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(54) **SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION**

(75) Inventors: **Alexander Straub**, Wuppertal (DE); **Thomas Lampe**, Wuppertal (DE); **Jens Pohlmann**, Wuppertal (DE); **Susanne Röhrig**, Essen (DE); **Elisabeth Perzborn**, Wuppertal (DE); **Karl-Heinz Schlemmer**, Wuppertal (DE); **Joseph Pernerstorfer**, Wuppertal (DE)

(73) Assignee: **Bayer HealthCare AG**, Leverkusen (DE)

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See application file for complete search history.

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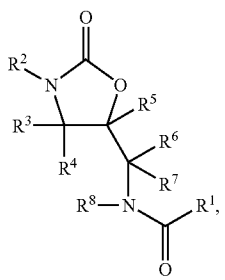
*Primary Examiner*—Kamal A. Saeed
*Assistant Examiner*—Rebecca Anderson
(74) *Attorney, Agent, or Firm*—Connolly Bove Lodge & Hutz LLP

(57) **ABSTRACT**

The invention relates to the field of blood coagulation. Novel oxazolidinone derivatives of the general formula (I)

(I)



processes for their preparation and their use as medicinally active compounds for the prophylaxis and/or treatment of disorders are described.

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# SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

This application is a 371 of PCT/EP00/12492 filed 11 Dec. 2000.

The present invention relates to the field of blood coagulation. In particular, the present invention relates to novel oxazolidinone derivatives, to processes for their preparation and to their use as active compounds in medicaments.

Blood coagulation is a protective mechanism of the organism which helps to "seal" defects in the wall of the blood vessels quickly and reliably. Thus, loss of blood can be avoided or kept to a minimum. Haemostasis after injury of the blood vessels is effected mainly by the coagulation system in which an enzymatic cascade of complex reactions of plasma proteins is triggered. Numerous blood coagulation factors are involved in this process, each of which factors converts, on activation, the respectively next inactive precursor into its active form. At the end of the cascade comes the conversion of soluble fibrinogen into insoluble fibrin, resulting in the formation of a blood clot. In blood coagulation, traditionally the intrinsic find the extrinsic system, which end in a joint reaction path, are distinguished. Here factor Xa, which is formed from the proenzyme factor X, plays a key role, since it connects the two coagulation paths. The activated serine protease Xa cleaves prothrombin to thrombin. The resulting thrombin, in turn, cleaves fibrinogen to fibrin, a fibrous/gelatinous coagulant. In addition, thrombin is a potent effector of platelet aggregation which likewise contributes significantly to haemostasis.

Maintenance of normal haemostasis—between bleeding and thrombosis—is subject to a complex regulatory mechanism. Uncontrolled activation of the coagulant system or defective inhibition of the activation processes may cause formation of local thrombi or embolisms in vessels (arteries, veins, lymph vessels) or in heart cavities. This may lead to serious disorders, such as myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses; hereinbelow, these disorders are collectively also referred to as thromboembolic disorders. In addition, in the case of consumption coagulopathy, hypercoagulability may—systemically—result in disseminated intravascular coagulation.

These thromboembolic disorders are the most frequent cause of morbidity and mortality in most industrialized countries (Pschyrembel, Klinisches Wörterbuch [clinical dictionary], 257$^{th}$ edition, 1994, Walter de Gruyter Verlag, page 199 ff., entry "Blutgerinnung" [blood coagulation]; Römpp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Blutgerinnung"; Lubert Stryer, Biochemie [biochemistry], Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, page 259 ff.).

The anticoagulants, i.e. substances for inhibiting or preventing blood coagulation, which are known from the prior art have various, often grave disadvantages. Accordingly, in practice, an efficient treatment method or prophylaxis of thromboembolic disorders is very difficult and unsatisfactory.

In the therapy and prophylaxis of thromboembolic disorders, use is firstly made of heparin, which is administered parenterally or subcutaneously. Owing to more favourable pharmacokinetic properties, preference is nowadays more



avoid the known disadvantages described below, which are involved in heparin therapy. Thus, heparin is ineffective when administered orally and has a relatively short half-life. Since heparin inhibits a plurality of factors of the blood coagulation cascade at the same time, the action is nonselective. Moreover, there is a high risk of bleeding; in particular, brain haemorrhages and gastrointestinal bleeding may occur, which may result in thrombopenia, drug-induced alopecia or osteoporosis (Pschyrembel, Klinisches Wörterbuch, 257$^{th}$ edition, 1994, Walter de Gruyter Verlag, page 610, entry "Heparin"; Römpp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Heparin").

A second class of anticoagulants are the vitamin K antagonists. These include, for example, 1,3-indanediones, and especially compounds such as warfarin, phenprocoumon, dicumarol and other coumarin derivatives which inhibit the synthesis of various products of certain vitamin K-dependent coagulation factors in the liver in a nonselective manner. Owing to the mechanism of action, however, the onset of the action is very slow (latency to the onset of action 36 to 48 hours). It is possible to administer the compounds orally; however, owing to the high risk of bleeding and the narrow therapeutic index, a time-consuming individual adjustment and monitoring of the patient are required. Moreover, other adverse effects, such as gastrointestinal disturbances, hair loss and skin necroses, have been described (Pschyrembel, Klinisches Wörterbuch, 257$^{th}$ edition, 1994, Walter de Gruyter Verlag, page 292 ff., entry "coumarin derivatives"; Ullmann's Encyclopedia of Industrial Chemistry, 5$^{th}$ edition, VCH Verlagsgesellschaft, Weinheim, 1985–1996, entry "vitamin K").

Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa (cf. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research 1999, 93, 203; F. Al-Obeidi, J. A. Ostrem, Factor Xa inhibitors by classical and combinatorial chemistry, DDT 1998, 3, 223; F. Al-Obeidi, J. A. Ostrem, Factor Xa inhibitors, Exp. Opin. Ther. Patents 1999, 9, 931; B. Kaiser, Thrombin and factor Xa inhibitors, Drugs of the Future 1998, 23, 423; A. Uzan, Antithrombotic agents, Emerging Drugs 1998, 3, 189; B.-Y. Zhu, R. M. Scarborough, Curr. Opin. Card. Pulm. Ren. Inv. Drugs 1999, 1 (1), 63). It has been shown that, in animal models, various both peptidic and nonpeptidic compounds are effective as factor Xa inhibitors.

Accordingly, it is an object of the present invention to provide novel substances for controlling disorders, which substances have a wide therapeutic spectrum.

In particular, they should be suitable for a more efficient prophylaxis and/or treatment of thromboembolic disorders, avoiding—at least to some extent—the disadvantages of the prior art described above, where the term "thromboembolic disorders" in the context of the present invention is to be understood as meaning, in particular, serious disorders, such as myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses.

It is another object of the present invention to provide novel anticoagulants which inhibit the blood coagulation factor Xa with increased selectivity, avoiding—at least to

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