Oxazolidinones for the treatment and/or prophylaxis of heart failure

The present invention relates to the use of selective inhibitors of coagulation factor Xa, in particular of oxazolidinones of the formula (I), for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure as well as their use for the preparation of pharmaceutical drugs for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure.

Oxazolidinones of the formula (I) are known from WO-A-01/047919 and act in particular as selective inhibitors of coagulation factor Xa and as anticoagulants.

Oxazolidinones of the formula (I) inhibit the coagulation factor Xa selectively. It has been possible to demonstrate an antithrombotic effect of factor Xa inhibitors in numerous animal models (cf. U. Sinha, P. Ku, J. Malinowski, B. Yan Zhu, R.M. Scarborough, C.K. Marlowe, P.W. Wong, P. Hua Lin, S.J. Hollenbach, Antithrombotic and hemostatic capacity of factor Xa versus thrombin inhibitors in models of venous and arteriovenous thrombosis, *European Journal of Pharmacology* **2000**, *395*, 51-59; A. Betz, Recent advances in Factor Xa inhibitors, *Expert Opin. Ther. Patents* **2001**, *11*, 1007; K. Tsong Tan, A. Makin, G.Y.H. Lip, Factor X inhibitors, *Exp. Opin. Investig. Drugs* **2003**, *12*, 799; J. Ruef, H.A. Katus, New antithrombotic drugs on the horizon, *Expert Opin. Investig. Drugs* **2003**, *12*, 781; M.M. Samama, Synthetic direct and indirect factor Xa inhibitors, *Thrombosis Research* **2002**, *106*, V267; M.L. Quan, J.M. Smallheer, The race to an orally active Factor Xa inhibitor, Recent advances, *J. Current Opinion in Drug Discovery & Development* **2004**, *7*, 460-469) and in clinical studies on patients (The Ephesus Study, *Blood* **2000**, *96*, 490a; The Penthifra Study, *Blood* **2000**, *96*, 490a; The Pentamaks Study, *Blood* **2000**, *96*, 490a-491a; The Pentathlon Study, *Blood* **2000**, *Vol 96*, 491a). Factor Xa inhibitors can therefore be employed preferably in medicaments for the prophylaxis and/or treatment of thromboembolic disorders.

Selective factor Xa inhibitors show a broad therapeutic window. It has been possible to demonstrate in numerous animal models that selective factor Xa inhibitors show an antithrombotic effect without or only marginally prolongating the bleeding time (cf. RJ Leadly, Coagulationfactor Xa inhibition: biological background and rationale, *Curr. Top. Med. Chem.* **2001**, *1*, 151-159). Therefore, an individually dosage for anticoagulants of the class of selective factor Xa inhibitors is not required.

Heart failure, synonym to congestive heart failure (CHF) or cardiac failure or acute and chronic heart failure, is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues or can do so only from an elevated filling pressure (W S Colucci, E.Braunwald. Pathophysiology of Heart Failure page 394-420 in Heart Disease, A Textbook of Cardiovascular Medicine, ed. E. Braunwald, WB Saunders

Company, 5TH edition). It is usually caused by a defect in myocardial contraction, i.e. due to myocardial infarction or hypertension. In the presence of a disturbance in myocardial contractility or an excessive hemodynamic burden placed on the ventricle, or both, the heart depends on a number of adaptive mechanisms for maintenance of its pumping function. One important mechanism e.g. is the remodelling process of the heart in response to the initial pathologic event, which can lead to a progressive deterioration of cardiac function.

Pathophysiological features of heart failure encompass chronic procoagulant blood state predisposing to thromboembolism. Clinical studies have demonstrated an increased incidence of venous and arterial thrombosis in CHF subjects [White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107 (23 suppl 1):14-18]. There is good evidence linking elevated- markers of hypercoagulability and thrombotic events with adverse outcome in patients, and increased rates of morbidity and mortality. Activated coagulation activity is evidenced by elevated TNF, thrombin–antithrombin complexes (TAT), D-dimer, prothrombin fragment F1 + 2, fibrinopeptide A, IL–6 (Garg RK et al. Prog Cardiovasc Dis. 1998; 41:225-236. Davis CJ et al. Int J Cardiol 2000; 75:15-21).

Hypercoagulability, venous and arterial thrombosis, including e.g. pulmonary embolism (PE), myocardial infarction, stroke, can worsen the cardiac function, can trigger decompensation and can damage other organ and tissues in individuals with CHF, thus increasing morbidity and mortality rates. In addition, CHF can affect the clinical outcome of patients with thrombosis and PE, and both conditions worsen outcome.

In addition to their important role in the activation of the coagulation system leading to hypercoagulability and thrombosis, Factor Xa and thrombin are known to exhibit variant pleiotropic effects. Thus, they are potent mitogens that induce proliferation. They induce and/or augments vasoconstriction. Signaling by thrombin leads to proinflammatory cytokine release. Treatment with FXa inhibitors, besides their inhibition of blood coagulation, may suppress the mitogenic, vasoconstrictive and inflammatory stimuli of FXa and thrombin, the latter by inhibition of the generation of thrombin.

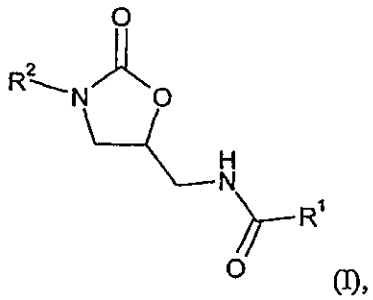
Antithrombotic therapy with either aspirin or warfarin resulted in reduction in the rates of clinical events compared with subjects who did not receive antithrombotic drugs. Anticoagulation by warfarin therapy also reduced the rates of hospitalization for CHF, but at the cost of increased major bleeding rates. The use of aspirin may increase the risk of hospitalization for CHF. [1) Dunkman WB, Johnson GR, Carson PE, Bhat G, Farrell L, Cohn JN. Incidence of thromboembolic events in congestive heart failure. The V-HEFT VA Cooperative Studies Group. Circulation 1993;

87 (6 Suppl): V194-V1101. 2) Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and risk of stroke after myocardial infarction. N Engl J Med 1997; 336; 251-257. 3) The CONSENSUS Trial Study Group. Effect of enalapril on mortility in severe congestive heart failure. Results of Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987, 316:1429-1435. 4) Dries DL, Rosenberg YD, Waclawiw MA, Domanski MJ. Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials. J Am Coll Cardiol 1997; 29: 1074-1080].

It has now been found, surprisingly, that selective inhibitors of coagulation factor Xa, in particular of oxazolidinones of the formula (I), are also suitable for the prophylaxis and/or treatment of heart failure and/or disorders related to heart failure.

The present invention therefore relates to the use of selective factor Xa inhibitors for preparing medicaments or pharmaceutical compositions for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure.

The present invention therefore relates in particular to the use of compounds of the formula (I)



(I),

in which

R^1 is 2-thiophene which is substituted in position 5 by a radical from the group of chlorine, bromine, methyl or trifluoromethyl,

R^2 is D-A-:

where:

the radical "A" is phenylene;

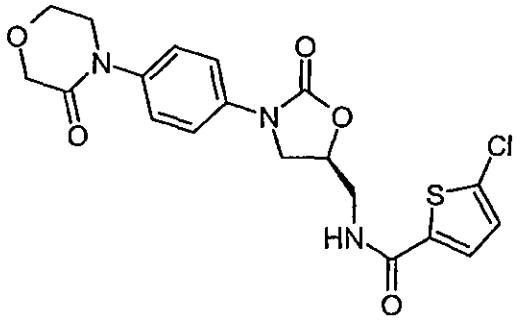
where:

the group "A" defined above may optionally be substituted once or twice in the meta position relative to the linkage to the oxazolidinone by a radical from the group of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl or cyano,

the radical "D" is a saturated 5- or 6-membered heterocycle which is linked via a nitrogen atom to "A", which has a carbonyl group in direct vicinity to the linking nitrogen atom, and in which a ring carbon member may be replaced by a heteroatom from the series S, N and O;

and their pharmaceutically acceptable salts, solvates and solvates of the salts for preparing medicaments or pharmaceutical compositions for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure.

Very particular preference is likewise given in this connection to the use of the compound 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban; example 1) having the following formula



and its pharmaceutically acceptable salts, solvates and solvates of the salts for preparing medicaments or pharmaceutical compositions for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure.

To date, oxazolidinones have been described essentially only as antibiotics, and in a few cases also as MAO inhibitors and fibrinogen antagonists (Review: B. Riedl, R. Endermann, *Exp. Opin. Ther. Patents* 1999, *9*, 625), and a small 5-[acylaminomethyl] group (preferably 5-[acetylaminomethyl]) appears to be essential for the antibacterial effect.

Substituted aryl- and heteroarylphenyloxazolidinones in which a monosubstituted or polysubstituted phenyl radical may be bonded to the N atom of the oxazolidinone ring and which may have in position 5 of the oxazolidinone ring an unsubstituted N-methyl-2-thiophenecarboxamide residue, and their use as substances with antibacterial activity are disclosed

in the U.S. patents US-A-5 929 248, US-A-5 801 246, US-A-5 756 732, US-A-5 654 435, US-A-5 654 428 and US-A-5 565 571.

In addition, benzamidine-containing oxazolidinones are known as synthetic intermediates in the synthesis of factor Xa inhibitors or fibrinogen antagonists (WO-A-99/31092, EP-A-623615).

Compounds according to the invention are the compounds of the formula (I) and salts, solvates and solvates of the salts thereof, the compounds of the formulae mentioned below covered by formula (I) and salts, solvates and solvates of the salts thereof and the compounds mentioned below as practical examples covered by formula (I) and salts, solvates and solvates of the salts thereof, insofar as the compounds of the formulae mentioned below covered by formula (I) are not already salts, solvates and solvates of the salts.

Depending on their structure, the compounds according to the invention can exist in stereo-isomeric forms (enantiomers, diastereomers). The present invention therefore includes the enantiomers or diastereomers and respective mixtures thereof. From such mixtures of enantiomers and/or diastereomers, the stereoisomerically homogeneous components can be isolated in known manner.

Insofar as the compounds according to the invention can occur in tautomeric forms, the present invention includes all tautomeric forms.

As salts in the context of the present invention, physiologically harmless salts of the compounds according to the invention are preferred. Also included are salts which are not themselves suitable for pharmaceutical applications, but can for example be used for the isolation or purification of the compounds according to the invention.

Physiologically harmless salts of the compounds according to the invention include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, e.g. salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethane-sulphonic acid, toluene-sulphonic acid, benzenesulphonic acid, naphthalen-edisulphonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically harmless salts of the compounds according to the invention also include salts of usual bases, such as for example and preferably alkali metal salts (e.g. sodium and potassium salts), alkaline earth salts (e.g. calcium and magnesium salts) and ammonium salts, derived from ammonia or organic amines with 1 to 16 C atoms, such as for example and preferably ethylamine, diethylamine, triethylamine, ethyl-diiso-propyl-amine, monoethanolamine, diethanolamine,

triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methyl-morpholine, arginine, lysine, ethylenediamine and *N*-methylpiperidine.

In the context of the invention those forms of the compounds according to the invention which in the solid or liquid state form a complex by coordination with solvent molecules are described as solvates. Hydrates are a specific form of solvates, wherein the coordination takes place with water. Hydrates are preferred as solvates in the context of the present invention.

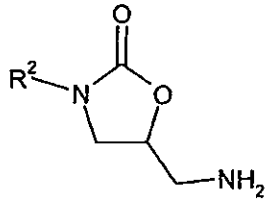
In addition, the present invention also includes prodrugs of the compounds according to the invention. The term "prodrugs" includes compounds which can themselves be biologically active or inactive, but are converted into compounds according to the invention (for example metabolically or hydrolytically) during their residence time in the body.

In the context of the present invention, unless otherwise specified, the substituents have the following meaning:

A saturated 5- or 6-membered heterocycle which is linked via a nitrogen atom to "A", which has a carbonyl group in direct vicinity to the linking nitrogen atom, and in which a ring carbon member may be replaced by a heteroatom from the series S, N and O, may be mentioned for example as: 2-oxo-pyrrolidine-1-yl, 2-oxo-piperidine-1-yl, 2-oxo-piperazine-1-yl, 2-oxo-morpholine-1-yl, 3-oxo-thiomorpholine-4-yl, 2-oxo-1,3-oxazolidine-1-yl, 2-oxo-1,3-oxazinan-1-yl, 2-oxo-imidazolidine-1-yl und 2-oxo-tetrahydropyrimidine-1-yl.

The compounds of the formula (I) can be prepared by either, in a process alternative,

[A] reacting compounds of the general formula (II)

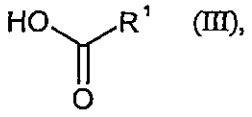


(II),

in which

the radical R^2 has the meaning indicated above,

with carboxylic acids of the general formula (III)



(III),

in which

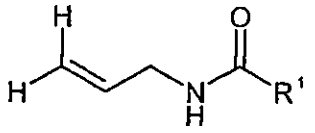
the radical R^1 has the meaning indicated above,

or else with the corresponding carbonyl halides, preferably carbonyl chlorides, or else with the corresponding symmetrical or mixed carboxylic anhydrides of the carboxylic acids of the general formula (III) defined above

in inert solvents, where appropriate in the presence of an activating or coupling reagent and/or of a base, to give compounds of the general formula (I)

or else in a process alternative

[B] converting compounds of the general formula (IV)

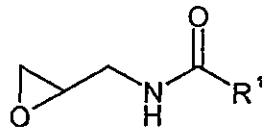


(IV),

in which

the radical R^1 has the meanings indicated above,

with a suitable selective oxidizing agent in an inert solvent into the corresponding epoxide of the general formula (V)



(V),

in which

the radical R^1 has the meanings indicated above,

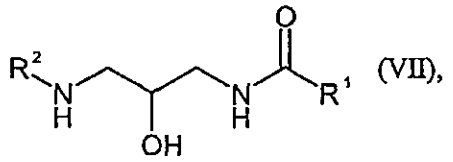
and are reacted in an inert solvent, where appropriate in the presence of a catalyst, with an amine of the general formula (VI)

$$R^2 - NH_2 \qquad (VI),$$

in which

the radical R^2 has the meaning indicated above,

initially preparing the compounds of the general formula (VII)


(VII),

in which

the radicals R^1 and R^2 have the meanings indicated above,

and

subsequently cyclizing in an inert solvent in the presence of phosgene or phosgene equivalents such as, for example, carbonyldiimidazole (CDI) to the compounds of the general formula (I).

Solvents suitable for the processes described above are in these cases organic solvents which are inert under the reaction conditions. These include halohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons such as benzene, xylene, toluene, hexane or cyclohexane, dimethylformamide, dimethyl sulfoxide, acetonitrile, pyridine, hexamethyl-phosphoric triamide or water.

It is likewise possible to employ solvent mixtures composed of the aforementioned solvents.

Activating or coupling reagents suitable for the processes described above are in these cases the reagents normally used for these purposes, for example *N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide • HCl, *N,N'*-dicyclohexylcarbodiimide, 1-hydroxy-1H-benzotriazole • H_2O and the like.

Suitable bases are the usual inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium or potassium hydroxide or alkali metal carbonates such as sodium or potassium carbonate or sodium or potassium methanolate or sodium or potassium ethanolate or potassium tert-butoxide or amides such as sodamide, lithium bis-(trimethylsilyl)amide or lithium diisopropylamide or amines such as triethylamine, diisopropylethylamine, diisopropylamine, 4-*N,N*-dimethylaminopyridine or pyridine.

The base can be employed in these cases in an amount of from 1 to 5 mol, preferably from 1 to 2 mol, based on 1 mol of the compounds of the general formula (II).

The reactions generally take place in a temperature range from –78°C to the reflux temperature, preferably in the range from 0°C to the reflux temperature.

The reactions can be carried out under atmospheric, elevated or reduced pressure (e.g. in the range from 0.5 to 5 bar), generally under atmospheric pressure.

Suitable selective oxidizing agents both the preparing epoxides and for the oxidation which is optionally carred out to the sulfone, sulfoxide or N-oxide are, for example, m-chloroperbenzoic acid (MCPBA), sodium metaperiodate, N-methylmorpholine N-oxide (NMO), monoperoxyphthalic acid or osmium tetroxide.

The conditions used for preparing the epoxides are those customary for these preparations.

For detailed conditions for the process of oxidation, which is carried out where appropriate, to the sulfone, sulfoxide or N-oxide, reference may be made to the following literature: M.R. Barbachyn *et al. J. Med. Chem.* 1996, *39*, 680 and WO-A-97/10223.

The compounds of the formulae (II), (III), (IV) and (VI) are known per se to the skilled worker or can be prepared by conventional methods. For oxazolidinones, in particular the 5-(aminomethyl)-2-oxooxazolidines required, cf. WO-A-98/01446; WO-A-93/23384; WO-A-97/03072; J.A. Tucker *et al. J. Med. Chem.* 1998, *41*, 3727; S.J. Brickner *et al. J. Med. Chem.* 1996, *39*, 673; W.A. Gregory *et al. J. Med. Chem.* 1989, *32*, 1673.

The process for the synthesis of the compounds of the general formula (I) is described in detail in WO-A-01/047919.

For the purpose of the present invention "heart failure" include, in particular, serious disorders such as Cardiac Failure, Chronic Heart Failure, Congestive Heart Failure, Congestive Cardiac Failure, Acute Heart Failure, Acute Decompensated Heart Failure, Systolic Heart Failure,

Diastolic Heart Failure, Right Heart Failure, Left Heart Failure, Heart Insufficiency, Cardiac Insufficiency, Chronic Cardiac Insufficiency, Cardiac Decompensation, High Output Heart Failure, Low Output Heart Failure, Cardiomyopathy, Dilated Cardiomyopathy and Hypertrophic Cardiomyopathy.

For the purpose of the present invention "disorders related to heart failure" include, in particular, progressive deterioration of cardiac function, decompensation of the heart and thereof damage of other organs and tissues, hypercoagulability, arterial and venous thromboembolic events, pulmonary embolism (PE), myocardial infarction and stroke.

Furthermore, the present invention relates to a method for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure of the human or animal body with the use of an effective quantity of a selective factor Xa inhibitor or of a medicament, comprising at least one selective factor Xa inhibitor in combination with one or more pharmacologically acceptable auxiliaries or excipients.

Furthermore, the present invention relates to a method for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure of the human or animal body with the use of an effective quantity of at least one compound of the formula (I) or of a medicament, comprising at least one compound of the formula (I) in combination with one or more pharmacologically acceptable auxiliaries or excipients.

Furthermore, the present invention relates to a method for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure of the human or animal body with the use of an effective quantity of at least the compound 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide or of a medicament, comprising at least the compound 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarbox-amide in combination with one or more pharmacologically acceptable auxiliaries or excipients.

The present invention further provides medicaments and pharmaceutical compositions comprising at least one compound of the formula (I) according to the invention together with one or more pharmacologically acceptable auxiliaries or excipients, which medicaments and pharmaceutical compositions can be used for the indications mentioned above.

In one embodiment, the invention provides a method for preventing the formation of thrombi in the microvasculature and macrovasculature, wherein the method comprises administering on a chronic

basis to the mammal a therapeutically effective amount of at least one compound of the formula (I) such as rivaroxaban.

In another embodiment, the method provides for the improved survival that occur in the mammal, the method comprising the steps of administering on a chronic basis to the mammal a therapeutically effective amount of at least one compound of the formula (I) such as rivaroxaban, wherein the previously specified events' frequency are reduced relative to the frequency established by a recognized standard of care.

In another embodiment, the compounds of formula (I) are suitable to improve morbidity and mortality for a broad spectrum individuals with heart failure, which also means patients with heart failure with and without artificial heart valves, patients with atrial fibrillation, coronary heart disease, hospitalized patients due to their illnesses (medically ill patients).

In another embodiment, rivaroxaban is suitable to improve morbidity and mortality for a broad spectrum individuals with heart failure, which also means patients with heart failure with and without artificial heart valves, patients with atrial fibrillation, coronary heart disease, hospitalized patients due to their illnesses (medically ill patients).

In another embodiment, the method provides for a reduction of the number of hospitalizations required for the care of the individual, the method comprising the steps of administering on a chronic basis to the mammal a therapeutically effective amount of at least one compound of the formula (I) such as rivaroxaban, wherein the previously specified event's frequency is reduced relative to the frequency established by a recognized standard of care.

In another embodiment, the method provides for a replacement therapy in the mammal for other anticoagulant and antiplatelet therapies that represent current guideline based standards of care, the method comprising the steps of administering on a chronic basis to the mammal a therapeutically effective amount of at least one compound of the formula (I) such as rivaroxaban. The frequency of events that are observed in the mammal are equal to or reduced relative to the frequency established by the recognized standard of care which is being replaced.

In another embodiment, the present invention also relates to the combinations of

A) compounds of the formula (I) together with

B) other pharmaceutical drugs, especially with platelet aggregation inhibitors, anticoagulants, fibrinolytics, antilipemics, coronary therapeutics and/or vasodilative agents.

"Combinations" in the context of the present application are not only pharmaceutical formulations, which comprise all components (so-called fixed-dose combinations), and combination packages, which keep all components separate from each other, but also components which are administered simultaneously or temporary staggered, provided that they are used for the prophylaxis and/or treatment of the same disease. In addition, it is possible to combine two or more drugs together, which are dual or multiple combinations, respectively.

The individual drugs of the combinations are known from literature and are mostly commercially available.

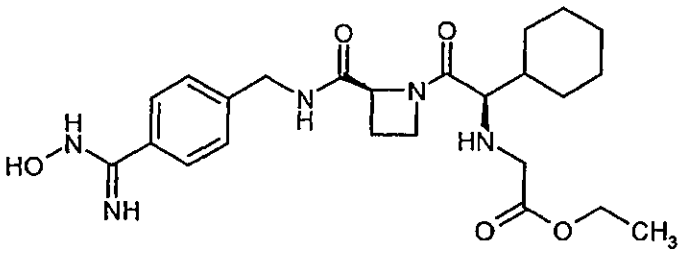
Platelet aggregation inhibitors are for example acetylsalicylic acid (like Aspirin), ticlopidine (Ticlid) and clopidogrel (Plavix),

or integrin antagonists like for example glycoproteine IIb/IIIa antagonists like for example abciximab, eptifibatide, tirofibane, lamifiban, lefradafiban and fradafiban.

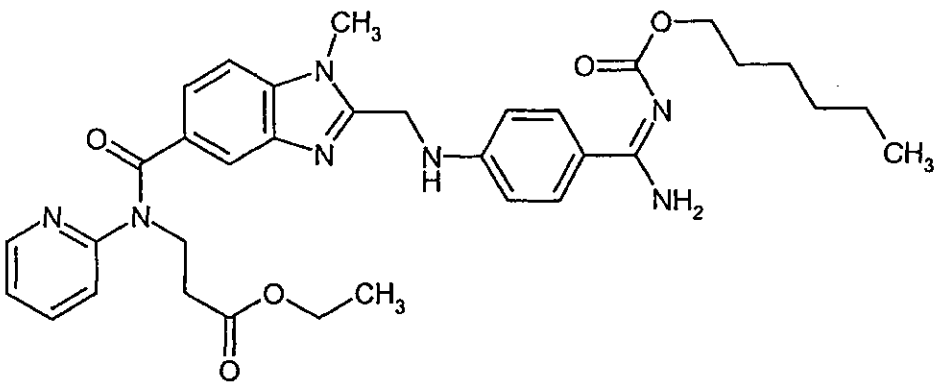
Anticoagulants are for example heparine (UFH), low molecular weight heparine (LMWH) like for example tinzaparin, certoparin, parnaparin, nadroparin, ardeparin, enoxaparin, reviparin, dalteparin, danaparoid and direct thrombin inhibitors (DTI).

Direct thrombin inhibitors are for example:

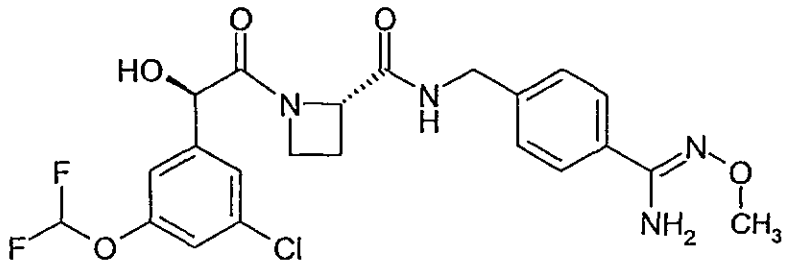
- **Exanta (ximelagatran)**



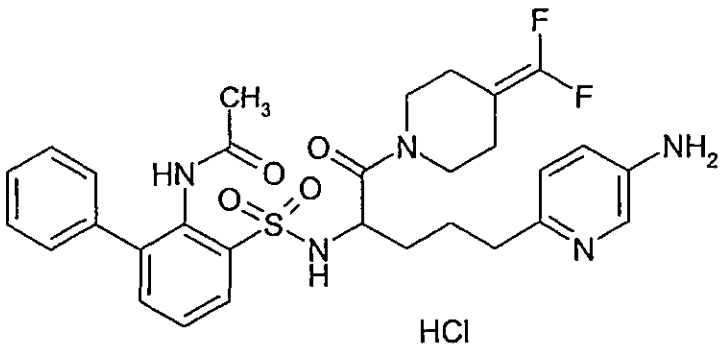
- **Rendix (dabigatran)**



- **AZD-0837** [AstraZeneca Annual Report **2006**, March 19th, 2007]

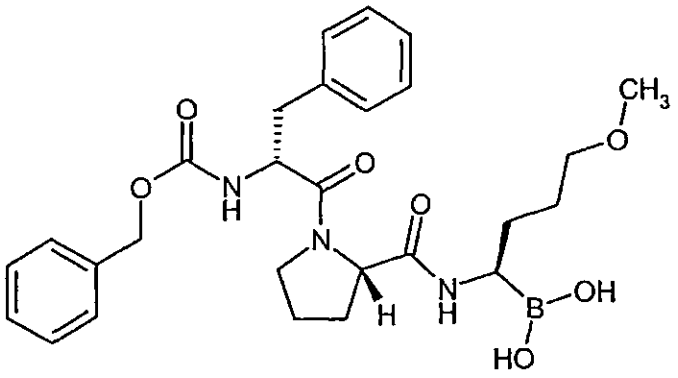


- **SSR-182289A** [J. Lorrain *et al. Journal of Pharmacology and Experimental Therapeutics* **2003**, *304*, 567-574; J.-M. Altenburger *et al. Bioorg.Med.Chem.* **2004**, *12*, 1713-1730]

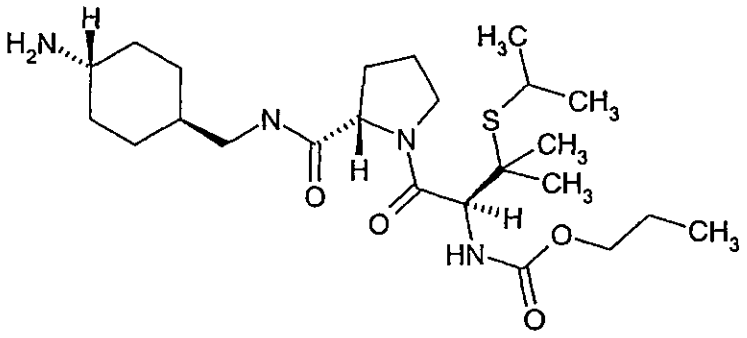


- **TGN-167** [S. Combe *et al. Blood* **2005**, *106*, abstract 1863 (ASH 2005)]

- ***N*-[(Benzyloxy)carbonyl]-D-phenylalanyl-*N*-[(1*R*)-1-(dihydroxyboranyl)-4-methoxybutyl]-*L*-prolinamide** [WO 2005/084685]



- **Sofigatran** [*WHO Drug Information* **2007**, *21*, 77]



- **MCC-977** [Mitsubishi Pharma website pipeline **2006**, July 25th, 2006]

- **MPC-0920** [Press Release: „Myriad Genetics Begins Phase 1 Trial of Anti-Thrombin Drug MPC-0920", Myriad Genetics Inc, May 2nd, 2006]

Plasminogen activators (thrombolytics/fibrinolytics) are for example tissue plasminogen activator (t-PA), streptokinase, reteplase and urokinase.

Antilipemics are in particular HMG-CoA-(3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors like for example lovastatin (Mevacor; US 4,231,938), simvastatin (Zocor; US 4,444,784), pravastatin (Pravachol; US 4,346,227), fluvastatin (Lescol; US 5,354,772) and atorvastatin (Lipitor; US 5,273,995).

Coronary therapeutics/vasodilative agents are in particular ACE (angiotensin converting enzyme) inhibitors like for example captopril, lisinopril, enalapril, ramipril, cilazapril, benazepril, fosinopril, quinapril and perindopril, or AII (angiotensin II) receptor antagonists like for example embusartan (US 5,863,930), losartan, valsartan, irbesartan, candesartan, eprosartan and temisartan, or ß adrenoceptor antagonists like for example carvedilol, alprenolol, bisoprolol, acebutolol, atenolol, betaxolol, carteolol, metoprolol, nadolol, penbutolol, pindolol, propanolol and timolol, or

alpha 1 adrenoceptor antagonists like for example prazosin, bunazosin, doxazosin and terazosin, or diuretics like for example hydrochlorothiazide, furosemide, bumetanide, piretanide, torasemide, amiloride and dihydralazine, or aldosterone antagonists like for example spironolactone and eplerenone, or positive inotropes like for example digoxin, or calcium channel blockers like for example verapamil and diltiazem, or dihydropyridine derivatives like for example nifedipine (Adalat) and Nitrendipine (Bayotensin), or donors of nitric oxide like for example isosorbid-5-mononitrate, isosorbid-dinitrate and glyceroltrinitrate, or compounds, which effect the increase in cyclic guanosine monophosphate (cGMP), like for example stimulators of the soluble guanylate cyclase (WO 98/16223, WO 98/16507, WO 98/23619, WO 00/06567, WO 00/06568, WO 00/06569, WO 00/21954, WO 00/66582, WO 01/17998, WO 01/19776, WO 01/19355, WO 01/19780, WO 01/19778, WO 07/045366, WO 07/045367, WO 07/045369, WO 07/045370, WO 07/045433).

Furthermore, the present invention relates to drugs which comprise at least one compound according to the invention, together with one or more inert, non-toxic and pharmaceutically appropriate adjuvants, as well as their use for the above-mentioned purposes.

Furthermore, the present invention relates to drugs which comprise at least one compound according to the invention, together with one or more of the above-mentioned combination drug, especially for the use for the prophylaxis and/or treatment of the above-mentioned diseases.

The compounds according to the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable manner, such as for example by the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, dermal, transdermal, conjunctival or aural routes or as an implant or stent.

For these administration routes, the compounds according to the invention can be administered in suitable administration forms.

For oral administration, administration forms which function according to the state of the art, releasing the compound according to the invention rapidly and/or in a modified manner, which contain the compounds according to the invention in crystalline and/or amorphized and/or dissolved form, such as for example tablets (uncoated or coated tablets, for example with gastric juice-resistant or delayed dissolution or insoluble coatings, which control the release of the compound according to the invention), tablets rapidly disintegrating in the oral cavity or films/wafers, films/lyophilisates, capsules (for example hard or soft gelatine capsules), dragees, granules, pellets, powders, emulsions, suspensions, aerosols or solutions are suitable.

Parenteral administration can be effected omitting an absorption step (e.g. intravenous, intra-arterial, intracardial, intraspinal or intralumbar administration) or involving absorption (e.g. intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal administration). Suitable administration forms for parenteral administration include injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilisates or sterile powders.

For the other administration routes, for example inhalation formulations (including powder inhalers and nebulisers), nasal drops, solutions or sprays, tablets for lingual, sublingual or buccal administration, tablets, films/wafers or capsules, suppositories, oral or ophthalmic preparations, vaginal capsules, aqueous suspensions (lotions, shakable mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (e.g. plasters), milk, pastes, foams, dusting powders, implants or stents are suitable.

Oral or parenteral administration, in particular oral and intravenous administration, are preferred.

The compounds according to the invention can be converted into the stated administration forms. This can be effected in a manner known per se by mixing with inert, non-toxic, pharmaceutically suitable additives. These additives include carriers (for example microcrystalline cellulose, lactose or mannitol), solvents (e.g. liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecylsulphate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (e.g. antioxidants such as for example ascorbic acid), colourants (e.g. inorganic pigments such as for example iron oxide) and flavour or odour correctors.

In general, to achieve effective results in parenteral administration it has been found advantageous to administer quantities of about 0.001 to 30 mg/kg, preferably about 0.01 to 1 mg/kg body weight. In oral administration, the dosage is about 0.01 bis 100 mg/kg, preferably about 0.01 to 30 mg/kg and quite especially preferably 1 to 30 mg/kg body weight.

Nonetheless it can sometimes be necessary to deviate from the said quantities, namely depending on body weight, administration route, individual response to the active substance, nature of the preparation and time or interval at which administration takes place. Thus in some cases it can be sufficient to manage with less than the aforesaid minimum quantity, while in other cases the stated upper limit must be exceeded. In the event of administration of larger quantities, it may be advisable to divide these into several individual administrations through the day.

The present invention is illustrated by the examples below; however, these examples are not meant to restrict the invention in any way.

The percentages in the tests and examples which follows are, unless otherwise stated, by weight; parts are by weight. Solvent ratios, dilution ratios and concentrations reported for liquid/liquid solutions are each based on the volume.

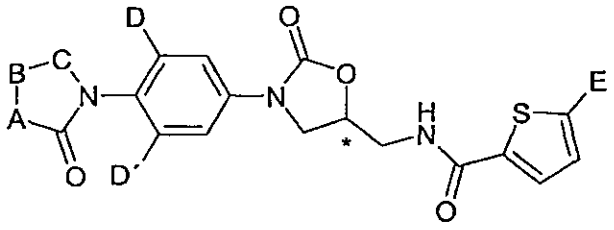
Examples

A Preparation examples

Starting materials

The syntheses of the starting materials are described in detail in WO-A-01/047919.

Synthesis examples



Example	A-B-C	D	D´	E
1	$CH_2OCH_2CH_2$	H	H	Cl
2	$CH_2CH_2CH_2$	H	H	Cl
3	$CH_2CH_2CH_2$	H	H	CH_3
4	$CH_2CH_2CH_2$	H	H	Br
5	$CH_2OCH_2CH_2$	H	H	CH_3
6	$CH_2OCH_2CH_2$	H	H	Br
7	OCH_2CH_2	H	H	Cl
8	$CH_2CH_2CH_2$	H	H	Br
9	$CH_2CH_2CH_2$	H	H	CH_3
10	$OCH_2CH_2CH_2$	H	H	Cl
11	$CH_2CH_2CH_2$	F	H	Cl
12	$CH_2OCH_2CH_2$	H	H	Cl
13	$CH_2CH_2CH_2$	CF_3	H	Cl

Example	A-B-C	D	D´	E
14	$CH_2OCH_2CH_2$	Cl	H	Cl
15	$CH_2OCH_2CH_2$	CF_3	H	Cl
16	$CH_2OCH_2CH_2$	CH_3	H	Cl
17	$CH_2OCH_2CH_2$	CN	H	Cl
18	$CH_2CH_2CH_2$	Cl	H	Cl
19	$CH_2OCH_2CH_2$	CH_3	CH_3	Cl
20	$CH_2OCH_2CH_2$	NH_2	H	Cl
21	$CH_2OCH_2CH_2$	F	H	Br
22	$CH_2CH_2CH_2$	F	H	Br
23	$CH_2CH_2CH_2CH_2$	H	H	Br
24	$CH_2CH_2CH_2$	F	H	Cl
25	$CH_2OCH_2CH_2$	F	H	Cl
26	$CH_2CH_2CH_2CH_2$	H	H	Cl

The syntheses of the synthesis examples are described in detail in WO-A-01/047919.

B Assessment of the physiological activity

1. Physiological activity of compounds of the formula (I)

The compounds of the formula (I) act in particular as selective inhibitors of coagulation factor Xa and do not inhibit, or also inhibit only at distinctly higher concentrations, other serine proteases such as plasmin or trypsin.

Inhibitors of coagulation factor Xa are referred to as "selective" when their IC_{50} values for factor Xa inhibition are 100-fold, preferably 500-fold, in particular 1000-fold, smaller than the IC_{50} values for the inhibition of other serine proteases, in particular plasmin and trypsin, reference being made concerning the test methods for the selectivity to the test methods of Examples A.a.1) and A.a.2) described below.

The particularly advantageous biological properties of the compounds of the formula (I) can be ascertained by the following methods.

a) Test description (in vitro)

a.1) Measurement of factor Xa inhibition

The enzymatic activity of human factor Xa (FXa) was measured via the conversion of an FXa-specific chromogenic substrate. In this case, factor Xa eliminates p-nitroaniline from the chromogenic substrate. The determinations were carried out in microtiter plates as follows.

The test substances were dissolved in various concentrations in DMSO and incubated with human FXa (0.5 nmol/l dissolved in 50 mmol/l tris buffer [C,C,C-tris(hydroxymethyl)-aminomethane], 150 mmol/l NaCl, 0.1% BSA (bovine serum albumine), pH = 8,3) at 25°C for 10 minutes. Pure DMSO serves as control. The chromogenic substrate (150 µmol/l Pefachrome® FXa from Pentapharm) was then added. After incubation at 25°C for 20 minutes, the extinction at 405 nm was determined. The extinctions of the test mixtures with test substance were compared with the control mixtures without test substance, and the IC_{50} values were calculated therefrom.

a.2) Selectivity determination

Selective FXa inhibition was demonstrated by investingating the inhibition by the test substances of other human serine proteases such as trypsin, plasmin. The enzymatic activity of trypsin (500 mU/ml) and plasmin (3.2 nmol/l) was determined by dissolving these enzymes in tris buffer (100 mmol/l, 20 mmol/l $CaCl_2$, pH = 8.0) and incubating with test substance or solvent for 10 minutes. The enzymatic reaction was then started by adding the appropriate specific chromogenic

substrates (Chromozym Trypsin® from Boehringer Mannheim, Chromozym Plasmin® from Boehringer Mannheim), and the extinction was determined at 405 nm after 20 minutes. All determinations were carried out at 37°C. The extinctions of the test mixtures with test substance were compared with the control samples without test substance, and the IC_{50} values were calculated therefrom.

a.3) Determination of the anticoagulant effect

The anticoagulant effect of the test substances was determined in vitro in human plasma. For this purpose, human blood was collected in a 0.11 molar sodium citrate solution in the sodium citrate/blood mixing ratio of 1/9. The blood was thoroughly mixed after collection and centrifuged at about 2000 g for 10 minutes. The supernatant was removed by pipette. The prothrombin time (PT, synonym: Quick's test) was determined in the presence of varying concentrations of test substance or the appropriate solvent using a commercially available test kit (Neoplastin® from Boehringer Mannheim). The test compounds were incubated with the plasma at 37°C for 10 minutes. Coagulation was then induced by adding thromboplastin, and the time of onset of coagulation was determined. The concentration of test substance which brings about a doubling of the prothrombin time was found.

b) Determination of the antithrombotic effect (in vivo)

b) Arteriovenous shunt model (rat)

Fasting male rats (strain: HSD CPB:WU) weighing 200-250 g were anesthetized with a Rompun/Ketavet solution (12 mg/kg/50 mg/kg). Thrombus formation was induced in an arteriovenous shunt by a method based on that described by Christopher N. Berry et al., Br. J. Pharmacol. (1994), 113, 1209-1214. For this purpose, the left jugular vein and the right carotid artery were exposed. An extracorporeal shunt was formed between the two vessels using a 10 cm-long polyethylene tube (PE 60). This polyethylene tube was secured in the middle by tying in a further 3 cm-long polyethylene tube (PE 160) which contained a roughened nylon thread forming a loop to produce a thrombogenic surface. The extracorporeal circulation was maintained for 15 minutes. The shunt was then removed and the nylon thread with the thrombus was immediately weighed. The blank weight of the nylon thread had been found before the start of the experiment. The test substances were administered either intravenously through the tail vein or orally by gavage to conscious animals before setting up the extracorporeal circulation.

C **Practical Examples of Pharmaceutical Compositions**

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound according to the invention, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (BASF Co., Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg, diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of compound according to the invention, lactose and starch is granulated with a 5% solution (w/w) of the PVP in water. After drying, the granulate is mixed with the magnesium stearate for 5 minutes. This mixture is compressed with a normal tablet press (tablet format: see above). As a guideline, a compression force of 15 kN is used for the compression.

Orally Dosable Suspension:

Composition:

1000 mg of the compound according to the invention, 1000 mg of ethanol (96%), 400 mg of Rhodigel® (xanthan gum from FMC Co., Pennsylvania, USA) and 99 g water.

10 ml of oral suspension correspond to a single dose of 100 mg of the compound according to the invention.

Production:

The Rhodigel is suspended in ethanol, and the compound according to the invention is added to the suspension. The water is added with stirring. The mixture is stirred for ca. 6 hrs until completion of the swelling of the Rhodigel.

Orally dosable solution:

Composition:

500 mg of the compound according to the invention, 2.5 g of polysorbate and 97 g of polyethylene glycol 400. 20 g of oral solution correspond to a single dose of 100 mg of the compound according to the invention.

Production:

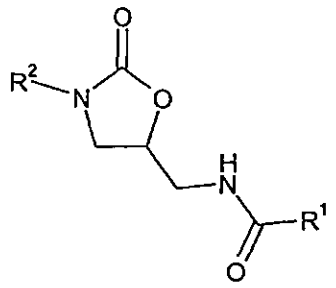
The compound according to the invention is suspended with stirring in the mixture of polyethylene glycol and polysorbate. The stirring process is continued until the complete dissolution of the compound according to the invention.

i.v. Solution:

The compound according to the invention is dissolved in a physiologically compatible solvent (e.g. isotonic sodium chloride solution, 5% glucose solution and/or 30% PEG 400 solution) at a concentration below the saturation solubility. The solution is sterile-filtered and filled into sterile and pyrogen-free injection containers.

Claims

1. Use of a compound of the formula (I)



(I),

in which

R^1 is 2-thiophene which is substituted in position 5 by a radical from the group of chlorine, bromine, methyl or trifluoromethyl,

R^2 is D-A-:

where:

the radical "A" is phenylene;

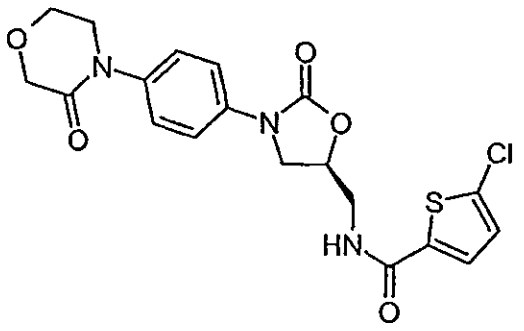
where:

the group "A" defined above may optionally be substituted once or twice in the meta position relative to the linkage to the oxazolidinone by a radical from the group of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl or cyano,

the radical "D" is a saturated 5- or 6-membered heterocycle which is linked via a nitrogen atom to "A", which has a carbonyl group in direct vicinity to the linking nitrogen atom, and in which a ring carbon member may be replaced by a heteroatom from the series S, N and O;

and their pharmaceutically acceptable salts, solvates and solvates of the salts for preparing medicaments or pharmaceutical compositions for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure.

2. Use according to claim 1, characterized in that the compound of the formula (I) is 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



or its pharmaceutically acceptable salts, solvates and solvates of the salts.

3. Use of a compound of the formula (I) according to claim 1 or 2, characterized in that heart failure is Cardiac Failure, Chronic Heart Failure, Congestive Heart Failure, Congestive Cardiac Failure, Acute Heart Failure, Acute Decompensated Heart Failure, Systolic Heart Failure, Diastolic Heart Failure, Right Heart Failure, Left Heart Failure, Heart Insufficiency, Cardiac Insufficiency, Chronic Cardiac Insufficiency, Cardiac Decompensation, High Output Heart Failure, Low Output Heart Failure, Cardiomyopathy, Dilated Cardiomyopathy and/or Hypertrophic Cardiomyopathy.

4. Use of a compound of the formula (I) according to claim 1 or 2, characterized in that disorders related to heart failure are progressive deterioration of cardiac function, decompensation of the heart and thereof damage of other organs and tissues, hypercoagulability, arterial and venous thromboembolic events, pulmonary embolism (PE), myocardial infarction and/or stroke.

5. Use of a compound of the formula (I) according to claim 1 or 2, characterized in that disorders related to heart failure are progressive deterioration of cardiac function, decompensation of the heart and thereof damage of other organs and tissues and/or hypercoagulability.

6. Method for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure of the human or animal body with the use of an effective quantity of at least one compound of the formula (I) according to claim 1 or 2, or of a medicament, comprising at least one compound of the formula (I) according to

claim 1 or 2, in combination with one or more pharmacologically acceptable auxiliaries or excipients

7. Method for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure according to claim 6, characterized in that heart failure is Cardiac Failure, Chronic Heart Failure, Congestive Heart Failure, Congestive Cardiac Failure, Acute Heart Failure, Acute Decompensated Heart Failure, Systolic Heart Failure, Diastolic Heart Failure, Right Heart Failure, Left Heart Failure, Heart Insufficiency, Cardiac Insufficiency, Chronic Cardiac Insufficiency, Cardiac Decompensation, High Output Heart Failure, Low Output Heart Failure, Cardiomyopathy, Dilated Cardiomyopathy and/or Hypertrophic Cardiomyopathy.

8. Method for the treatment and/or prophylaxis of heart failure and/or disorders related to heart failure according to claim 6, characterized in that disorders related to heart failure are progressive deterioration of cardiac function, decompensation of the heart and thereof damage of other organs and tissues, hypercoagulability, arterial and venous thromboembolic events, pulmonary embolism (PE), myocardial infarction and/or stroke.