, according to the invention, i.e., alkylling the non-bonded pair of electrons of the nitrogen moieties with an alkylling agent such as methylhalide, particularly methyl iodide, or dimethyl sulfate. Quaternarium results in the nitrogen moiety becoming positively charged and having a negative counter ion associated therewith.

As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds of this invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein there is not an acid labile group.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents, or by methods according to this invention.

The present invention is further exemplified but not limited by the following illustrative examples which illustrate...
the preparation of the compounds according to the invention.

[0029] In the nuclear magnetic resonance spectra (NMR) the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significance: s=singlet; d=doublet; t=triplet; m=multiplet; dd=doublet of doublets; ddd=doublet of doublets of doublets; dt=doublet of triplets, b=broad.

Reference EXAMPLE 56

Compound 56

[0030]

[0031] To a solution of N-a-Boc-D-Phenylalanine (38 mmol) in 80 mL of dry tetrahydrofuran is added N-methyl morpholine (38 mmol) in a single portion, followed by isobutyl chloroformate (38 mmol) in a similar fashion, at -20°C. The reaction mixture is stirred for 10 minutes at -20°C and filtered into a preformed ethereal solution of diazomethane (~70 mmol) at 0°C. The resulting solution is allowed to stand at 0°C for 20 minutes. Excess diazomethane is decomposed by the dropwise addition of glacial acetic acid and solvents are removed in vacuo. The resulting oil is dissolved in 150 mL of dry methanol. A solution of silver benzoate (8 mmol) in 17 mL of triethylamine is slowly added with stirring, at room temperature. The resulting black reaction mixture is stirred for 45 minutes at room temperature. Methanol is removed in vacuo and the residue taken up in 700 mL of ethyl acetate. The mixture is filtered through celite and washed sequentially with saturated sodium bicarbonate (3X150 mL), water (1X150 mL), 1N potassium bisulfate (3x150 mL) and brine (1X150 mL). The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo, and purified by flash chromatography (3:1 hexanes:ethyl acetate).

Reference EXAMPLE 57

Compound 57

[0032]

[0033] Compound 57 is prepared using the procedure described for Compound 56, substituting N-a-Boc-D-alanine.

Reference EXAMPLE 58

Compound 58

[0034]

[0035] Compound 58 is prepared using the procedure described for Compound 56, substituting N-a-Boc-D-homophenyllalanine.
A solution of Compound 56 (11 mmol) in 70 mL of dry tetrahydrofuran is cooled to -78°C and a solution of lithium hexamethyldisilazane in tetrahydrofuran (33 mmol) is added via syringe at such a rate that the temperature did not rise above -60°C. The reaction mixture is warmed to -25°C over 40 minutes and recooled to -78°C. A solution of 3-cyanobenzyl bromide (27 mmol) in 20 mL of tetrahydrofuran is added via syringe at such a rate that the temperature did not rise above -60°C. The reaction mixture is allowed to come to room temperature and stirred at room temperature for 1 hour. 125 mL of saturated sodium bicarbonate is added and tetrahydrofuran is removed in vacuo. The remaining material is partitioned between 500 mL of ethyl acetate and 150 mL of saturated sodium bicarbonate. The organic phase is further washed with saturated sodium bicarbonate (2x100 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, concentrated in vacuo. The solid material is filtered off and discarded. The filtrate, containing the desired product, is concentrated in vacuo.

Compound 63 is prepared following the method described for Compound 62, substituting the product obtained in Example 57.
[0041] Compound 64 is prepared following the method described for Compound 62, substituting the product obtained in Example 58.

Reference EXAMPLE 68

Compound 68

[0042]

[0043] To a solution of Compound 62 (5 mmol) in 60 mL of methylene chloride is added 20 mL of trifluoroacetic acid, dropwise at 0°C. The resulting solution is stirred for 2 hours at 0°C. Solvents are removed \textit{in vacuo} and the residue purified by reverse phase HPLC using a gradient of 30% to 70% acetonitrile in water containing 0.1% trifluoroacetic acid. Acetonitrile is removed in vacuo and the remaining material partitioned between saturated sodium bicarbonate and ethyl acetate. The aqueous layer is extracted twice with ethyl acetate and the combined organic layers are dried over magnesium sulfate, filtered, and concentrated in vacuo.

Reference EXAMPLE 69

Compound 69

[0044]

[0045] Compound 69 is prepared according to the method described in Example 68, substituting the product obtained in Example 63.
Compound 70

[0046] Compound 70 is prepared according to the method described in Example 68, substituting the product obtained in Example 64.

Reference EXAMPLE 74

Compound 74

[0048] Solution (A): To a solution of 11.8 mL of n-butyllithium in hexanes (19 mmol) in 13 mL of tetrahydrofuran is added a solution of 1-bromo-2-fluorobenzene (19 mmol) in 2 mL of tetrahydrofuran, dropwise via syringe at -78°C. Stirring at -78 °C is continued for 1 hour. A solution of zinc chloride (19 mmol) in 38 mL of tetrahydrofuran is added over 2 minutes at -78°C. The resulting solution is allowed to come to room temperature over 40 minutes.

Solution (B): To a solution of bis(triphenylphosphine)palladium dichloride (1 mmol) in 11 mL of tetrahydrofuran is added diisobutyl aluminum hydride (1 mmol) as a solution in hexanes, at room temperature, followed by methyl iodobenzoate (16 mmol) in a single portion at room temperature.

Solution (A) is added to solution (B) and the reaction mixture allowed to stir at room temperature overnight. The reaction mixture is diluted with 300 mL of diethyl ether and washed with 1N hydrochloric acid (3x75 mL) and brine. The organic layer is dried over magnesium sulfate, filtered, and concentrated in vacuo.

Reference EXAMPLE 77

Compound 77

[0051] Compound 77 is prepared according to the method described in EXAMPLE 74, substituting 3,4-ethylenedioxy bromobenzene in the preparation of Solution (A).
To a suspension of Compound 74 (1.6 mmol) in 10 mL of methanol and 20 mL of tetrahydrofuran is added 10 mL of 2N sodium hydroxide, dropwise at room temperature. The resulting solution is allowed to stir at room temperature for 2 hours. Organic solvents are removed in vacuo and the residue diluted with 20 mL of water and brought to pH 2 with 1N hydrochloric acid. Solid material is filtered off and dried under vacuum.

Compound 96 is prepared according to the method described for Compound 93, substituting the product obtained in Example 77.

Compound 99 is prepared according to the method described for Compound 93, substituting the product obtained in Example 82.
To a solution of Compound 96 (2 mmol) in 10 mL of DMF is added diisopropyl ethylamine (2 mmol) in a single portion at room temperature, followed by 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2 mmol) in a similar fashion. The reaction mixture is stirred for 2 minutes at room temperature and a solution of Compound 70 (2 mmol) in 15 mL of dimethylformamide is added in a single portion. Stirring is continued overnight at room temperature. The reaction mixture is diluted with 300 mL of ethyl acetate and washed sequentially with 1N hydrochloric acid (3x75 mL), water, saturated sodium bicarbonate (3x75 mL) and brine. The organic phase is dried over magnesium sulfate, filtered and concentrated in vacuo.

Reference EXAMPLE 114

Compound 114

Compound 114 is prepared using the same procedure described for Compound 107, substituting Compound 99 for Compound 96 and substituting Compound 68 for Compound 70.

Reference EXAMPLE 123

Compound 123
Compound 123 is prepared using the same procedure described for Compound 107, substituting Compound 99 for 96 and substituting Compound 69 for Compound 70.

Reference EXAMPLE 129

Compound 129

To a solution of Compound 107 (1.2 mmol) in 10 mL of methanol and 10 mL of tetrahydrofuran is added 10 mL of 2N sodium hydroxide, dropwise at 0°C. The solution is allowed to come to room temperature and stirred at room temperature for 2.5 hours. The solution is cooled to 0°C and 1N hydrochloric acid is added until the pH is 7. Organic solvents are removed in vacuo and the residue diluted with 25 mL of water. 1N hydrochloric acid is added to bring the pH down to 2 and the mixture is extracted with ethyl acetate (3x75 mL). The combined organic extracts are dried over magnesium sulfate, filtered, concentrated, and dried under vacuum.

The acid (1.1 mmol) is dissolved in 15 mL of tetrahydrofuran and cooled to -20°C. N-methyl morpholine (1.45 mmol) is added in a single portion, followed by isobutyl chloroformate (1.45 mmol) dropwise via syringe. The reaction mixture is allowed to stir at -20°C for 20 minutes. The reaction mixture is filtered into a solution of sodium borohydride (11 mmol) in 20 mL of water at 0°C. Stirring is continued 1.5 hours at 0°C. The reaction mixture is diluted with 300 mL of ethyl acetate and washed with water (3x100 mL) and brine. The organic phase is dried over magnesium sulfate, filtered, and concentrated. The resulting alcohol is purified by flash chromatography (2:3 ethyl acetate:hexanes).

Reference EXAMPLE 159a

Compound 159

[0067]
To a solution of Compound 129 (1 mmol) in 50 mL of dry methanol is added crushed 3Å molecular sieves (approximately 1 g). The mixture is stirred for 10 minutes at 0°C and hydrogen chloride gas is bubbled through the reaction mixture for 10 minutes at 0°C. The reaction mixture is allowed to come to room temperature and stirred overnight. Nitrogen gas is bubbled through the reaction mixture for 5 minutes and methanol is removed in vacuo. The residue is dried under vacuum to remove all traces of hydrogen chloride, then remixed with 75 mL of dry methanol. The mixture is then cooled to 0°C and ammonia gas is bubbled through the reaction mixture for 10 minutes. The reaction mixture is allowed to come to room temperature, then heated at 60°C for 3 hours. After cooling to room temperature, nitrogen gas is bubbled through the reaction for 5 minutes and the mixture is filtered through celite, concentrated in vacuo, and purified by reverse phase HPLC using a gradient of 20% to 80% acetonitrile in water buffered with 0.1% trifluoroacetic acid. Acetonitrile is removed in vacuo and the aqueous phase lyophilized to provide the desired product as its trifluoroacetate salt.

Reference EXAMPLE 159b

Compound 159

[0069] 1H NMR (300 MHz, d6 DMSO) 6 9.21 (s, 2H), 9.01 (s, 2H), 8.22 (d, 1H, J=9.6 Hz), 7.85 (d, 2H, J=7.2 Hz), 7.70 (d, 2H, J=7.2 Hz), 7.62-7.38 (m, 4H), 7.25-7.05 (m, 7H), 6.93 (d, 1H, J=8.4 Hz), 4.90-4.65 (m, 1H), 4.24 (s, 4H), 4.18-4.05 (m, 2H), 2.78-2.63 (m, 2H), 2.65-2.45 (m, 2H), 2.08-1.75 (m, 3H). MS, LRFAB, calc. 591, found 592 (M+H)+.

[0071] Into a solution of Compound 129 (1 mmol) in 20 mL of pyridine and 4 mL of triethylamine is bubbled hydrogen sulfide for 10 minutes at room temperature. The solution is allowed to stir at room temperature overnight. Nitrogen gas is bubbled through the reaction for 5 minutes and solvents are removed in vacuo. The residue is dried under vacuum, then dissolved in 15 mL of dry acetone. To this solution is added 5 mL of methyl iodide and this solution is heated at 50°C for 1 hour, then concentrated in vacuo. The residue is dissolved in 20 mL of methanol and ammonium acetate (2
mmol) is added in a single portion at room temperature. The reaction mixture is heated at 65°C for 2 hours. After cooling, methanol is removed in vacuo and the residue purified by reverse phase HPLC using a gradient of 20% to 80% acetonitrile in water buffered with 0.1% trifluoroacetic acid. Acetonitrile is removed in vacuo and the aqueous phase lyophilized to provide the desired product as its trifluoroacetate salt.

The following compounds are prepared from the appropriate starting materials by procedures substantially similar to the procedures described above.

Reference EXAMPLE 239

Compound 239

This material is prepared following the procedure described for compound 123 and substituting benzimidazole-5-carboxylic acid for 99.

Reference EXAMPLE 240

Compound 240

This material is prepared following the procedure described for compound 123 and substituting quinoline-7-carboxylic acid for 99.

Reference EXAMPLE 241

Compound 241
[0078] This material is prepared following the procedure described for compound 123 and substituting N-(4-pyridyl)piperidine-4-carboxylic acid for 99.

Reference EXAMPLE 242

Compound 242

[0079]

[0080] This material is prepared following the procedure described for compound 123 and substituting 2-(1-piperazinyl)pyridine-5-carboxylic acid for 99.

Reference EXAMPLE 243

Compound 243

[0081]
This material is prepared following the procedure described for compound 123 and substituting 2-(4-pyridinyl)-1,3-thiazole-4-carboxylic acid for 99.

Reference EXAMPLE 244

Compound 244

This material is prepared following the procedure described for compound 123 and substituting 4-(5-(1,2,4-thiadiazolyl))benzoic acid for 99.

Reference EXAMPLE 245

Compound 245
[0086] This material is prepared following the procedure described for compound 123 and substituting 2-(2-pyridyl) thiophene-5-carboxylic acid for 99.

Reference EXAMPLE 246

Compound 246

[0087]

[0088] This material is prepared following the procedure described for compound 123 and substituting 2-(3-pyridyl) thiophene-5-carboxylic acid for 99.

Reference EXAMPLE 247

Compound 247

[0089]
This material is prepared following the procedure described for compound 123 and substituting 2-(4-pyridyl) thiophene-5-carboxylic acid for 99.

Reference EXAMPLE 248

Compound 248

This material is prepared following the procedure described for compound 123 and substituting 3-(2-pyridyl) thiophene-5-carboxylic acid for 99.

Reference EXAMPLE 249

Compound 249
This material is prepared following the procedure described for compound 123 and substituting 3-(3-pyridyl) thiophene-5-carboxylic acid for 99.

Reference EXAMPLE 250

Compound 250

This material is prepared following the procedure described for compound 123 and substituting 3-(4-pyridyl) thiophene-5-carboxylic acid for 99.

Reference EXAMPLE 251

Compound 251
[0098] This material is prepared following the procedure described for compound 123 and substituting 4-(1-imidazolyl) benzoic acid for 99.

Reference EXAMPLE 252

Compound 252

[0099]

[0100] This material is prepared following the procedure described for compound 123 and substituting 4-(4-imidazolyl) benzoic acid for 99.

Reference EXAMPLE 253

Compound 253

[0101]
This material is prepared following the procedure described for compound 123 and substituting 4-(2-imidazolyl)benzoic acid for 99.

Reference EXAMPLE 254

Compound 254

This material is prepared following the procedure described for compound 123 and substituting 3-(1-imidazolyl)benzoic acid for 99.

Reference EXAMPLE 255

Compound 255
This material is prepared following the procedure described for compound 123 and substituting 2-(1-imidazolyl)-pyridine-5-carboxylic acid for 99.

Reference EXAMPLE 256

Compound 256

This material is prepared following the procedure described for compound 123 and substituting 2-(1-pyrrolyl)-pyridine-5-carboxylic acid for 99.

Reference EXAMPLE 257

Compound 257
[0110] This material is prepared following the procedure described for compound 123 and substituting 4-(1-pyrrol)benmic acid for 99.

Reference EXAMPLE 258

Compound 258

[0111]

[0112] This material is prepared following the procedure described for compound 123 and substituting 5-(3-pyridyl)-1,3-thiazole-2-carboxylic acid for 99.

Reference EXAMPLE 259

Compound 259

[0113]
This material is prepared following the procedure described for compound 123 and substituting 2-phenyl-5-methyl-1,2,3-triazole-4-carboxylic acid for 99.

Reference EXAMPLE 260

Compound 260

This material is prepared following the procedure described for compound 123 and substituting 2-(2,4-difluorophenyl)-1,3-thiazole-4-carboxylic acid for 99.

Reference EXAMPLE 261

Compound 261
[0118] This material is prepared following the procedure described for compound 123 and substituting 2-(2,3-dichlorophenyl)-1,3-thiazole-4-carboxylic acid for 99.

Reference EXAMPLE 262

Compound 262

[0119]

[0120] This material is prepared following the procedure described for compound 123 and substituting 3-phenyl-5-methyl-1,2-diazole-4-carboxylic acid for 99.

Reference EXAMPLE 263

Compound 263

[0121]
This material is prepared following the procedure described for compound 123 and substituting 1,2-phthalimide-4-carboxylic acid for 99.

Reference EXAMPLE 264

Compound 264

This material is prepared following the procedure described for compound 123 and substituting 3-aza-b-carboline-4-carboxylic acid for 99.

Reference EXAMPLE 265

Compound 265
This material is prepared following the procedure described for compound 123 and substituting 2-methyl-1-azaindolizine-3-carboxylic acid for 99.

Reference EXAMPLE 266

Compound 266

This material is prepared following the procedure described for compound 56 and substituting N-a-Boc-O-benzyl-D-serine.

Reference EXAMPLE 267

Compound 267

This material is prepared following the procedure described for compound 62 and substituting Compound 266.
Reference EXAMPLE 268

Compound 268

[0131]

\[
\begin{align*}
\text{BnO} & \text{NH}_2 \\
& \text{COOCH}_3 \\
& \text{CN}
\end{align*}
\]

[0132] This material is prepared following the procedure described for compound 68 and substituting Compound 267.

Reference EXAMPLE 269

Compound 269

[0133]

\[
\begin{align*}
\text{BocHN} & \text{BnO} \\
& \text{NH} \\
& \text{COOCH}_3 \\
& \text{CN}
\end{align*}
\]

[0134] This material is prepared following the procedure described for compound 114 and substituting Compound 268.

Reference EXAMPLE 270

Compound 270

[0135]
This material is prepared following the procedure described for compound 129 and substituting Compound 269.

EXAMPLE 271

Compound 271

This material is prepared following the procedure described for compound 159a and substituting Compound 239. MS: (M+H)+ 395.

EXAMPLE 272

Compound 272
This material is prepared following the procedure described for compound 159a and substituting Compound 240. MS: (M+H)^+ 406.

EXAMPLE 273

Compound 273

This material is prepared following the procedure described for compound 159a and substituting Compound 241. MS: (M+H)^+ 439.

EXAMPLE 274

Compound 274
[0144] This material is prepared following the procedure described for compound 159a and substituting Compound 242. MS: (M+H)+ 440.

EXAMPLE 275

Compound 275

[0145]  

[0146] This material is prepared following the procedure described for compound 159a and substituting Compound 243. MS: (M+H)+ 439.

EXAMPLE 276

Compound 276

[0147]
EXAMPLE 277

Compound 277

This material is prepared following the procedure described for compound 159a and substituting Compound 244. MS: (M+H)+ 439.

EXAMPLE 278

Compound 278

This material is prepared following the procedure described for compound 159a and substituting Compound 245. 1H NMR (DMSO-d6) δ 8.56-8.50 (m, 1H), 7.94-7.82 (m, 2H), 7.70 (s, 2H), 7.66-7.46 (m, 4H), 7.38-7.30 (m, 1H), 4.46-4.32 (m, 1H), 3.60 (s, 3H), 3.13-2.95 (m, 3H), 1.32 (d, J=7.2Hz, 3H). MS: (M+H)+ 438.
This material is prepared following the procedure described for compound 159a and substituting Compound 246. $^1$H NMR (DMSO-$d_6$) δ 9.06 (s, 1H), 8.68-8.62 (m, 1H), 8.53 (d, J=8.4Hz, 1H), 7.85-7.78 (m, 1H), 7.75 (d, J=3.6Hz, 1H), 7.68 (d, J=3.6Hz, 1H), 7.65-7.45 (m, 4H), 4.48-4.33 (m, 1H), 3.57 (s, 3H), 3.13-3.00 (m, 3H), 1.32 (d, J=7.2Hz, 3H). MS: (M+H)$^+$ 438.

EXAMPLE 279

Compound 279

This material is prepared following the procedure described for compound 159a and substituting Compound 247. $^1$H NMR (DMSO-$d_6$) δ 8.70 (s, 1H), 8.52 (d, J=9.6Hz, 1H), 8.18-8.08 (m, 1H), 7.96 (d, J=3.6Hz, 1H), 7.82 (d, J=3.6Hz, 1H), 7.65-7.45 (m, 4H), 4.50-4.35 (m, 1H), 3.57 (s, 3H), 3.13-3.02 (m, 3H), 1.34 (d, J=7.2Hz, 3H). MS: (M+H)$^+$ 438.

EXAMPLE 280

Compound 280

This material is prepared following the procedure described for compound 159a and substituting Compound 247. $^1$H NMR (DMSO-$d_6$) δ 8.70 (s, 1H), 8.52 (d, J=9.6Hz, 1H), 8.18-8.08 (m, 1H), 7.96 (d, J=3.6Hz, 1H), 7.82 (d, J=3.6Hz, 1H), 7.65-7.45 (m, 4H), 4.50-4.35 (m, 1H), 3.57 (s, 3H), 3.13-3.02 (m, 3H), 1.34 (d, J=7.2Hz, 3H). MS: (M+H)$^+$ 438.
This material is prepared following the procedure described for compound 159a and substituting Compound 248. ¹H NMR (DMSO-d₆) δ 8.66 (d, J=6.0Hz, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.20-8.11 (m, 1H), 8.04 (d, J=7.2Hz, 1H), 7.65-7.44 (m, 5H), 4.50-4.35 (m, 1H), 3.60 (s, 3H), 3.17-3.02 (m, 3H), 1.33 (d, J=7.2Hz, 3H). MS: (M+H)⁺ 438.

EXAMPLE 281

Compound 281

This material is prepared following the procedure described for compound 159a and substituting Compound 249. ¹H NMR (DMSO-d₆) δ 9.15-9.02 (m, 1H), 8.75-8.61 (m, 1H), 8.54 (d, J=8.4Hz, 1H), 8.22 (d, J=8.4Hz, 1H), 7.88-7.78 (m, 1H), 7.65-7.45 (m, 4H), 4.50-4.35 (m, 1H), 3.57 (s, 3H), 3.17-3.02 (m, 3H), 1.35 (d, J=7.2Hz, 3H). MS: (M+H)⁺ 438.

EXAMPLE 282

Compound 282
EXAMPLE 283

Compound 283

EXAMPLE 284

Compound 284
This material is prepared following the procedure described for compound 159a and substituting Compound 252. $^1$H NMR (DMSO-$d_6$) $\delta$ 9.0 (s, 1H), 8.5 (d, J=5.0Hz, 1H), 8.1 (s, 1H), 8.0 (d, J=5.0Hz, 2H), 7.9 (d, J=5.0Hz, 2H), 7.5-7.7 (m, 4H), 4.4-4.6 (m, 1H), 3.6 (s, 3H), 3.0-3.2 (m, 3H), 1.4 (d, J=5.0Hz, 3H). MS: (M+H)$^+$ 421.

EXAMPLE 285

Compound 285

This material is prepared following the procedure described for compound 159a and substituting Compound 253. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.5 (d, J=5.0Hz, 1H), 7.80-8.10 (m, 4H), 7.8 (d, J=5.0Hz, 2H), 7.5-7.7 (m, 4H), 4.4-4.6 (m, 1H), 3.6 (s, 3H), 3.0-3.1 (m, 3H), 1.4 (d, J=5.0Hz, 3H). MS: (M+H)$^+$ 421.

EXAMPLE 286

Compound 286

This material is prepared following the procedure described for compound 159a and substituting Compound 254. $^1$H NMR (DMSO-$d_6$) $\delta$ 8.5 (d, J=5.0Hz, 1H), 7.80-8.10 (m, 4H), 7.8 (d, J=5.0Hz, 2H), 7.5-7.7 (m, 4H), 4.4-4.6 (m, 1H), 3.6 (s, 3H), 3.0-3.1 (m, 3H), 1.4 (d, J=5.0Hz, 3H). MS: (M+H)$^+$ 421.
This material is prepared following the procedure described for compound 159a and substituting Compound 254. MS: (M+H)^+ 421.

EXAMPLE 287

Compound 287

This material is prepared following the procedure described for compound 159a and substituting Compound 255. MS: (M+H)^+ 422.

EXAMPLE 288

Compound 288
[0172] This material is prepared following the procedure described for compound 159a and substituting Compound 256. MS: (M+H)^+ 421.

EXAMPLE 289

Compound 289

[0173]

[0174] This material is prepared following the procedure described for compound 159a and substituting Compound 257. MS: (M+H)^+ 420.

EXAMPLE 290

Compound 290

[0175]
This material is prepared following the procedure described for compound 159a and substituting Compound 258. MS: (M+H)$^+$ 439.

EXAMPLE 291

Compound 291

This material is prepared following the procedure described for compound 159a and substituting Compound 259. MS: (M+H)$^+$ 436.

EXAMPLE 292

Compound 292
This material is prepared following the procedure described for compound 159a and substituting Compound 260. MS: (M+H)⁺ 473.

EXAMPLE 293

Compound 293

This material is prepared following the procedure described for compound 159a and substituting Compound 261. MS: (M+H)⁺ 507.

EXAMPLE 294

Compound 294
This material is prepared following the procedure described for compound 159a and substituting Compound 262. MS: (M+H)+ 434.

EXAMPLE 295

Compound 295

This material is prepared following the procedure described for compound 159a and substituting Compound 263. MS: (M+H)+ 421.

EXAMPLE 296

Compound 296
This material is prepared following the procedure described for compound 159a and substituting Compound 264. MS: (M+H)^+ 444.

**EXAMPLE 297**

Compound 297

This material is prepared following the procedure described for compound 159a and substituting Compound 265. MS: (M+H)^+ 408.

**EXAMPLE 298**

Compound 298
This material is prepared following the procedure described for compound 159b and substituting Compound 269.

EXAMPLE 299

Compound 299

This material is prepared following the procedure described for compound 159b and substituting Compound 270.

EXAMPLE 300

Compound 300
To a solution of compound 298 (1 mmol) in 20 mL of CH₂Cl₂ is added 5 mL of TFA at 0°C with stirring. Stirring is continued for 1 hour at 0°C and all solvents are removed in vacuo.

EXAMPLE 301

Compound 301

To a solution of compound 300 (1 mmol) in 25 mL of methanol is added approximately 50 mg of 10% palladium on charcoal. The mixture is shaken under a positive pressure of hydrogen (55 psi) for 24 hours and filtered. The filtrate is concentrated in vacuo and purified by reverse phase HPLC. ¹H NMR (DMSO-d₆) δ 8.3 (d, J=6.0Hz, 1H), 8.0 (d, J=5.0Hz, 2H), 7.8 (d, J=5.0Hz, 2H), 7.7 (d, J=6.0Hz, 2H), 7.4-7.7 (m, 6H), 4.3-4.5 (m, 1H), 4.2 (s, 2H), 3.8 (d, J=4.0Hz, 2H), 3.7 (s, 3H), 3.2-3.4 (m, 3H), 3.1-3.2 (m, 2H). MS: (M+H)+ 475.

EXAMPLE 302

Compound 302
EXAMPLE 303

Compound 303 is prepared in a manner identical to compound 301, starting from compound 302.  

H NMR (DMSO-\(d_6\)) \(\delta\) 8.4 (d, \(J=5.0\text{Hz}, 1\text{H}\)), 8.0 (d, \(J=5.0\text{Hz}, 2\text{H}\)), 7.8 (d, \(J=5.0\text{Hz}, 2\text{H}\)), 7.7 (d, \(J=4.0\text{Hz}, 2\text{H}\)), 7.5-7.7 (m, 6H), 4.2 (s, 2H), 4.1-4.2 (m, 1H), 4.0 (dd, \(J=8.0, 2.0\text{Hz}, 1\text{H}\)), 3.8 (s, 2H), 3.7 (dd, \(J=8.0, 2.0\text{Hz}, 1\text{H}\)), 3.0 (d, \(J=5.0\text{Hz}, 2\text{H}\)), 2.2-2.4 (m, H). MS: (M+H)+ 448.

EXAMPLE 304

Compound 304

[0203]
Compound 304 is prepared by procedures substantially similar to those used to prepare compound 301, starting from the appropriate materials. $^1$H NMR (CD$_3$OD) $\delta$ 7.94 (d, J=10.8 Hz, 2H), 7.85-7.72 (m, 4H), 7.70-7.45 (m, 6H), 4.32-4.23 (m, 1H), 4.22 (s, 2H), 3.62 (s, 3H), 3.83-3.55 (m, 2H), 3.18-3.02 (m, 2H), 0.94 (t, J=8.4 Hz, 3H). MS: (M+H)$^+$ 474.

EXAMPLE 305

Compound 305

Compound 306 is prepared by procedures substantially similar to those used to prepare compound 301, starting from the appropriate materials. $^1$H NMR (CD$_3$OD) $\delta$ 7.94 (d, J=10.8 Hz, 2H), 7.85-7.72 (m, 4H), 7.68-7.45 (m, 6H), 4.42-4.30 (m, 1H), 4.22 (s, 2H), 3.61 (s, 3H), 3.15-3.02 (m, 3H), 1.72-1.58 (m, 2H), 1.51-1.32 (m, 2H), 0.93 (t, J=8.4 Hz, 3H). MS: (M+H)$^+$ 488.

EXAMPLE 306

Compound 306
Compound 306 is prepared by procedures substantially similar to those used to prepare compound 301, starting from the appropriate materials. \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 7.93 (d, J=10.8Hz, 2H), 7.85-7.72 (m, 4H), 7.70-7.45 (m, 6H), 4.42-4.30 (m, 1H), 4.22 (s, 2H), 3.62 (s, 3H), 3.14-3.02 (m, 3H), 1.78-1.60 (m, 2H), 1.45-1.25 (m, 4H), 0.90 (t, J=8.4Hz, 3H). MS: (M+H)\(^+\) 502.

The molecules described herein inhibit blood coagulation by virtue of their ability to inhibit the penultimate enzyme in the coagulation cascade, factor Xa, rather than thrombin. Both free factor Xa and factor Xa assembled in the prothrombinase complex (Factor Xa, Factor Va, calcium and phospholipid) are inhibited. Factor Xa inhibition is obtained by direct complex formation between the inhibitor and the enzyme and is therefore independent of the plasma co-factor antithrombin III. Effective factor Xa inhibition is achieved by administering the compounds either by oral administration, continuous intravenous infusion, bolus intravenous administration or any other parenteral route such that it achieves the desired effect of preventing the factor Xa induced formation of thrombin from prothrombin.

Anticoagulant therapy is indicated for the treatment and prophylaxis of a variety of thrombotic conditions of both the venous and arterial vasculature. In the arterial system, abnormal thrombus formation is primarily associated with arteries of the coronary, cerebral and peripheral vasculature. The diseases associated with thrombotic occlusion of these vessels principally include acute myocardial infarction (AMI), unstable angina, thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, stroke, intermittent claudication and bypass grafting of the coronary (CABG) or peripheral arteries. Chronic anticoagulant therapy may also be beneficial in preventing the vessel luminal narrowing (restenosis) that often occurs following PTCA and CABG, and in the maintenance of vascular access patency in long-term hemodialysis patients. With respect to the venous vasculature, pathologic thrombus formation frequently occurs in the veins of the lower extremities following abdominal, knee and hip surgery (deep vein thrombosis, DVT). DVT further predisposes the patient to a higher risk of pulmonary thromboembolism. A systemic, disseminated intravascular coagulopathy (DIC) commonly occurs in both vascular systems during septic shock, certain viral infections and cancer. This condition is characterized by a rapid consumption of coagulation factors and their plasma inhibitors resulting in the formation of life-threatening thrombin throughout the microvasculature of several organ systems. The indications discussed above include some, but not all, of the possible clinical situations where anticoagulant therapy is warranted. Those experienced in this field are well aware of the circumstances requiring either acute or chronic prophylactic anticoagulant therapy.

These compounds may be used alone or in combination with other diagnostic, anticoagulant, antiplatelet or fibrinolytic agents. For example adjunctive administration of factor Xa inhibitors with standard heparin, low molecular weight heparin, direct thrombin inhibitors (i.e. hirudin), aspirin, fibrinogen receptor antagonists, streptokinase, urokinase and/or tissue plasminogen activator may result in greater antithrombotic or thrombolytic efficacy or efficiency. The compounds described herein may be administered to treat thrombotic complications in a variety of animals such as primates including humans, sheep, horses, cattle, pigs, dogs, rats and mice. Inhibition of factor Xa is useful not only in the anticoagulant therapy of individuals having thrombotic conditions but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, any factor Xa inhibitor can be added to or contacted with any medium containing or suspected of containing factor Xa and in which it is desired that blood coagulation be inhibited.

In addition to their use in anticoagulant therapy, factor Xa inhibitors may find utility in the treatment or prevention of other diseases in which the generation of thrombin has been implicated as playing a pathologic role. For example,
thrombin has been proposed to contribute to the morbidity and mortality of such chronic and degenerative diseases as arthritis, cancer, atherosclerosis and Alzheimer’s disease by virtue of its ability to regulate many different cell types through specific cleavage and activation of a cell surface thrombin receptor. Inhibition of factor Xa will effectively block thrombin generation and therefore neutralize any pathologic effects of thrombin on various cell types.

Accordingly, the invention provides a method of inhibiting factor Xa comprising contacting a factor Xa inhibitory amount of a compound of formula I with a composition containing Factor Xa. According to a further feature of the invention there is provided a method of inhibiting the formation of thrombin comprising contacting Factor Xa inhibitory amount of a compound of formula I with a composition containing Factor Xa.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of Factor Xa, for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of formula I or a composition containing a compound of formula I. “Effective amount” is meant to describe an amount of compound of the present invention effective in inhibiting Factor Xa and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of Formula I in association with a pharmaceutically acceptable carrier or coating.

In practice compounds of the present invention may generally be administered parenterally, intravenously, subcutaneously intramuscularly, colonically, nasally, intraperitoneally, rectally or orally.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary procedures, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.01 to about 100, preferably about 0.01 to about 10, mg/kg body weight per day by oral administration, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by intravenous administration, and from about 0.01 to about 50, preferably 0.01 to 10, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.
The ability of the compounds in the present invention to act as inhibitors of factor Xa, thrombin, trypsin, tissue-
humans and other mammals. Enzyme Assays:
tests described in the literature and below which tests results are believed to correlate to pharmacological activity in
one or more of the aforementioned therapeutic class agents
known to be HMGCoA reductase inhibitors, compounds of the fibrate class,
antagonists and alpha-
Ki [I+
control velocity (IC50). The apparent Ki values are then determined according to the Cheng-
The initial velocities measured are used to calculate the amount of inhibitor which resulted in a 50% reduction of the
microplate reader (Molecular Devices). Under these conditions, less than 10% of the substrate is utilized in all assays.

Human Plasma Based Clotting Assay:

Activated partial thromboplastin clotting times are determined in duplicate on a MLA Electra 800 instrument. A
volume of 100 \mu l of citrated normal human pooled plasma (George King Biomedical) is added to a cuvette containing
100 \mu l of a compound according to the invention in Tris/NaCl buffer (pH 7.5) and placed in the instrument. Following a
3 minute warming period the instrument automatically adds 100 \mu l of activated cephaloplastin reagent (Actin, Dade)
followed by 100 \mu l of 0.035 M CaCl2 to initiate the clotting reaction. Clot formation is determined spectrophotometrically
and measured in seconds. Compound potency is quantitated as the concentration required to double a control clotting
time measured with human plasma in the absence of the compound according to the invention.
Experimental In Vivo Rabbit Venous Thrombosis Model:

This is a well characterized model of fibrin rich venous thrombosis that is validated in the literature and shown to be sensitive to several anticoagulant drugs including heparin (Antithrombotic Effect of Recombinant Truncated Tissue Factor Pathway Inhibitor (TFPI-1-161) in Experimental Venous Thrombosis-a Comparison with Low Molecular Weight Heparin, J. Holst, B. Lindblad, D. Bergqvist, O. Nordfang, P.B. Ostergaard, J.G.L. Petersen, G. Nielsen and U. Hedner. Thrombosis and Haemostasis 71, 214-219 (1994). The purpose of utilizing this model is to evaluate the ability of compounds to prevent the formation of venous thrombi (clots) in vivo generated at a site of injury and partial stasis in the jugular vein.

Male and female New Zealand white rabbits weighing 1.5-2 kg are anesthetized with 35 mg/kg of ketamine and 5 mg/kg xylazine in a volume of 1 mL/kg (i.m.). The right jugular vein is cannulated for infusion of anesthetic (ketamine/xylazine 17/2.5 mg/kg/hr at a rate of approximately 0.5 mL/hr) and administration of test substances. The right carotid artery is cannulated for recording arterial blood pressure and collecting blood samples. Body temperature is maintained at 39°C with a GAYMAR T-PUMP. The left external jugular vein is isolated and all side branches along an exposed 2-3 cm of vessel are tied off. The internal jugular vein is cannulated, just above the bifurcation of the common jugular, and the tip of the cannula is advanced just proximal to the common jugular vein. A 1 cm segment of the vein is isolated with non-traumatic vascular clamps and a relative stenosis is formed by tying a ligature around the vein with an 18G needle just below the distal most clamp. This creates a region of reduced flow and partial stasis at the injury site. The isolated segment is gently rinsed with saline 2-3 times via the cannula in the internal jugular. Thereafter the isolated segment is filled with 0.5 mL of 0.5% polyoxyethylene ether (W-1) for 5 minutes. W-1 is a detergent which disrupts the endothelial cell lining of the segment, thus providing a thrombogenic surface for initiating clot formation. After 5 minutes the W-1 is withdrawn from the segment, and the segment is again gently rinsed with saline 2-3 times. The vascular clamps are then removed, restoring blood flow through this portion of the vessel. Clot formation is allowed to form and grow for 30 minutes after which the vein is cut just below the stenotic ligature and inspected for blood flow (the absence of blood flow is recorded as complete occlusion). The entire isolated segment of vein is then ligated and the formed clot is removed and weighed (wet weight). The effect of test agents on final clot weights is used as the primary end point. Animals are maintained for an additional thirty minutes to obtain a final pharmacodynamic measure of anticoagulation. Drug administration is initiated 15 minutes prior to vascular injury with W-1 and continued through the period of clot formation and maturation. Three blood samples (3 mL ea.) are obtained for evaluation of hemostatic parameters: one just prior to administration of W-1; a second 30 minutes after removal of the vascular clamps and a third at the termination of the experiment. Antithrombotic efficacy is expressed as a reduction in the final clot weight in preparations treated with a compound according to the invention relative to vehicle treated control animals.

Experimental In Vivo Rat Arterial Thrombosis Model:

The antithrombotic efficacy of factor Xa inhibitors against platelet-rich arterial thrombosis may be evaluated using a well characterized rat carotid artery FeCl₂-induced thrombosis model (Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis, W.A. Schumacher, C.L. Heran, T.E. Steinbacher, S. Youssef and M.L. Ogletree. Journal of Cardiovascular Pharmacology, 22, 526-533 (1993); Rat Model of Arterial Thrombosis Induced by Ferric Chloride, K.D. Kurtz, B.W. Main, and G.E. Sandusky. Thrombosis Research, 60, 269-280 (1990); The Effect of Thrombin Inhibition in a Rat Arterial Thrombosis Model, R.J. Broersma, L.W. Kutcher and E.F. Heminger. Thrombosis Research 64 405-412 (1991). This model is widely used to evaluate the antithrombotic potential of a variety of agents including heparin and the direct acting thrombin inhibitors.

Sprague Dawley rats weighing 375-450 g are anesthetized with sodium pentobarbital (50 mg/kg i.p.). Upon reaching an acceptable level of anesthesia, the ventral surface of the neck is shaved and prepared for aseptic surgery. Electrocardiogram electrodes are connected and lead II is monitored throughout the experiment. The right femoral vein and artery are cannulated with PE-50 tubing for administration of a compound according to the invention and for obtaining blood samples and monitoring blood pressure, respectively. A midline incision is made in the ventral surface of the neck. The trachea is exposed and intubated with PE-240 tubing to ensure airway patency. The right carotid artery is isolated and two 4-0 silk sutures are placed around the vessel to facilitate instrumentation. An electromagnetic flow probe (0.95-1.0 mm lumen) is placed around the vessel to measure blood flow. Distal to the probe a 4x4 mm strip of paraffin is placed under the vessel to isolate it from the surrounding muscle bed. After baseline flow measurements are made, a 2x5 mm strip of filter paper previously saturated in 35% FeCl₂ is placed on top of the...
vessel downstream from the probe for ten minutes and then removed. The FeCl₂ is thought to diffuse into the underlying segment of artery and cause deendothelialization resulting in acute thrombus formation. Following application of the FeCl₂-soaked filter paper, blood pressure, carotid artery blood flow and heart rate are monitored for an observation period of 60 minutes. Following occlusion of the vessel (defined as the attainment of zero blood flow), or 60 minutes after filter paper application if patency is maintained, the artery is ligated proximal and distal to the area of injury and the vessel is excised. The thrombus is removed and weighed immediately and recorded as the primary end point of the study.

Following surgical instrumentation a control blood sample (B1) is drawn. All blood samples are collected from the arterial catheter and mixed with sodium citrate to prevent clotting. After each blood sample, the catheter is flushed with 0.5 mL of 0.9% saline. A compound according to the invention is administered intravenously (i.v.) starting 5 minutes prior to FeCl₂ application. The time between FeCl₂ application and the time at which carotid blood flow reached zero is recorded as time to occlusion (TTO). For vessels that did not occlude within 60 minutes, TTO is assigned a value of 60 minutes. Five minutes after application of FeCl₂, a second blood sample is drawn (B2). After 10 minutes of FeCl₂ exposure, the filter paper is removed from the vessel and the animal is monitored for the remainder of the experiment. Upon reaching zero blood flow blood a third blood sample is drawn (B3) and the clot is removed and weighed. Template bleeding time measurements are performed on the forelimb toe pads at the same time that blood samples are obtained. Coagulation profiles consisting of activated partial thromboplastin time (APTT) and prothrombin time (PT) are performed on all blood samples. In some instances a compound according to the invention may be administered orally. Rats are restrained manually using standard techniques and compounds are administered by intragastric gavage using a 18 gauge curved dosing needle (volume of 5 mL/kg). Fifteen minutes after intragastric dosing, the animal is anesthetized and instrumented as described previously. Experiments are then performed according to the protocol described above.

Claims

1. A compound of formula I,
or a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A compound according to claim 1, which is

or a pharmaceutically acceptable salt thereof or a solvate thereof.
3. A pharmaceutical composition comprising a pharmaceutically acceptable amount of the compound according to claims 1 or 2 and a pharmaceutically acceptable carrier.

4. The use of a compound of the formula I as claimed in claims 1 or 2 for the manufacture of a medicament for use as a blood anticoagulant.

**Patentansprüche**

1. Verbindung der Formel I

bei der es sich um
handelt, oder ein pharmazeutisch unbedenkliches Salz davon oder ein Solvat davon.

2. Verbindung der Formel I, bei der es sich um
handelt, oder ein pharmazeutisch unbedenkliches Salz davon oder ein Solvat davon.

3. Pharmazeutische Zusammensetzung, enthaltend eine pharmazeutisch unbedenkliche Menge der Verbindung nach den Ansprüchen 1 oder 2 und einen pharmazeutisch unbedenklichen Träger.

4. Verwendung einer Verbindung der Formel I gemäß den Ansprüchen 1 oder 2 zur Herstellung eines Arzneimittels zur Verwendung als blutgerinnungshemmendes Mittel.

Revendications

1. Composé de formule I,
qui est :
ou un sel pharmaceutiquement acceptable de celui-ci ou un solvate de celui-ci.

2. Composé selon la revendication 1, qui est
ou un sel pharmaceutiquement acceptable de celui-ci ou un solvate de celui-ci.

3. Composition pharmaceutique comprenant une quantité pharmaceutiquement acceptable du composé selon les revendications 1 ou 2 et un support pharmaceutiquement acceptable.

4. Utilisation d’un composé de formule I selon les revendications 1 ou 2 pour la fabrication d’un médicament destiné à être utilisé en tant qu’agent anti-coagulant du sang.
REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description


Non-patent literature cited in the description


