US 20030153610A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0153610 A1**

Straub et al. (43) **Pub. Date: Aug. 14, 2003**

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

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

Correspondence Address:
JEFFREY M. GREENMAN
VICE PRESIDENT, PATENTS AND LICENSING
BAYER CORPORATION
400 MORGAN LANE
WEST HAVEN, CT 06516 (US)

(21) Appl. No.: **10/181,051**

(22) PCT Filed: **Dec. 11, 2000**

(86) PCT No.: **PCT/EP00/12492**

(30) **Foreign Application Priority Data**

Dec. 24, 1999 (DE)..... 199 62 924.2

Publication Classification

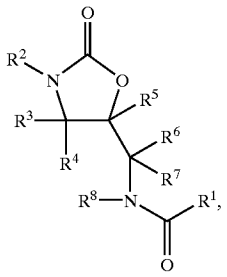
(51) **Int. Cl.**[7] **C07D 413/02**; A61K 31/421

(52) **U.S. Cl.** **514/376**; 548/229

(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.

SUBSTITUTED OXAZOLIDINONES AND THEIR IN THE FIELD OF BLOOD COAGULATION

[0001] 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.

[0002] 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.

[0003] 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.

[0004] These thromboembolic disorders are the most frequent cause of morbidity and mortality in most industrialized countries (Pschyrembel, Klinisches Wörterbuch [clinical dictionary], 257th 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.).

[0005] 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.

[0006] 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 and more given to low-molecular-weight heparin; however, even with low-molecular-weight heparin, it is not possible to 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, 257th edition, 1994, Walter de Gruyter Verlag, page 610, entry "Heparin"; Römpp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Heparin").

[0007] 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, 257th edition, 1994, Walter de Gruyter Verlag, page 292 ff., entry "coumarin derivatives"; Ullmann's Encyclopedia of Industrial Chemistry, 5th edition, VCH Verlagsgesellschaft, Weinheim, 1985-1996, entry "vitamin K").

[0008] 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.

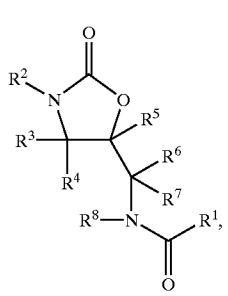
[0009] Accordingly, it is an object of the present invention to provide novel substances for controlling disorders, which substances have a wide therapeutic spectrum.

[0010] 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.

[0011] 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 some extent—the problems of the therapeutic methods for thromboembolic disorders known from the prior art.

[0012] Accordingly, the present invention provides substituted oxazolidinones of the general formula (I)


(I)

[0013] in which:

[0014] R^1 represents optionally benzo-fused thiophene (thienyl) which may optionally be mono- or polysubstituted;

[0015] R^2 represents any organic radical;

[0016] R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents $(C_1$-$C_6)$-alkyl

[0017] and their pharmaceutically acceptable salts, hydrates and prodrugs,

[0018] except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

[0019] Preference is given here to compounds of the general formula (I),

[0020] in which

[0021] R^1 represents optionally benzo-fused thiophene (thienyl) which may optionally be mono- or polysubstituted by a radical from the group consisting of halogen; cyano; nitro; amino; aminomethyl; $(C_1$-$C_8)$-alkyl which for its part may optionally be mono- or polysubstituted by halogen; $(C_3$-$C_7)$-cycloalkyl; $(C_1$-$C_8)$-alkoxy; imidazolinyl; —C(=NH)NH_2; carbamoyl; and mono- and di-$(C_1$-$C_4)$-alkyl-aminocarbonyl,

[0022] R^2 represents one of the groups below:

[0023] A-,

[0024] A-M-,

[0025] D-M-A-,

[0026] B-M-A-,

[0027] B-,

[0028] B-M-,

[0029] B-M-B-,

[0030] D-M-B-,

[0031] where:

[0032] the radical "A" represents $(C_6$-$C_{14})$-aryl, preferably $(C_6$-$C_{10})$-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl;

[0033] the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the group consisting of S, N, NO (N-oxide) and O;

[0034] the radical "D" represents a saturated or partially unsaturated, mono- or bicyclic, optionally benzo-fused 4- to 9-membered heterocycle which contains up to three heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

[0035] the radical "M" represents —NH—, —CH_2—, —CH_2CH_2—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO—, —COO—, —OOC—, —S—, —SO_2— or represents a covalent bond;

[0036] where

[0037] the groups "A", "B" and "D" defined above may each optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; nitro; carbamoyl; pyridyl; $(C_1$-$C_6)$-alkanoyl; $(C_3$-$C_7)$-cycloalkanoyl; $(C_6$-$C_{14})$-arylcarbonyl; $(C_5$-$C_{10})$-heteroarylcarbonyl; $(C_1$-$C_6)$-alkanoyloxymethyloxy; $(C_1$-$C_4)$-hydroxy-alkylcarbonyl; —$COOR^{27}$; —SO_2R^{27}; $C(NR^{27}R^{28})$=NR^{29}; —$CONR^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OR^{30}; —$NR^{30}OR^{31}$, $(C_1$-$C_6)$-alkyl and $(C_3$-$C_7)$-cycloalkyl, where $(C_1$-$C_6)$-alkyl and $(C_3$-$C_7)$-cycloalkyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OR^{27}; —$NR^{28}R^{29}$; —$CO(NH)_v(NR^{27}R^{28})$ and —$C(NR^{27}R^{28})$=NR^{29},

[0038] where:

[0039] v is either 0 or 1 and

[0040] R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, $(C_1$-$C_4)$-alkyl, $(C_3$-$C_7)$-cycloalkyl, $(C_1$-$C_4)$-alkanoyl, carbamoyl, trifluoromethyl, phenyl or pyridyl, and/or

[0041] R^{27} and R^{28} or R^{27} and R^{29} toether with the nitrogen atom to which they are

attached form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group consisting of N, O and S, and

[0042] R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, —CH²C($NR^{27}R^{28}$)═NR^{29} or —COR^{33},

[0043] where

[0044] R^{33} represents (C_1-C_6)-alkoxy, (C_1-C_4)-alkoxy-(C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl-(C_1-C_4)-alkyl, (C_1-C_4)-aminoalkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyl-(C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_6)-alkenyl, (C_1-C_8)-alkyl, which may optionally be substituted by phenyl or acetyl, (C_6-C_{14})-aryl, (C_5-C_{10})-heteroaryl, trifluoromethyl, tetrahydrofuranyl or butyrolactone,

[0045] R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

[0046] and their pharmaceutically acceptable salts, hydrates and prodrugs,

[0047] except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

[0048] Preference is also given here to compounds of the general formula (I),

[0049] in which

[0050] R^1 represents thiophene (thienyl), in particular 2-thiophene, which may optionally be mono- or polysubstituted by halogen, preferably chlorine or bromine, by amino, aminomethyl or (C_1-C_8)-alkyl, preferably methyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen, preferably fluorine,

[0051] R^2 represents one of the groups below:

[0052] A-,

[0053] A-M-,

[0054] D-M-A-,

[0055] B-M-A-,

[0056] B-,

[0057] B-M-,

[0058] B-M-B-,

[0059] D-M-B-,

[0060] where:

[0061] the radical "A" represents (C_6-C_{14})-aryl, preferably (C_6-C_{10})-aryl, in particular phenyl or naphthyl, very particularly preferably phenyl;

[0062] the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 3 heteroatoms and/or hetero chain members, in particular up to 2 heteroatoms and/or hetero chain members, from the group consisting of S, N, NO (N-oxide) and O;

[0063] the radical "D" represents a saturated or partially unsaturated 4 to 7-membered heterocycle which contains up to three heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

[0064] the radical "M" represents —NH—, —CH_2—, —CH_2CH_2—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO—, —COO—, —OOC—, —S— or represents a covalent bond;

[0065] where

[0066] the groups "A", "B" and "D" defined above may in each case optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; nitro; carbamoyl; pyridyl; (C_1-C_6)-alkanoyl; (C_3-C_7)-cycloalkanoyl; (C_6-C_{14})-arylcarbonyl; (C_5-C_{10})-heteroarylcarbonyl; (C_1-C_6)-alkanoyloxymethyloxy; —$COOR^{27}$; —SO_2R^{27}; —$C(NR^{27}R^{28})$═NR^{29}; —CONR $R^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OR^{30}; —$NR^{30}R^{31}$, (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl,

[0067] where (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OR^{27}; —$NR^{28}R^{29}$; —$CO(NH)_v(NR^{27}R^{28})$ and —$C(NR^{27}R^{28})$═NR^{29},

[0068] where:

[0069] v is either 0 or 1 and

[0070] R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or (C_3-C_7)-cycloalkyl, and/or

[0071] R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to three, preferably up to two, identical or different heteroatoms from the group consisting of N, O and S, and

[0072] R^{30} and R^{31} are identical or different and independently of one another each rep-

resents hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_4)-alkanoyl, (C_6-C_{14})-arylcarbonyl, (C_5-C_{10})-heteroarylcarbonyl, (C_1-C_4)-alkylaminocarbonyl or —$CH_2C(NR^{27}R^{28})$=NR^{29},

[0073] R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

[0074] and their pharmaceutically acceptable salts, hydrates and prodrugs,

[0075] except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

[0076] Particular preference is given here to compounds of the general formula (I),

[0077] in which

[0078] R^1 represents thiophene (thienyl), in particular 2-thiophene, which may optionally be mono- or polysubstituted by halogen, preferably chlorine or bromine, or by (C_1-C_8)-alkyl, preferably methyl, where the (C_1-C_8)-alkyl radical for its part may optionally be mono- or polysubstituted by halogen, preferably fluorine,

[0079] R^2 represents one of the groups below:

[0080] A-,

[0081] A-M-,

[0082] D-M-A-,

[0083] B-M-A-,

[0084] B-,

[0085] B-M-,

[0086] B-M-B-,

[0087] D-M-B-,

[0088] where:

[0089] the radical "A" represents phenyl or naphthyl, in particular phenyl;

[0090] the radical "B" represents a 5- or 6-membered aromatic heterocycle which contains up to 2 heteroatoms from the group consisting of S, N, NO (N-oxide) and O;

[0091] the radical "D" represents a saturated or partially unsaturated 5- or 6-membered heterocycle which contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O;

[0092] the radical "M" represents —NH—, —O—, —NH—CH_2—, —CH_2—NH—, —OCH_2—, —CH_2O—, —CONH—, —NHCO— or represents a covalent bond;

[0093] where

[0094] the groups "A", "B" and "D" defined above may in each case optionally be mono- or polysubstituted by a radical from the group consisting of halogen; trifluoromethyl; oxo; cyano; pyridyl; (C_1-C_3)-alkanoyl; (C_6-C_{10})-arylcarbonyl; (C_5-C_6)-heteroarylcarbonyl; (C_1-C_3)-alkanoyloxymethyloxy; —$C(NR^{27}R^{28})$=NR^{29}; —$CONR^{28}R^{29}$; —$SO_2NR^{28}R^{29}$; —OH; —$NR^{30}R^{31}$; (C_1-C_4)-alkyl; and cyclopropyl, cyclopentyl or cyclohexyl,

[0095] where (C_1-C_4)-alkyl and cyclopropyl, cyclopentyl or cyclohexyl for their part may optionally be substituted by a radical from the group consisting of cyano; —OH; —OCH_3; —$NR^{28}R^{29}$; —$CO(NH)_v(NR^{27}R^{28})$ and —$C(NR^{27}R^{28})$=NR^{29},

[0096] where:

[0097] v is either 0 or 1, preferably 0, and

[0098] R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl

[0099] and/or

[0100] R^{27} and R^{28} or R^{27} and R^{29} together with the nitrogen atom to which they are attached may form a saturated or partially unsaturated 5- to 7-membered heterocycle having up to two identical or different heteroatoms from the group consisting of N, O and S, and

[0101] R^{30} and R^{31} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, cyclopropyl, cyclopentyl, cyclohexyl, (C_1-C_4)-alkylsulphonyl, (C_1-C_4)-hydroxyalkyl, (C_1-C_4)-aminoalkyl, di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-alkanoyl or phenylcarbonyl,

[0102] R^3, R^4, R^5, R^6, R^7 and R^8 are identical or different and each represents hydrogen or represents (C_1-C_6)-alkyl

[0103] and their pharmaceutically acceptable salts, hydrates and prodrugs,

[0104] except for compounds of the general formula (I) in which the radical R^1 is an unsubstituted 2-thiophene radical and the radical R^2 is simultaneously a mono- or polysubstituted phenyl radical and the radicals R^3, R^4, R^5, R^6, R^7 and R^8 are each simultaneously hydrogen.

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