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(54) Titre : NOUVELLES COMPOSITIONS PHARMACEUTIQUES POUR LE TRAITEMENT DE LA THROMBOSE
(54) Title: COMBINATIONS COMPRISING AT LEAST ONE DIRECT THROMBIN INHIBITOR FOR THE TREATMENT OF THROMBOSIS

(57) Abrégé/Abstract:
The present invention relates to novel pharmaceutical compositions comprising at least one direct thrombin inhibitor and at least one additional active compound selected from the groups consisting of platelet inhibitors, low molecular weight heparins (LMWH) and heparinoids as well as unfractionated heparin, factor X_a inhibitors, combined thrombin/factor X_a inhibitors, fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) and Vitamin K antagonists, optionally together with one or more pharmaceutically acceptable excipients or carriers for the treatment of thrombosis.

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(54) Title: COMBINATIONS COMPRISING AT LEAST ONE DIRECT THROMBIN INHIBITOR FOR THE TREATMENT OF THROMBOSIS

(57) Abstract: The present invention relates to novel pharmaceutical compositions comprising at least one direct thrombin inhibitor and at least one additional active compound selected from the groups consisting of platelet inhibitors, low molecular weight heparins (LMWH) and heparinoids as well as unfractionated heparin, factor X_a inhibitors, combined thrombin/factor X_a inhibitors, fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) and Vitamin K antagonists, optionally together with one or more pharmaceutically acceptable excipients or carriers for the treatment of thrombosis.

WO 2006/103206 A3

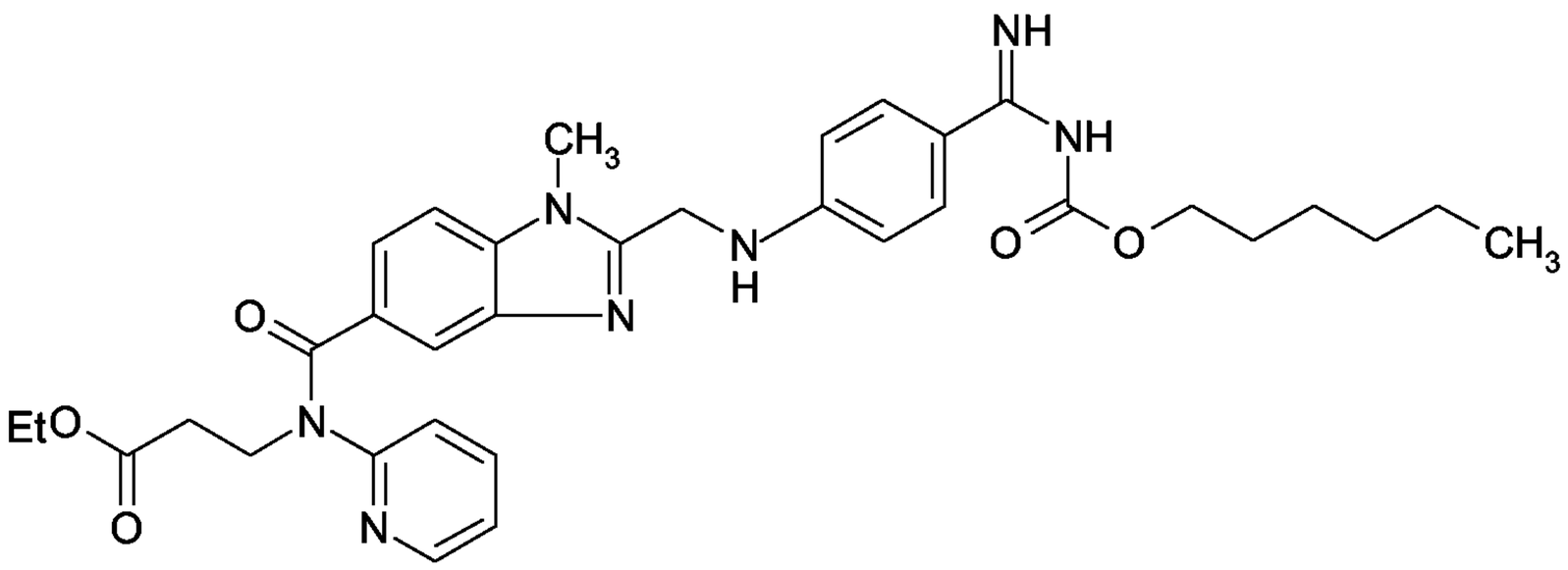
NEW PHARMACEUTICAL COMPOSITIONS FOR TREATMENT OF THROMBOSIS

The present invention relates to novel pharmaceutical compositions comprising one or more, preferably one, selected direct thrombin inhibitors (DTI) **1**, and at least one additional active compound **2**, processes for preparing them and their use as medicament in the treatment of thrombosis.

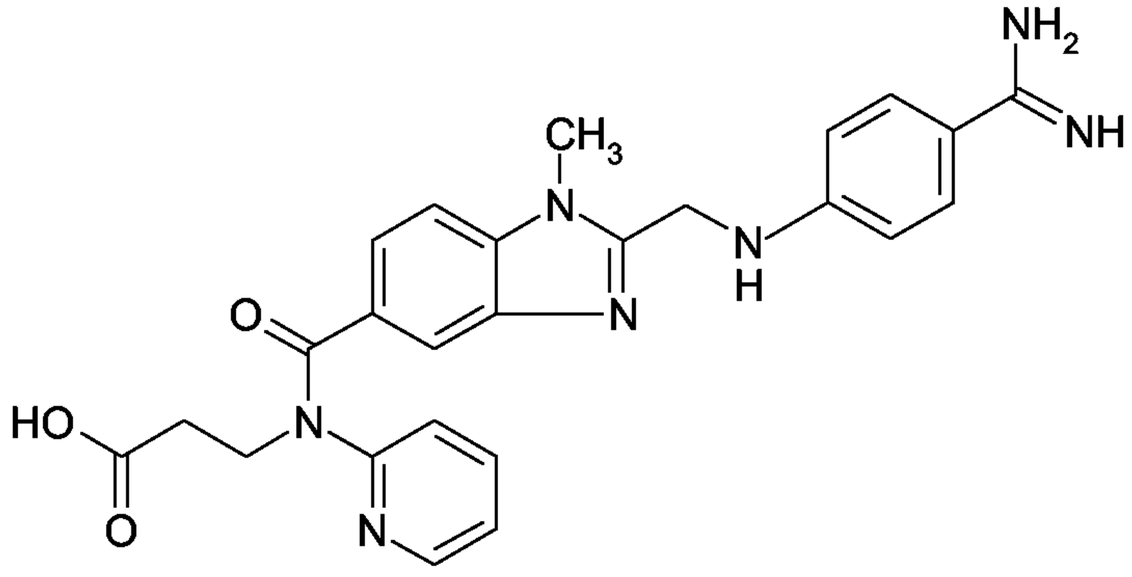
Detailed description of the invention

In a first aspect the present invention relates to pharmaceutical compositions comprising at least one direct thrombin inhibitor **1** selected from the group consisting of

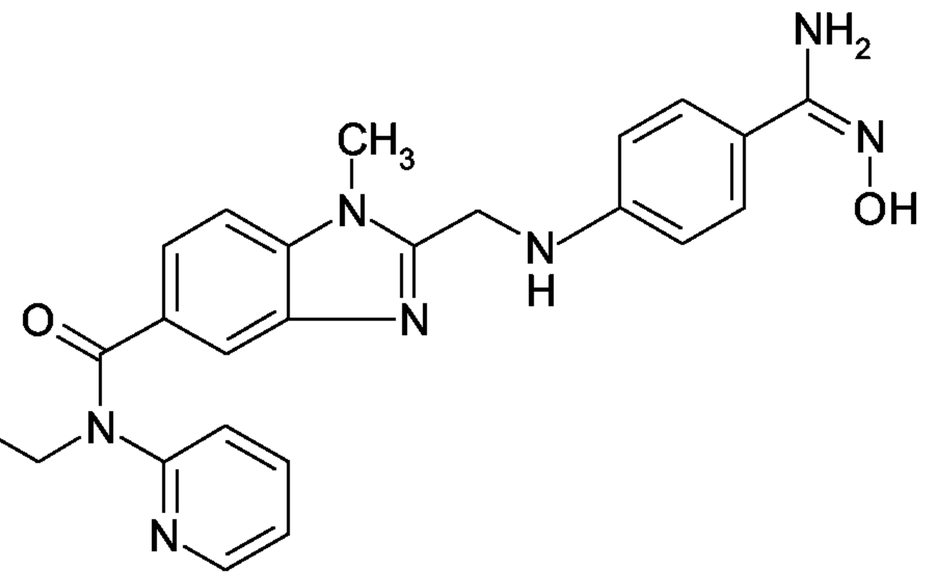
(**1.1**) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (dabigatran) having the following structure



(**1.2**) 1-methyl-2-(4-amidinophenylaminomethyl)-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-hydroxycarbonylethyl)-amide having the structure



(**1.3**) 1-methyl-2-[4-(*N*-hydroxyamidino)-phenylaminomethyl]-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonylethyl)-amide having the structure



(**1.4**) melagatran (inogatran),

(**1.5**) ximelagatran,

(**1.6**) hirudin,

(**1.7**) hirolog,

(**1.8**) argatroban,

optionally in the form of tautomers, racemates, enantiomers, diastereomers, pharmacologically acceptable acid addition salts, solvates or hydrates, prodrugs thereof,

and further comprising one or more additional active compounds **2** selected from the groups consisting of platelet inhibitors **2a,** low molecular weight heparins (LMWH) and heparinoids as well as unfractionated heparin **2b**, factor X_a inhibitors **2c**, combined thrombin/factor X_a inhibitors **2d,** fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** and Vitamin K antagonists **2f**, optionally together with one or more pharmaceutically acceptable excipients or carriers. All active components should be present in effective amounts.

The active compounds **1.1** to **1.3** are disclosed in the prior art, e.g. in WO 98/37075 and WO 04/014894.

Prodrugs of the drugs mentioned above are such derivatives containing one or more groups capable of being cleaved in vivo, particularly a group which can be converted

in-vivo into a carboxy group or/and a group capable of being cleaved in vivo from an imino or amino group. Compounds containing two groups capable of being cleaved in vivo are so-called double prodrugs. Groups which can be converted in-vivo into a carboxy group and groups capable of being cleaved in vivo from an imino or amino group are disclosed e.g. in WO 98/37075, being herewith incorporated by reference, as well as in other WO publications cited hereinbefore in connection with specific antithrombotics.

In the pharmaceutical compositions according to the present invention the direct thrombin inhibitors **1** may be contained in a form selected from tautomers, optical isomers, enantiomers, racemates, diastereomers, pharmacologically acceptable acid addition salts, solvates or hydrates, as far as such forms exist, depending on the individual compound. Pharmaceutical compositions comprising one or more, preferably one, compound **1** in form of a substantially pure enantiomer are preferred.

Pharmacological acceptable acid addition salts of direct thrombin inhibitors **1** comprise salts selected from the group consisting of the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrolactate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluolsulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydromaleate, hydrofumarate and hydromethansulphonate. Some of the compounds **1** may add more than one equivalent acid, e.g. two equivalents. The salts of hydrochloric acid, methanesulphonic acid, maleic acid, benzoic acid and acetic acid are especially preferred. The most preferred salt of **1** is the methansulfonic acid addition salt.

The pharmaceutical compositions according to the invention comprising at least one direct thrombin inhibitor **1** and at least one additonal active compound **2** are not restricted to binary combinations of actives. The combinations disclosed exemplary below comprising an direct thrombin inhibitor **1** together with an additional active compound **2** may comprise a third or a third and a fourth, preferably a third active compound, also selected from the group consisting of platelet inhibitors **2a,** low molecular weight heparins and heparinoids **2b**, factor X_a inhibitors **2c**, combined

thrombin/factor X_a inhibitors **2d**, fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** and Vitamin K antagonists **2f**. All components **2a** to **2f** mentioned specifically hereinafter are described in the prior art.

In a first preferred embodiment of the invention the pharmaceutical combination is binary, comprising an direct thrombin inhibitor **1** and an active compound selected from one of the classes **2a**, **2b**, **2c**, **2d**, **2e** and **2f**. A preferred binary combination contains compound **1.1** and either clopidogrel or acetylsalicylic acid (ASA).

In a second preferred embodiment of the invention the pharmaceutical combination is ternary, comprising an direct thrombin inhibitor **1**, and two compounds selected from the classes **2a**, **2b**, **2c**, **2d**, **2e** and **2f**, while the additional two compounds may belong to one and the same or two different classes selected from **2a**, **2b**, **2c**, **2d**, **2e** and **2f**. Preferably both additional compounds are selected from class **2a**. A preferred ternary combination contains compound **1.1**, clopidogrel and acetylsalicylic acid.

In a third embodiment of the invention the pharmaceutical combination is quarternary, comprising two direct thrombin inhibitors **1** and two active compounds selected from either one or from two different classes of **2a**, **2b**, **2c**, **2d**, **2e** and **2f**, preferably selected from either one or from two different classes of **2a**, **2b** and **2e**.

Any reference to an direct thrombin inhibitor **1** within the scope of the present invention should be understood as a reference to any specific direct thrombin inhibitor selected from compounds **1.1** to **1.8**. mentioned hereinbefore. Analogously, any reference to an active compound selected from the classes **2a**, **2b**, **2c**, **2d**, **2e** and **2f** within the scope of the present invention should be understood as a reference to any active compound of these classes mentioned specifically hereinbelow.

In the pharmaceutical combinations according to the invention the active substances may be combined in a single preparation, e.g. as a fixed dose combination comprising the active ingredients in one formulation together, or contained in two or more separate formulations, e.g. as a kit of parts adapted for simultaneous, separate

or sequential administration. Pharmaceutical compositions containing the active substances 1 and 2 in a single preparation are preferred according to the invention.

In all embodiments of the invention the direct thrombin inhibitors **1.1** is preferred, especially in form of its acid addition salt with methanesulfonic acid.

All pharmaceutical compositions of the present invention can be advantageously used in the following indications:

for the prevention and treatment of the consequences of thrombotic and thromboembolic diseases such as

deep vein thrombosis (DVT) pulmonary embolism, and other venous thrombotic events in patients at risk for such events (post-orthopedic surgery, medical patients, cancer patients, surgical patients),
stroke prevention in atrial fibrillation (SPAF),
stroke prevention in other populations at high risk for such events (heart failure or left ventricular dysfunction, high risk patients with myocardial infarction, patients with valve disease or valve replacement)
thrombosis and thombotic events in patients with acute myocardial infarction or acute coronary syndromes, including patients undergoing thrombolysis or those with stents or percutaneous coronary intervention (PCI), or both,
post-myocardial infarction (MI), in patients who have received thrombolysis or those with percutaneous coronary intervention or post coronary bypass surgery,
or other acute coronary syndromes
for prevention or treatment of thrombosis, in particular for treatment of patients with stents or percutaneous coronary intervention (PCI).

Preferred fields of application are chronic and acute thromboembolic diseases or events.

Particularly preferred fields of application are DVT and SPAF.

Thus a second aspect of the invention is a method of treating any of the indications mentioned hereinbefore comprising administering to a patient in need thereof a pharmaceutical composition according to the invention, comprising at least one of the selected direct thrombin inhibitors **1** in combination with one or more additional active compounds **2** selected from the groups consisting of platelet inhibitors **2a,** low molecular weight heparins and heparinoids as well as unfractionated heparin **2b**, factor X_a inhibitors **2c**, combined thrombin/factor X_a inhibitors **2d**, fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** and Vitamin K antagonists **2f**, optionally together with one or more pharmaceutically acceptable excipients. The expression "patient" is meant to comprise the mammal animal body, preferably the human body. The method of treatment is meant to encompass simultaneous as well as successive administration of the active components.

A third aspect of the invention is the use of any of the selected direct thrombin inhibitors **1** in combination with one or more additional active compounds **2** selected from the groups consisting of platelet inhibitors **2a,** low molecular weight heparins and heparinoids as well as unfractionated heparin **2b**, factor X_a inhibitors **2c**, combined thrombin/factor X_a inhibitors **2d**, fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** and Vitamin K antagonists **2f**, optionally together with one or more pharmaceutically acceptable excipients, for the manufacture of a pharmaceutical composition for treating any of the indications mentioned hereinbefore in a patient in need thereof. This aspect encompasses the preparation of all pharmaceutical compositions according to the invention mentioned hereinbefore or below.

Preferred embodiments of the pharmaceutical compositions of the invention as well as the indications to be treated apply analogously regarding to the second and third aspect of the invention.

Pharmaceutical compositions comprising an Direct thrombin inhibitor 1 and a platelet inhibitor 2a:

One embodiment of the invention is a pharmaceutical composition comprising an direct thrombin inhibitor **1** and a platelet inhibitor **2a**. Binary compositions containing

only one active **1** and one active **2a**, optionally together with one or more pharmaceutically acceptable excipients or carriers, are preferred. In the pharmaceutical combinations according to the invention preferred platelet inhibitors **2a** are selected from the group consisting of acetylsalicylic acid **2a.1**, clopidogrel **2a.2** and ticlopidine **2a.3**, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

According to the instant invention more preferred platelet inhibitors **2a** are selected from the group consisting of acetylsalicylic acid **2a.1,** clopidogrel **2a.2** and ticlopidine **2a.3**, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

Examples of pharmacologically acceptable acid addition salts of the platelet inhibitors **2a** according to the invention are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid, 4-phenylcinnamic acid, 5-(2,4-difluorophenyl)salicylic acid or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts of **2a**.

According to the invention, the salts of the platelet inhibitors **2a** selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate, 4-phenylcinnamate, 5-(2,4-difluorophenyl)salicylate, maleate and xinafoate are preferred.

In the pharmaceutical compositions according to the invention, the compounds **2a** may be present in the form of their racemates, enantiomers or mixtures thereof. The separation of the enantiomers from the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.).

Besides therapeutically effective quantities of **1** and **2a** the pharmaceutical compositions may contain in addition a pharmaceutically acceptable carrier. The

present invention encompasses both pharmaceutical compositions with or without pharmaceutically acceptable carriers.

Especially preferred pharmaceutical compositions according to the invention comprise the following specific combinations of direct thrombin inhibitors **1** and platelet inhibitors **2a**, either as free bases or pharmacologically acceptable acid addition salts:

1.1 and **2a.1**, **1.1** and **2a.2**, **1.1** together with both **2a.1** and **2a.2,**

particularly preferred are pharmaceutical compositions comprising
the methanesulfonate of **1.1** and **2a.1**,
the methanesulfonate of **1.1** and **2a.2,**
the methanesulfonate of **1.1** together with **2a.1** and **2a.2**.

The proportions in which the active substances **1** and **2a** may be used in the active substance combinations according to the invention are variable. Active substances **1** and **2a** may possibly be present in the form of salts, solvates or hydrates. Depending on the choice of the compounds **1** and **2a**, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various salt forms. The pharmaceutical combinations according to the invention may contain **1** and **2a** generally in ratios by weight ranging from 10 : 1 to 1 : 15, preferably from 8 : 1 to 12 : 1, e.g. 1 : 1 to 1 : 10 or 2 : 3.

If not specified otherwise, the weights and the weights ratios specified hereinbefore and below are based on the free bases of the actives.

For example, pharmaceutical compositions according to the invention usually contain a quantity of **1.1** per single dose between about 50 mg and 200 mg, e.g. 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg or 200 mg. Normally, a pharmaceutical composition containing **1.1** is administered once or twice daily, a twice daily administration is preferred. Oral administration of **1.1** is preferred.

1.3 is by preference administered subcutaneously. Since **1.1** and **1.3** are different prodrugs of the same active principle (i.e. of **1.2**), the dosage of **1.3** is to be adapted to the different administration route in a way that the plasma levels of the active principle will roughly be the same as those obtained by application of the above-mentioned amounts of **1.1**.

In a pharmaceutical composition according to the invention, **2a.1** (ASA) may be present in an amount between 50 mg and 500 mg; preferred dosages for **2a.1** are e.g. 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg and 500 mg.

In a pharmaceutical composition according to the invention, **2a.2** (clopidogrel) may be present in an amount between 75 mg and 600 mg; preferred dosages for **2a.2** are e.g. 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 575 mg and 600 mg.

The above-mentioned dosages for the compounds **1** resp. **2a** may be combined in any possible way for the binary and ternary combinations.

For instance, the normally recommended dose for the drug may be the dose disclosed in Rote Liste®2005, Editio Cantor Verlag Aulendorf, Germany, or to Physician's Desk Reference, 58 edition, 2004, e.g. exemplary for melagatran 3 mg/0.3ml s.c. two times a day, or for ximelagatran 24 mg orally two times a day.

Formulations and dosages: ASA

With respect to ASA any of the oral formulations on the market may be used. Reference is made to Rote Liste®2004, Editio Cantor Verlag Aulendorf, Germany, or to Physician's Desk Reference, 58 edition, 2004. This component of the medication may be administered orally in a daily dosage of 10 to 1000 mg, preferably 25 to 600 mg, e.g. 100 to 300 mg, most preferred 50 to 500 mg, for instance 75 mg twice a day.

Formulations and dosages: Clopidogrel

Suitable oral formulations of clopidogrel are disclosed in Rote Liste®2004, Editio Cantor Verlag Aulendorf, Germany, or in Physician's Desk Reference, 58 edition, 2004, and may contain from 25 mg to 1000 mg, preferably from 75 mg to 600 mg, and most preferably from 75 mg to 400 mg of clopidogrel. For example, the formulation used may contain 25 mg, 50 mg, 75 mg, 150 mg, 250 mg, or 500 mg of clopidogrel. Oral administration may be in one or divided doses of two, three, or four times daily. A single daily dose is preferred. Clopidogrel is on the market under the brand names Plavix® and Iscover®.

Formulations and dosages: Ticlopidine

Suitable oral formulations of ticlopidine are disclosed in Rote Liste®2004, Editio Cantor Verlag Aulendorf, Germany, or in Physician's Desk Reference, 58 edition, 2004, and may contain from 25 mg to 600 mg, preferably from 100 mg to 400 mg, and most preferably from 200 mg to 300 mg of ticlopidine. For example, the formulation may contain 25 mg, 50 mg, 75 mg, 150 mg, 250 mg, or 500 mg of ticlopidine. Oral administration may be in one or divided doses of two, three, or four times daily. A single daily dose is preferred.

It is clear to anyone skilled in the art that the suggested dosages per single dose specified above are not to be regarded as being limited to the numerical values actually stated. Fluctuations of about ± 2.5 mg, particularly in the decimal range, are also included, as will be apparent to the skilled man. In these dosage ranges, the active substances **1** and **2a** may be present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the combinations in which the preferred direct thrombin inhibitor **1.1** is used and in which **2a** denotes ASA and/or clopidogrel, the pharmaceutical compositions according to the invention may contain for instance the following quantities for each single dose: 150 mg of **1** and 75 mg of clopidogrel and / or 200 mg of ASA .

The dosage of **1.1** may range from 50 to 400 mg/day.

The dosage of **2a.1** may range from 50 to 500 mg/day, preferably from 75 to 325 mg/day.

The dosage of **2a.2** may range from 75 to 600 mg/day.

Pharmaceutical compositions comprising an direct thrombin inhibitor 1 and a low molecular weight heparin 2b:

One embodiment of the invention is a pharmaceutical composition comprising an direct thrombin inhibitor **1** and a low molecular weight heparins (LMWH) resp. heparinoids resp. unfractionated heparin **2b**. Binary compositions containing only one active compound **1** and one active compound **2b**, optionally together with one or more pharmaceutically acceptable excipients or carriers, are preferred. In the pharmaceutical combinations according to the invention preferred heparins **2b** are selected from the group consisting of enoxaparin, reviparin, dalteparin, tinzaparin, nadroparin and danaparoid.

Suitable doses resp. dose ranges for the active compounds **2b** are:

enoxaparin: 40 mg qd, 30 mg bid, 1.5 mg/kg once daily or 1.0 mg/kg twice daily

reviparin: 1750 U/day

dalteparin: 2500-5000 IU/day

tinzaparin: 50-75 IU/kg or 3500 IU/day

nadroparin: 3075 IU/day

danaparoid: 750 IU/day.

Compounds **2b** are usually administered parentally, by preference subcutaneously.

Furthermore, suitable doses and formulations for compounds **2b** are described in Rote Liste®2005, Editio Cantor Verlag Aulendorf, Germany, or to Physician's Desk Reference, 58 edition, 2004.

The dose ranges of **1** have already been given above.

Preferably, the compound **2b** is enoxaparin.

Any reference to steroids **2b** within the scope of the present invention includes a reference to the salts or derivatives which may be formed from the heparins. Examples of possible salts or derivatives include: sodium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmi-

tates, pivalates or furoates. In some cases the compounds of formula **2b** may also occur in the form of their hydrates. Any reference to heparins **2b** within the scope of the present invention also includes a reference to the compounds **2b** in the form of their diastereomers, mixtures of diastereomers or in the form of the racemates.

The proportions in which the active substances **1** and **2b** may be used in the active substance combinations according to the invention are variable. Active substances **1** and **2b** may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds **1** and **2b**, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various compounds and their different potencies.

Pharmaceutical compositions comprising an direct thrombin inhibitor 1 and a factor X_a inhibitor 2c:

One embodiment of the invention is a pharmaceutical composition comprising an direct thrombin inhibitor **1** and a factor X_a inhibitor **2c**. Binary compositions containing only one active **1** and one active **2c**, optionally together with one or more pharmaceutically acceptable excipients or carriers, are preferred. In the pharmaceutical combinations according to the invention preferred a factor X_a inhibitors **2c** are selected from the group consisting of

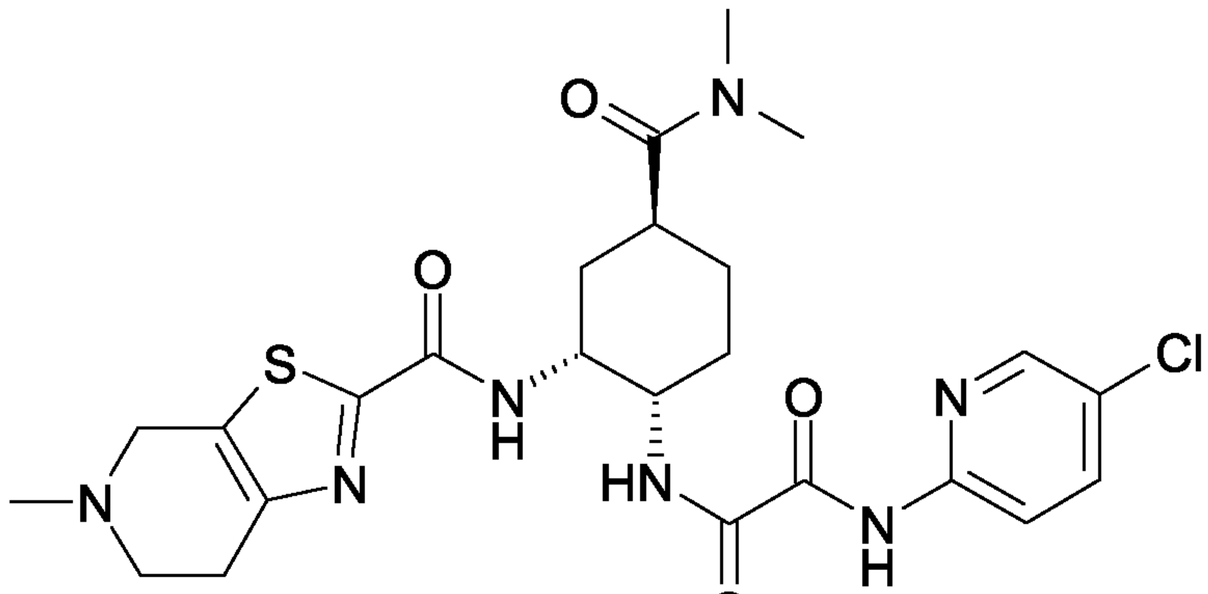
(1) fondaparinux,

(2) idraparinux,

(3) Razaxaban (DPC-906; Curr Hematol Rep. 2004 Sep; 3(5): 357-62),

(4) Apixaban (BMS-562247)

(5) N-(4-Bromo-2-{[(5-chloropyridin-2-yl)amino]carbonyl}-6-hydroxyphenyl)-1-isopropylpiperidin-4-carboxamid (JP 2005179272)



(6) (WO 2005/47296)

(10) 5-chloro-N-[((5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl)methyl]-2-thiophencarboxamide (BAY-59-7939, WO 04/60887)

(11) 1-(indole-6-carbonyl-D-phenylglycinyl)-4-(1-methyl-piperidin-4yl)piperazine (LY-517717, WO 02/100847)

(12) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide (WO 03/037220)

(13) 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-isobutyramide (WO 02/062748)

(14) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[4-(pyrrolidin-1-yl-carbonyl)-3-trifluoromethyl-phenyl]-propionamide (WO 02/062748)

(15) 2-(3-carbamimidoyl-phenyl)-N-[3-bromo-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-3-(pyridin-4-yl)-propionamide (WO 02/062748)

(16) N-(5-carbamimidoyl-2-hydroxy-benzyl)-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide (WO 02/062778)

(17) ethyl 2-(3-carbamimidoyl-phenyl)-2-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzoylamino]-acetate (WO 02/062778)

(18) (1) N-(5-Amidino-2-hydroxy-benzyl)-3-trifluormethyl-4-(3-aminomethyl-1,4,5,6-tetrahydro-cyclopentapyrazol-1-yl)-benzamide (WO 02/072558)

(19) 6) N-[1-(5-Amidino-2-hydroxy-phenyl)-ethyl]- 3-trifluormethyl-4-(4,5,6,7-tetrahydro-benzimidazol-1-yl)-benzamide (WO 02/072558)

(20) N-(5-Amidino-2-hydroxy-benzyl)-3-trifluormethyl-4-(3-methyl-1,4,5,6-tetrahydro-cyclopentapyrazol-1-yl)-benzamide (WO 02/072558)

(21) 2-(5-amidino-2-hydroxy-phenyl)-N-[3-trifluoromethyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-3-phenyl-propionamide (WO 04/013115)

(22) 4-hydroxy-3-{[6-chloro-7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]aminomethyl}-benzamidine (WO 2004/080970)

(23) 4-hydroxy-3-{[7-methoxy-6-(pyrrolidin-1-yl-carbonyl)-isoquinolin-1-yl]aminomethyl}-benzamidine (WO 2004/080970)

(24) 4-hydroxy-3-{2-phenyl-1-[7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-ylamino]-ethyl}-benzamidine (WO 2004/080970)

(25) 4-hydroxy-3-{[6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]aminomethyl}-benzamidine (WO 2004/080970)

(26) 4-hydroxy-3-{[7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]aminomethyl}-benzamidine (WO 2004/080970)

(27) ethyl 3-(3-amidino-phenyl)-3-{[6-chloro-7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]amino}-propionate (WO 2004/080970)

(28) 3-(3-amidino-phenyl)-3-{[6-chloro-7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]amino}-propionic acid (WO 2004/080970)

(29) N-benzoyl-4-hydroxy-3-{[7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]aminomethyl}-benzamidine (WO 2004/080970)

(30) N-hydroxy-4-hydroxy-3-{[6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]aminomethyl}-benzamidine (WO 2004/080970)

(31) N-acetoxymethoxycarbonyl-4-hydroxy-3-{[6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinazolin-4-yl]aminomethyl}-benzamidine (WO 2004/080970)

their stereoisomers such as enantiomers and diastereomers, mixtures of stereoisomers such as racemates, prodrugs, pharmacologically acceptable salts, solvates, e.g. hydrates, and physical modifications thereof, e.g. polymorphs.

Prodrugs of the drugs mentioned above are such derivatives containing one or more groups capable of being cleaved in vivo, particularly a group which can be converted in-vivo into a carboxy group or/and a group capable of being cleaved in vivo from an imino or amino group. Compounds containing two groups capable of being cleaved in vivo are so-called double prodrugs. Groups which can be converted in-vivo into a carboxy group and groups capable of being cleaved in vivo from an imino or amino group are disclosed e.g. in WO 98/37075, being herewith incorporated by reference, as well as in other WO publications cited hereinbefore in connection with specific antithrombotics.

The dose of fondaparinux is of about 2.5 mg/kg/day. Both fondaparinux and idraparinux are by preference administered subcutaneously.
The dose ranges of **1** have already been given above.

Pharmaceutically acceptable salt forms of the active compounds within the pharmaceutical composition of the present invention are prepared for the most part by conventional means. Where the component compound contains a carboxylic acid group, a suitable salt thereof may be formed by reacting the compound with an appropriate base to provide the corresponding base addition salt. Examples of such bases are alkali metal hydroxides including potassium hydroxide, sodium hydroxide, and lithium hydroxide; alkaline earth metal hydroxides such as barium hydroxide and

calcium hydroxide; alkali metal alkoxides, *e.g.*, potassium ethanolate and sodium propanolate; and various organic bases such as piperidine, diethanolamine, and *N*-methylglutamine. Also included are the aluminum salts of the component compounds of the present invention.

For certain component compounds acid addition salts may be formed by treating said compounds with pharmaceutically acceptable organic and inorganic acids, *e.g.*, hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, *etc.*; and alkyl- and mono-arylsulfonates such as ethanesulfonate, toluenesulfonate, and benzene-sulfonate; and other organic acids and their corresponding salts such as acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate, *etc.*

Accordingly, the pharmaceutically acceptable acid addition salts of the component compounds of the present invention include, but are not limited to: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, *iso*-butyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate.

Particularly preferred examples of pharmacologically acceptable acid addition salts of the compounds **2c** according to the invention are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, 1-hydroxy-2-naphthalenecarboxylic acid or maleic acid. If desired, mixtures of the abovementioned acids may also be used to prepare the salts **2c**.

In the pharmaceutical compositions according to the invention, the compounds **2c** may be present in the form of their racemates, enantiomers or mixtures thereof. The separation of the enantiomers from the racemates may be carried out using methods known in the art (e.g. by chromatography on chiral phases, etc.).

The proportions in which the active substances **1** and **2c** may be used in the active substance combinations according to the invention are variable. Active substances **1** and **2c** may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds **1** and **2c**, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various salt forms.

Pharmaceutical compositions comprising an direct thrombin inhibitor 1 and a combined thrombin/factor X_a inhibitor 2d:

One embodiment of the invention is a pharmaceutical composition comprising an direct thrombin inhibitor **1** and a combined thrombin/factor X_a inhibitor **2d**. Binary compositions containing only one active compound **1** and one active compound **2d**, optionally together with one or more pharmaceutically acceptable excipients or carriers, are preferred.

Combined thrombin/factor X_a inhibitors applicable within the scope of the invention are known in the art. Within the scope of the present invention the term combined thrombin/factor X_a inhibitors **2d** denotes compounds selected from the compounds:

(32) 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5-[N-(hydroxycarbonylmethyl)-quinoline-8-sulphonylamino]-benzimidazole (US-6121308)

(33) (R)-2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole (WO 00/01704)

(34) 2-(4-amidinophenylaminomethyl)-1-methyl-5-[1-(carboxymethylaminomethyl)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole (WO 01/47896)

(35) (R)-2-[4-(N-phenylcarbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(n-propyloxycarbonylmethylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole (WO 01/47896)

(36) 3-{[6-(N-acetyl-N-cyclopentylamino)-7-methyl-isoquinolin-1-yl]aminomethyl}-4-hydroxy-benzamidine (WO 2004/080970)

(the following compounds are disclosed in WO 2004/056784)

(37) *N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-3-methyl-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(38) *N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-3-ethyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(39) *N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-3-chloro-4-(2-aminomethyl-pyrrolidin-1-yl-carbonyl)-benzamide

(40) 3-chloro-*N*-(5-chloro-1*H*-benzimidazol-2-yl-methyl)-4-(3-oxo-piperazin-1-yl-carbonyl)-benzamide

(41) *N*-[1-(5-bromo-1*H*-benzimidazol-2-yl)-ethyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(42) *N*-[(5-chloro-1*H*-benzimidazol-2-yl)-phenyl-methyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(43) *N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methyl-butyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(44) (*S*)-*N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)]ethyl-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(45) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-3-chloro-4-[(2*R*/*S*)-2-amino-methyl-pyrrolidin-1-yl-carbonyl)-benzamide

(46) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphanyl-propyl]-3-chloro-4-[(2*S*)-2-(*N-tert.*-butoxycarbonyl-aminomethyl)-pyrrolidin-1-yl-carbonyl]-benzamide

(47) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-butyl]-3-chloro-4-[(2*S*)-2-amino-methyl-pyrrolidin-1-yl-carbonyl]-benzamide

(48) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphanyl-propyl]-3-chloro-4-[(2*S*)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-benzamide

(49) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphinyl-propyl]-3-chloro-4-[(2*S*)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-benzamide

(50) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphonyl-propyl]-3-chloro-4-[(2*S*)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-benzamide

(51) *N*-[(1*S*)-5-(benzyloxycarbonylamino)-1-(5-chloro-1*H*-benzimidazol-2-yl)-pentyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(52) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-phenyl-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(53) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphanyl-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(54) *N*-[(1*S*)-3-benzyloxycarbonyl-1-(5-chloro-1*H*-benzimidazol-2-yl)-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(55) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-(pyrrolidin-1-yl-carbonyl)-propyl]-

3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(56) *N*-[(1*R*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-hydroxy-ethyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(57) *N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-2-methoxy-ethyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(58) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methoxy-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(59) *N*-[(1*R*)-2-(C-*tert*.butoxycarbonyl-methyloxy)-1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(60) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphinyl-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(61) *N*-[(5-chloro-1*H*-benzimidazol-2-yl)-phenyl-methyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(62) *N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-phenyl-methyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-3-methyl-benzamide

(63) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphonylamino-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(64) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[3-(2-chloro-ethyl)-ureido]-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(65) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-butyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(66) 3-bromo-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphanyl-propyl]-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(67) 3-chloro-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-(methylsulphanyl)-propyl]-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(68) 3-bromo-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-(methylsulphonyl)-propyl]-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(69) 3-bromo-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphinyl-propyl]-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(70) 3-chloro-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-4-[(2*R*)-2-(methyl-sulphonylamino-methyl)-pyrrolidin-1-yl-carbonyl]-benzamide

(71) (1*R*)-3-bromo-*N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-2-hydroxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(72) (1*R*)-3-methyl-*N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-2-methoxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(73) (1*R*)-3-chloro-*N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-2-hydroxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(74) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(3*R*,*S*)-3-dimethylamino-pyrrolidin-1-yl]-carbonyl-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(75) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(2*R*)-2-hydroxymethyl-pyrrolidin-1-yl-carbonyl]-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(76) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(2*S*)-2-hydroxymethyl-pyrrolidin-1-yl-carbonyl]-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(77) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-(2-methyl-2,6-diaza-spiro[3.4]oct-6-yl-carbonyl)-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(78) *N*-{(1*S*)-3-[(1*R*)-2-(aminocarbonyl)-pyrrolidin-1-yl-carbonyl]-1-(5-chloro-1*H*-benzimidazol-2-yl)-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(79) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(2*R*)-2-*tert*.butoxycarbonyl-aminomethyl-pyrrolidin-1-yl-carbonyl]-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(80) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(3*R*,*S*)-hydroxymethyl-pyrrolidin-1-yl)-carbonyl]-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(81) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-(1,1-dioxo-1-thiomorpholine-4-yl-carbonyl]-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(82) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(4-methyl-3-oxo-piperazin-1-yl-carbonyl)-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(83) *N*-[(1*R*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-methoxy-ethyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(84) 3-chloro-*N*-[(1*R*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-methoxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(85) 3-bromo-*N*-[(1*R*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-methoxy-ethyl]-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(86) 3-bromo-*N*-[(1*R*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-methoxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(87) 3-methyl-*N*-[(1*R*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-hydroxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(88) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(2*S*)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(89) *N*-{(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-[(2*R*)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-propyl}-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(90) 3-chloro-*N*-[(1*R*,*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-4-[(2*R*)-2-methoxymethyl-pyrrolidin-1-yl-carbonyl]-benzamide

(91) 3-chloro-*N*-[1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-4-(3,4,5,6-tetrahydro-2H-[2,3]-bipyridinyl-1-yl-carbonyl)-benzamide

(92) *N*-[(1*R*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-2-methoxy-ethyl]-4-(pyrrolidin-1-yl-carbonyl)-3-trifluoromethyl-benzamide

(93) *N*-[(1*S*)-1,3-bis-(5-chloro-1*H*-benzimidazol-2-yl)-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(94) 3-chloro-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-4-[(2*R*/*S*)-2-dimethyl-aminomethyl-pyrrolidin-1-yl-carbonyl]-benzamide

(95) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methanesulphonylamino-propyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-3-methyl-benzamide

(96) *N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-butyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-3-methyl-benzamide

(97) 3-chloro-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-butyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(98) 3-bromo-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-butyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(99) 4-(*N*-acetyl-*N*-cyclopentyl-amino)-*N*-[(1*S*)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methylsulphanyl-ethyl]-3-methyl-benzamide

(100) 3-chloro-*N*-[(1*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-ethyl]-4-[(2*R*)-2-(pyrrolidin-1-yl-methyl)-pyrrolidin-1-yl-carbonyl]-benzamide

(101) 3-bromo-N-[(1R)-1-(5-bromo-1H-benzimidazol-2-yl)-2-methoxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(102) 3-bromo-N-[(1R)-1-(5-chloro-1H-benzimidazol-2-yl)-2-ethoxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(103) N-[(1R)-2-allyloxy-1-(5-chloro-1H-benzimidazol-2-yl)-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-3-methyl-benzamide

(104) 3-bromo-N-[(1R)-1-(5-chloro-1H-benzimidazol-2-yl)-2-prop-2-ynyloxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(105) N-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-(1H-tetrazol-5-yl)-propyl]-3-methyl-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(106) N-[(1R)-1-(5-chloro-1H-benzimidazol-2-yl)-2-hydroxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-3-trifluoromethyl-benzamide

(107) 3-chloro-N-[(1R)-1-(5-bromo-1H-benzimidazol-2-yl)-2-hydroxy-ethyl]-4-(2,5-dihydro-pyrrol-1-yl-carbonyl)-benzamide

(108) 3-bromo-N-[(1R)-1-(5-bromo-1H-benzimidazol-2-yl)-2-hydroxy-ethyl]-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(109) 3-methyl-N-[(1R)-1-(5-bromo-1H-benzimidazol-2-yl)-2-hydroxy-ethyl]-4-(pyrrolidin-1-yl-carbonyl)-benzamide

(the following compounds are disclosed in WO 2004-058743)

(110) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-(2-aminomethyl-pyrrolidin-1-yl-carbonyl)-quinazoline

(111) 6-chloro-4-[1-(S)-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-(2,5-dihydro-pyrrol-1-yl-carbonyl)-quinazoline

(112) 6-chloro-4-[1-(*S*)-(5-chloro-1*H*-benzimidazol-2-yl)-ethylamino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(113) 4-[1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphanyl-propylamino]-6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinoline

(114) 4-[1-(5-chloro-1*H*-benzimidazol-2-yl)-ethylamino]-6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinoline

(115) 4-[1-(5-chloro-1*H*-benzimidazol-2-yl)-ethylamino]-6-methyl-7-(3-oxo-piperazin-1-yl-carbonyl)-quinoline

(116) 4-[(1*R*/*S*)-1-(5-chloro-1*H*-benzimidazol-2-yl)-ethylamino]-6-methyl-7-[(2*R*)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinoline

(117) 4-[1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methylsulphanyl-propylamino]-6-methyl-7-(3-oxo-piperazin-1-yl-carbonyl)-quinoline

(118) 4-[1-(5-chloro-1*H*-benzimidazol-2-yl)-3-methanesulphonyl-propylamino]-6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinoline

(119) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-[(2R)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(120) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-hydroxy-ethylamino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(121) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-hydroxy-ethylamino]-7-[(2R)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(122) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-hydroxycarbonylpropylamino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(123) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-benzyloxycarbonylpropyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(124) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methylsulphanyl-propyl-amino]-7-[(2R)-2-tert.-butyloxycarbonyl-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(125) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methylsulphanyl-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(126) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methoxy-propylamino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(127) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphonyl-propylamino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(128) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methylsulphanyl-propyl-amino]-7-[(2R)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(129) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphinyl-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(130) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-benzyloxycarbonylpropyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(131) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-hydroxy-ethylamino]-7-(piperazin-3-on-1-yl-carbonyl)-quinazoline

(132) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-hydroxycarbonylpropyl-amino]-7-[(2S)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(133) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphonyl-propylamino]-7-[(2R)-2-tert.-butyloxycarbonyl-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(134) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphonyl-propylamino]-7-[(2R)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(135) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-(thiazolidin-3-yl-carbonyl)-quinazoline

(136) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-ethoxycarbonylpropyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(137) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(138) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-6-methyl-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(139) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphinyl-propyl-amino]-7-[(2R)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(140) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methylsulphanyl-propylamino]-6-methyl-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(141) 6-bromo-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-(2,5-dihydro-pyrrol-1-yl-carbonyl)-quinazoline

(142) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-ethoxycarbonylpropyl-amino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(143) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methylsulphanyl-propylamino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(144) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-butylamino]-7-(2,5-dihydro-pyrrol-1-yl-carbonyl)-quinazoline

(145) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methylsulphanyl-propyl-amino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(146) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(147) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-diethylaminocarbonyl-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(148) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-[N-methyl-N-piperidin-4-yl-amino]-carbonyl-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(149) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-[4-methyl-piperazin-1-yl]-carbonyl-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(150) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(C-piperidin-4-yl-methyl-amino)-carbonyl-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(151) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(N-benzyl-N-methyl-amino)-carbonyl-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(152) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-allyloxycarbonylpropyl-amino]-6-methyl-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(153) 6-bromo-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-allyloxycarbonylpropyl-amino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(154) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(155) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphonyl-propylamino]-1-oxy-7-[(2R)-2-aminomethyl-pyrrolidin-1-yl-carbonyl]-quinazoline

(156) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-[(2S)-2-(pyrrolidin-1-yl-methyl)-pyrrolidin-1-yl-carbonyl]-quinazoline

(157) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-[(2R/S)-2-aminomethyl-thiazolidinyl-carbonyl]-quinazoline

(158) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphonyl-propylamino]-7-[(2R)-2-(methanesulphonyl-aminomethyl)-pyrrolidin-1-yl-carbonyl]-quinazoline

(159) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[(1,2,3,4-tetrahydroiso-quinolin-1-yl)-carbonyl-propyl-amino]}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(160) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(benzylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(161) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[(N-methyl-N-phenethyl-amino-carbonyl)-propyl-amino]}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(162) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(hydroxyethylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(163) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[(C-pyridin-3-yl-methylamino-carbonyl)-propyl-amino]}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(164) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[(1-oxa-3,8-diaza-spiro[4.5]decan-2-on-8-yl)-carbonyl]-propyl-amino}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(165) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(morpholin-4-yl-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(166) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(C-cyclohexyl-methylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(167) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(methoxyethylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(168) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(dimethylaminoethyl-amino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(169) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(cyclopropylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(170) 6-chloro-4-{(1R/S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-[C-(2R/S)-tetrahydro-furan-2-yl-methylamino-carbonyl)-propyl-amino]}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(171) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(dimethylaminopropylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(172) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(aminoethylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(173) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(2,2,2-trifluoroethylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(174) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[N-(2-dimethylamino-ethyl)-N-methyl-amino-carbonyl]-propyl-amino}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(175) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(N-piperidin-2-yl-amino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(176) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[C-(tetrahydropyran-4-yl)-methylamino-carbonyl]-propyl-amino}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(177) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(4-hydroxypiperidin-1-yl-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(178) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[C-(pyridin-4-yl)-methylamino-carbonyl]-propyl-amino}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(179) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(N-methylaminocarbonyl-methyl-N-methyl-amino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(180) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[N-(2-(1H)-imidazol-4-yl)-ethyl)-N-methyl-amino-carbonyl]-propyl-amino}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(181) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(1-thiazolidin-3-yl-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(182) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(N-cyclopropyl-N-methyl-amino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(183) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(N-cyclopropylmethyl-N-methyl-amino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(184) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(cyclopentylamino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(185) 6-chloro-4-[1-(5-chloro-1H-benzimidazol-2-yl)-3-(N-piperidin-4-yl-amino-carbonyl)-propyl-amino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(186) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[C-(pyridin-2-yl)-methylamino-carbonyl]-propyl-amino}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(187) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-hydroxycarbonyl-propylamino]-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(188) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-(5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3a]pyridin-4-yl)-quinazoline

(189) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-(1,1-dioxo-isothiazolidin-2-yl)-propyl-amino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(190) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-methanesulphonylamino-propyl-amino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(191) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-3-(methylsulphanyl)-propylamino]-6-methoxy-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(192) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-6-methoxy-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(193) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-7-(thiazolidinyl-carbonyl)-quinazoline

(194) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-6-methyl-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(195) 4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-6-methyl-7-(thiazolidinyl-carbonyl)-quinazoline

(196) 6-bromo-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-7-(2,5-dihydropyrrol-1-yl-carbonyl)-quinazoline

(197) 6-bromo-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-7-(thiazolidinyl-carbonyl)-quinazoline

(198) 6-chloro-4-[(1S)-1-(5-chloro-1H-benzimidazol-2-yl)-ethylamino]-7-(6,7,8,9-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-4-yl)-quinazoline

(199) 6-chloro-4-{1-(5-chloro-1H-benzimidazol-2-yl)-3-[2-(pyridin-4-yl-amino)-ethylamino-carbonyl]-propylamino}-7-(pyrrolidin-1-yl-carbonyl)-quinazoline

(200) 4-[(1S)-1-(5-bromo-1H-benzimidazol-2-yl)-2-methoxy-ethylamino]-6-chloro-7-(2,5-dihydropyrrolyl-carbonyl)-quinazoline and

(201) 4-[(1S)-1-(5-bromo-1H-benzimidazol-2-yl)-ethylamino]-6-chloro-7-(2,5-dihydro-pyrrolyl-carbonyl)-quinazoline.

or a pharmaceutically acceptable salt thereof.

Any reference to the abovementioned compounds **2d** within the scope of the present invention includes a reference to any pharmaceutically acceptable acid addition salts thereof which may exist. By the physiologically or pharmaceutically acceptable acid addition salts which may be formed from **2d** are meant, according to the invention, pharmaceutically acceptable salts selected from among the salts of hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids.

Any reference to the abovementioned active ingredients **2d** within the scope of the present invention includes a reference to any alkali metal and alkaline earth metal salts thereof which may exist. If the compounds **2d** are present in the form of their basic salts, the sodium or potassium salts are particularly preferred.

The pharmaceutical combinations of **1** and **2d** according to the invention are preferably administered by parenteral or oral route, the latter being particularly preferred. For oral or parenteral administration the pharmaceutical compositions according to the invention may be administered e.g. in the form of solutions and tablets.

Pharmaceutical compositions comprising an direct thrombin inhibitor 1 and an fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) 2e:

One embodiment of the invention is a pharmaceutical composition comprising an direct thrombin inhibitor **1** and an fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e**. Binary compositions containing only one active **1** and one active **2e**, optionally together with one or more pharmaceutically acceptable excipients or carriers, are preferred. In the pharmaceutical combinations according to the invention preferred fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** are selected from the group consisting of fradafiban, lefradafinban, abciximab (ReoPro), eptifibatide (Integrilin) and tirofiban (Aggrastat), optionally in the form of enantiomers, mixtures of enantiomers or the racemates.

Any reference to fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** within the scope of the present invention includes a reference to the salts, preferably pharmacologically acceptable acid addition salts, or derivatives which may be formed from the fibrinogen receptor antagonists. Examples of pharmacologically acceptable acid addition salts of the fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** according to the invention are the pharmaceutically acceptable salts which are selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid. Preferred salts are selected from the group consisting of acetate, hydrochloride, hydrobromide, sulphate, phosphate, maleate and methanesulphonate.

Any reference to the abovementioned fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** within the scope of the present invention includes a reference to any alkali metal and alkaline earth metal salts thereof which may exist. If the compounds **2e** are present in the form of their basic salts, the sodium or potassium salts are particularly preferred.

The pharmaceutical combinations of **1** and **2e** according to the invention are preferably administered by parenteral or oral route, the latter being particularly preferred. For oral or parenteral administration the pharmaceutical compositions

according to the invention may be administered e.g. in the form of solutions and tablets.

Suitable doses for the compounds **2e** are:

abciximab: 0.25 mg /kg iv bolus + 10 mcg/kg/h iv infusion
eptifibatide: 80-135 mcg/kg iv bolus + 0.5-1.0 mcg/kg/min iv infusion
tirofiban: 0.15 mcg/kg/min

Suitable dosages for compounds **1** have already been given above.

Pharmaceutical compositions comprising an direct thrombin inhibitor 1 and an Vitamin K antagonist 2f:

One embodiment of the invention is a pharmaceutical composition comprising an direct thrombin inhibitor **1** and Vitamin K antagonists **2f**. Binary compositions containing only one active **1** and one active **2f**, optionally together with one or more pharmaceutically acceptable excipients or carriers, are preferred. In the pharmaceutical combinations according to the invention preferred Vitamin K antagonists **2f** are selected from the group consisting of Warfarin and Phenprocoumon, optionally in the form of enantiomers, mixtures of enantiomers or the racemates.

Any reference to Vitamin K antagonists **2f** within the scope of the present invention includes a reference to the salts, preferably pharmacologically acceptable salts, or derivatives which may be formed from the Vitamin K antagonists. Examples of pharmacologically acceptable salts of the Vitamin K antagonists **2f** according to the invention is the sodium salt.

Any reference to the abovementioned Vitamin K antagonists **2f** within the scope of the present invention includes a reference to any alkali metal and alkaline earth metal salts thereof which may exist. If the compounds **2f** are present in the form of their basic salts, the sodium or potassium salts are particularly preferred.

The pharmaceutical combinations of **1** and **2f** according to the invention are preferably administered by parenteral or oral route, the latter being particularly preferred. For oral or parenteral administration the pharmaceutical compositions according to the invention may be administered e.g. in the form of solutions and tablets.

Suitable doses for the compounds **2f** are:

Warfarin (sodium salt): 5 mg tablets

Phenprocoumon: 3 mg tablets

Suitable dosages for compounds **1** have already been given above.

The actives of the combinations according to the invention may be administered simultaneously, separately or sequentially. The preferred route of administration depends on the indication to be treated. Both components **1** and **2** may be administered orally, intravenously, subcutaneously, topically or rectally, using suitable formulations known in the art, such as tablets, coated tablets, pills, granules or granular powder, syrups, emulsions, suspensions, solutions, ointments, transdermal patches or suppositories, optionally together with inert and non-toxic pharmaceutically acceptable excipients or solvents.

The compositions according to the invention may be given for instance orally, intravenously, subcutaneously, by intramuscular injection, intraperitoneally, intranasally or transdermally, using suitable formulations known in the art, such as tablets, coated tablets, pills, capsules, granules or granular powder, aerosols, syrups, emulsions, suspensions, powders, solutions or transdermal patches, optionally together with inert and non-toxic pharmaceutically acceptable excipients or solvents.

Within the scope of the present invention, the term carrier may optionally be used instead of the term excipient.

The preparations according to the invention may contain the combination of active substances **1** and **2** either together in one formulation or in two separate formulations. These formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

Any aforementioned possible doses applicable for the combinations according to the invention are to be understood as referring to doses per single application. However, these examples are not be understood as excluding the possibility of administering the combinations according to the invention multiple times. Depending on the medical need patients may receive also multiple applications. As an example patients may receive the combinations according to the invention for instance two or three times in the morning of each treatment day. As the aforementioned dose examples are only to be understood as dose examples per single application multiple application of the combinations according to the invention leads to multiple doses of the aforementioned examples. The application of the compositions according to the invention can be for instance once a day, or depending on the duration of action of the agents twice a day, or once every 2 or 3 days.

The Examples which follow serve to illustrate the present invention in more detail without restricting the scope of the invention to the following embodiments by way of example.

Examples of Formulations

The following examples of formulations, which may be obtained analogously to methods known in the art, serve to illustrate the present invention more fully without restricting it to the contents of these examples. Examples of formulations comprising an direct thrombin inhibitor **1** selected from compounds **1.1** to **1.8** as the only active ingredient are disclosed in the prior art, e.g. in WO 98/37075 and WO 04/014894. Additionally, suitable formulations for a drug may be the formulations disclosed in Rote Liste®2005, Editio Cantor Verlag Aulendorf, Germany, or in Physician's Desk Reference, 58 edition, 2004.

Example 1: Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 2: Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:

Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

Example 3: Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 9 mm.

Example 4: Tablet containing 350 mg of active substance

Preparation:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 12 mm.

Example 5: Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatin capsules in a capsule filling machine.

Example 6: Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 0 hard gelatin capsules in a capsule filling machine.

Example 7: Suppositories containing 100 mg of active substance

1 suppository contains:

Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	840.0 mg
	2,000.0 mg

Example 8 and 9 are formulation particularly adapted for the methanesulfonate of compound **1.1**. A detailed description of the preparation thereof is given in WO 03/074056, which is hereby incorporated by reference.

Example 8: Pellets for capsules

	percentage composition				per capsule [mg]	per capsule [mg]
	core material	insulating layer	active substance layer	total		
tartaric acid	61.3	-	-	61.3	176.7	353.4
gum arabic	3.1	2.8		5.9	17.0	34.0
talc	-	5.6	3.2	8.8	25.4	50.7
hydroxypropylcellulose	-	-	4.0	4.0	11.5	23.1
active substance	-	-	20.0	20.0	57.7*	115.3**
total				100.0	288.3	576.5

*) corresponds to 50 mg of the compound of the active substance base

**) corresponds to 100 mg of the compound of the active substance base

Example 9: Pellets for capsules

	percentage composition				per capsule [mg]	per capsule [mg]
	core material	insulating layer	active substance layer	total		
tartaric acid	38.5	-	-	38.5	55.5	166.5
gum arabic	1.9	1.7		3.6	5.2	15.6
talc	-	3.5	6.4	9.9	14.3	42.8
hydroxypropylcellulose	-	-	8.0	8.0	11.5	34.6
active substance	-	-	40.0	40.0	57.7*	173.0**
total				100.0	144.2	432.5

*) corresponds to 50 mg of the compound of the active substance base

**) corresponds to 150 mg of the compound of the active substance base

Claims

1. Pharmaceutical composition comprising at least one direct thrombin inhibitor **1** selected from the group consisting of compounds

(**1.1**) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (dabigatran),

(**1.2**) 1-methyl-2-(4-amidinophenylaminomethyl)-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-hydroxycarbonylethyl)-amide,

(**1.3**) 1-methyl-2-[4-(*N*-hydroxyamidino)-phenylaminomethyl]-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonylethyl)-amide

(**1.4**) melagatran (inogatran),

(**1.5**) ximelagatran,

(**1.6**) hirudin,

(**1.7**) hirolog and

(**1.8**) argatroban,

optionally in the form of tautomers, racemates, enantiomers, diastereomers, pharmacologically acceptable acid addition salts, solvates or hydrates, prodrugs thereof,

and further comprising one or more additional active compounds **2** selected from the groups consisting of platelet inhibitors **2a,** low molecular weight heparins (LMWH) and heparinoids as well as unfractionated heparin **2b**, factor X_a inhibitors **2c**, combined thrombin/factor X_a inhibitors **2d**, fibrinogen receptor antagonists (glycoprotein IIb/IIa antagonists) **2e** and Vitamin K antagonists **2f**, optionally together with one or more pharmaceutically acceptable excipients or carriers.

2. The pharmaceutical composition of claim 1 as a binary combination, containing an direct thrombin inhibitor **1** and an active compound **2** selected from one of the classes **2a**, **2b**, **2c**, **2d**, **2e** and **2f**, optionally together with one or more pharmaceutically acceptable excipients or carriers.

3. The pharmaceutical composition of claim 2, wherein the active compound **2** is a platelet inhibitor **2a**.

4. The pharmaceutical composition of claim 2, wherein the active compound **2** is a low molecular weight heparin (LMWH) or a heparinoid or an unfractionated heparin **2b**.

5. The pharmaceutical composition of claim 2, wherein the active compound **2** is a factor X_a inhibitor **2c**.

6. The pharmaceutical composition of claim 2, wherein the active compound **2** is a combined thrombin/factor X_a inhibitor **2d**.

7. The pharmaceutical composition of claim 2, wherein the active compound **2** is a fibrinogen receptor antagonist (glycoprotein IIb/IIa antagonist) **2e**.

8. The pharmaceutical composition of claim 2, wherein the active compound **2** is a Vitamin K antagonists **2f**.

9. The pharmaceutical composition of claim 1 as a ternary combination, containing one direct thrombin inhibitor **1** and two active compounds selected from the class of platelet inhibitors **2a,** optionally together with one or more pharmaceutically acceptable excipients or carriers.

10. The pharmaceutical composition of claim 1 as a ternary combination, containing two direct thrombin inhibitors **1** and an active compound selected from one of the classes **2a**, **2b**, **2c**, **2d**, **2e** and **2f**, optionally together with one or more pharmaceutically acceptable excipients or carriers.

11. The pharmaceutical composition of claim 1 as a quarternary combination, containing two direct thrombin inhibitors **1** and two active compounds selected from either one or from two different classes of **2a**, **2b**, **2c**, **2d**, **2e** and **2f**, optionally together with one or more pharmaceutically acceptable excipients or carriers.

12. The pharmaceutical composition of claim 1 as a quarternary combination, containing two direct thrombin inhibitors **1** and two active compounds selected from the class of platelet inhibitors **2a**, optionally together with one or more pharmaceutically acceptable excipients or carriers.

13. The pharmaceutical composition of one of claims 1, 2, 3, 9, 10, 11 and 12, wherein the platelet inhibitor **2a** is selected from the group consisting of acetylsalicylic acid **2a.1**, clopidogrel **2a.2** and ticlopidine **2a.3**, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof.

14. The pharmaceutical composition of one of claims 1 to 13, wherein the direct thrombin inhibitor is compound **1.1**.

15. The pharmaceutical composition of one of claims 1 to 14, wherein the direct thrombin inhibitor is the methanesulfonate of compound **1.1**.

16. The pharmaceutical composition of one of claims 1, 2, 3, 9, 10, 11, 12, 13, 14 or 15, wherein the platelet inhibitor is acetylsalicylic acid **2a.1**.

17. The pharmaceutical composition of one of claims 1, 2, 3, 9, 10, 11, 12, 13, 14 or 15, wherein the platelet inhibitor is clopidogrel **2a.2**.

18. The binary pharmaceutical composition according to claim 3 containing the methanesulfonate of compound **1.1** and acetylsalicylic acid **2a.1.**

19. The binary pharmaceutical composition according to claim 3 containing the methanesulfonate of compound **1.1** and clopidogrel **2a.2.**

20. The ternary pharmaceutical composition according to claim 9 containing the methanesulfonate of compound **1.1,** acetylsalicylic acid **2a.1** and clopidogrel **2a.2.**

21. Pharmaceutical composition according to one of claims 1 to 20, characterised in that it is in the form of a preparation suitable for inhalative, oral, intravenous, topical,

subcutaneous, intramuscular, intraperitoneal, intranasal, transdermal or rectal administration.

22. Pharmaceutical composition according to one of claims 1 to 21, characterised in that it is in the form of a preparation suitable for oral administration.

23. Pharmaceutical composition according to one of claims 1 to 21, characterised in that it is in the form of a preparation suitable for intravenous administration.

24. Pharmaceutical composition according to one of claims 1 to 21, characterised in that it is in the form of a preparation suitable for subcutaneous administration.

25. A method for preventing or treating the consequences of thrombotic and thromboembolic diseases comprising administering a therapeutically effective amount of pharmaceutical composition according to any of claims 1 to 24 to a patient in need thereof.

26. The method according to claim 25 wherein the thrombotic or thromboembolic disease is selected from the following indications:

deep vein thrombosis (DVT) pulmonary embolism, and other venous thrombotic events in patients at risk for such events (post-orthopedic surgery, medical patients, cancer patients, surgical patients),
stroke prevention in atrial fibrillation (SPAF),
stroke prevention in other populations at high risk for such events (heart failure or left ventricular dysfunction, high risk patients with myocardial infarction, patients with valve disease or valve replacement)
thrombosis and thombotic events in patients with acute myocardial infarction or acute coronary syndromes, including patients undergoing thrombolysis or those with stents or percutaneous coronary intervention (PCI), or both,
post-myocardial infarction (MI), in patients who have received thrombolysis or those with percutaneous coronary intervention or post coronary bypass surgery,
or other acute coronary syndromes

for prevention or treatment of thrombosis, in particular for treatment of patients with stents or percutaneous coronary intervention (PCI).

27. The method of claim 26 wherein indication is selected from DVT and SPAF.

28. The use of a pharmaceutical composition according to one of claims 1 to 24 for the manufacture of a medicament for treating an indication selected from indications:
deep vein thrombosis (DVT) pulmonary embolism, and other venous thrombotic events in patients at risk for such events (post-orthopedic surgery, medical patients, cancer patients, surgical patients),
stroke prevention in atrial fibrillation (SPAF),
stroke prevention in other populations at high risk for such events (heart failure or left ventricular dysfunction, high risk patients with myocardial infarction, patients with valve disease or valve replacement)
thrombosis and thombotic events in patients with acute myocardial infarction or acute coronary syndromes, including patients undergoing thrombolysis or those with stents or percutaneous coronary intervention (PCI), or both,
post-myocardial infarction (MI), in patients who have received thrombolysis or those with percutaneous coronary intervention or post coronary bypass surgery,
or other acute coronary syndromes
for prevention or treatment of thrombosis, in particular for treatment of patients with stents or percutaneous coronary intervention (PCI).

29. The use of claim 28, wherein the indication is selected from DVT and SPAF.