SUBSTITUTED OXAZOLIDINES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

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 and 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], 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.).

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 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").

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 non-selective 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").

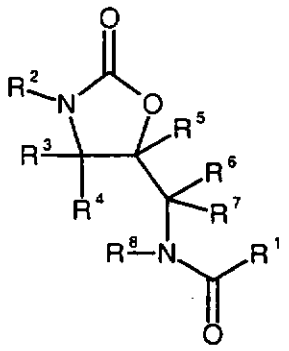
Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa (cf. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research **1999**, *93*, 203; F. Al-Obeidi, J. 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 some extent - the problems of the therapeutic methods for thromboembolic disorders known from the prior art.

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



(I),

in which:

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

R^2 represents any organic radical;

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

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

in which

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,

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

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

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;

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;

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;

where

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}; -$NR^{30}R^{31}$, (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 $-C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1 and

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

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

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, $-CH_2C(NR^{27}R^{28})=NR^{29}$ or $-COR^{33}$,

where

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,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

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

in which

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,

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

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

where
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}; -$C(NR^{27}R^{28})=NR^{29}$; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OR^{30}; -$NR^{30}R^{31}$, (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl,

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 -$C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1 and

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

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

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, (C_1-C_4)-alkanoyl, (C_6-C_{14})-arylcarbonyl, (C_5-C_{10})-heteroarylcarbonyl, (C_1-C_4)-alkylaminocarbonyl or $-CH_2C(NR^{27}R^{28})=NR^{29}$,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

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

in which

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,

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:
the radical "A" represents phenyl or naphthyl, in particular phenyl;
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;
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;
the radical "M" represents –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or represents a covalent bond;

where
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,

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},

where:

v is either 0 or 1, preferably 0, and

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

and/or

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

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,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

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

in which

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

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

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

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;

the radical "D" represents a saturated or partially unsaturated 5- or 6-membered heterocycle which contains a nitrogen atom and optionally a further heteroatom and/or hetero chain member from the group consisting of S, SO, SO_2 and O; or contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2 and O;

the radical "M" represents –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or represents a covalent bond;

where

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; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-alkyl; and cyclopropyl, cyclopentyl or cyclohexyl,

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 $-C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1, preferably 0, and

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

and/or

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

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,

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_4)-alkyl

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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.

Very particular preference is given here to compounds of the general formula (I),

in which

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

R^2 represents D-A-:

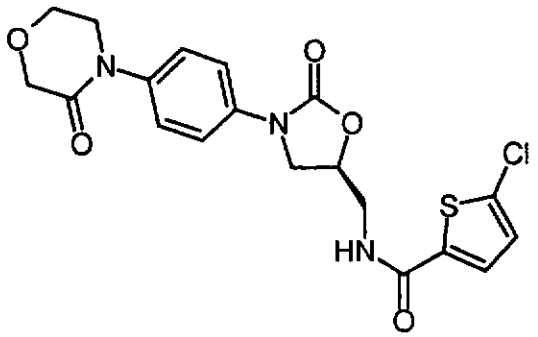
where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle, which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;

where
the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen

and their pharmaceutically acceptable salts, hydrates and prodrugs.

Very particular preference is also given here to the compound having the following formula



and to its pharmaceutically acceptable salts, hydrates and prodrugs.

In the compounds of the general formula (I) above, the radical

R^1 may in particular represent optionally benzo-fused thiophene (thienyl) which may optionally be mono- or polysubstituted by a radical from the group consisting of halogen; cyano; nitro; (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)-alkylaminocarbonyl.

In the compounds of the general formula (I), the radical

R^1 may preferably represent 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, preferably the methyl radical, may for its part optionally be mono- or polysubstituted by halogen, preferably fluorine.

In the compounds of the general formula (I), the radicals

R^3, R^4, R^5, R^6, R^7 and R^8 may be identical or different and may represent, in particualr, hydrogen or (C_1-C_6)-alkyl, preferably hydrogen or (C_1-C_4)-alkyl, very particularly preferably hydrogen.

The radical R^2, i.e. the organic radical, can in particular be selected from the substituent groups listed below:

In the compounds of the general formula (I), the radical

R^2 may, in particular, represent a group of the following formula:

$$Y\text{-}X'\text{-}(CH_2)_p\text{-}X\text{-}(CO)_n\text{-}(CH_2)_{o_1}\text{-}(CR^9R^{10})_m\text{-}(CH_2)_{o_2}\text{-}$$

where:

m is an integer from 0 to 6, preferably from 1 to 3,

n is either 0 or 1,

p is an integer from 0 to 3, preferably either 0 or 1,

o_1 is an integer 0 or 1,

o_2 is an integer 0 or 1,

R^9 and R^{10} are identical or different and each represents hydrogen; $(C_1\text{-}C_4)$-alkyl, preferably methyl; $(C_1\text{-}C_4)$-alkoxy, preferably methoxy; $(C_3\text{-}C_7)$-cycloalkyl; hydroxyl or fluorine,

X and X' are identical or different and each represents O; N-R^{11} or a covalent bond,

where R^{11} represents H; $(C_1\text{-}C_4)$-alkyl, preferably methyl, or $(C_3\text{-}C_7)$-cycloalkyl,

Y represents a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical which optionally contains 1 to 3 identical or different heteroatoms and/or hetero chain members from the group consisting of N, O, S, SO and SO_2,

where:
this radical Y may optionally be substituted by a 5- or 6-membered aromatic or a 3- to 7-membered saturated or partially unsaturated

cyclic hydrocarbon radical which optionally contains up to 3 identical or different heteroatoms from the group consisting of N, O and S and

where this radical may for its part optionally be substituted by a radical from the group consisting of cyano; hydroxyl; halogen; (C_1-C_4)-alkyl; $-C(=NR^{12})NR^{13}R^{13'}$; and $-NR^{14}R^{15}$,

where:

R^{12} represents hydrogen, (C_1-C_4)-alkyl or (C_3-C_7)-cycloalkyl;

R^{13} and $R^{13'}$ 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

R^{13} and $R^{13'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S;

R^{14} and R^{15} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl or (C_1-C_5)-alkanoyl;

and/or

this radical Y may furthermore optionally be substituted by a radical from the group consisting of oxo; cyano; thiono; halogen; $-OR^{16}$; $=NR^{16}$; $-NR^{16}R^{17}$; $-C(=NR^{18})NR^{19}R^{19'}$ and (C_1-C_4)-alkyl,

in which (C_1-C_4)-alkyl for its part may optionally be substituted by a radical from the group consisting of hydroxyl; cyano; $-NR^{16}R^{17}$ and $-C(=NR^{18})NR^{19}R^{19'}$,

where:

R^{16} and R^{17} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl, (C_3-C_7)-cycloalkyl or (C_1-C_3)-alkanoyl;

R^{18} represents hydrogen, (C_1-C_4)-alkyl or (C_3-C_7)-cycloalkyl;

R^{19} and $R^{19'}$ 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

R^{19} and $R^{19'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S.

Particular preference is given to compounds of the general formula (I) in which the radical

R^2 represents a group of the following formula:

$$Y\text{-}X'\text{-}(CH_2)_p\text{-}X\text{-}(CO)_n\text{-}(CH_2)_{o_1}\text{-}(CR^9R^{10})_m\text{-}(CH_2)_{o_2}\text{-}$$

where

m is an integer from 0 to 3,

n is an integer 0 or 1,

p is an integer 0 or 1,

o_1 is an integer 0 or 1,

o_2 is an integer 0 or 1,

R^9 and R^{10} are identical or different and each represents hydrogen; methyl; methoxy; hydroxyl or fluorine,

X and X' are identical or different and each represents O; N-R^{11} or a covalent bond,

where R^{11} represents H or methyl,

Y represents a 5- to 7-membered saturated cyclic hydrocarbon radical which optionally contains 1 or 2 identical or different heteroatoms and/or hetero chain members from the group consisting of N, O, S, SO and SO_2, in particular cyclohexyl, piperazinyl, morpholinyl, thiomorpholinyl, diazepinyl, pyrrolidinyl and piperidinyl,

where:

this radical Y may optionally be substituted by a 5- or 6-membered aromatic or a 5- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical which optionally contains up to 2 identical or different heteroatoms from the group consisting of N, O and S and

where this radical for its part may be substituted by a radical from the group consisting of cyano; hydroxyl; fluorine; chlorine; (C_1-C_4)-alkyl; -C(=NR^{12})$NR^{13}R^{13'}$; and -$NR^{14}R^{15}$,

where:

R^{12} represents hydrogen, methyl, ethyl, cyclopropyl, cyclopentyl or cyclohexyl;

R^{13} and $R^{13'}$ are identical or different and independently of one another each represents hydrogen, methyl, ethyl, cyclopropyl, cyclopentyl or cyclohexyl
and/or

R^{13} and $R^{13'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S, in particular piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl;

R^{14} and R^{15} are identical or different and independently of one another each represents hydrogen, methyl, ethyl, cyclopropyl, cyclopentyl or cyclohexyl or else acetyl;

and/or

this radical Y may furthermore optionally be substituted by a radical from the group consisting of oxo; cyano; thiono; fluorine; chlorine; -OH; $-OCH_3$; $=NR^{16}$; $-NH_2$; $-N(CH_3)_2$; $-C(=NR^{18})NR^{19}R^{19'}$ and methyl,

in which methyl for its part may optionally be substituted by a radical from the group consisting of hydroxyl; cyano; $-NR^{16}R^{17}$ and $-C(=NR^{18})NR^{19}R^{19'}$,

where:

R^{16} and R^{17} are identical or different and independently of one another each represents hydrogen, methyl, (C_3-C_7)-cycloalkyl or acetyl;

R^{18} reprsents hydrogen, methyl or (C_3-C_7)-cycloalkyl;

R^{19} and $R^{19'}$ are identical or different and independently of one another each represents hydrogen, methyl or (C_3-C_7)-cycloalkyl

and/or

R^{19} and $R^{19'}$ together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain up to 2 further heteroatoms from the group consisting of N, O and S, in particular piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl.

Likewise, in the compounds of the general formula (I), the radical

R^2 may represent a group of the formula below:

$$Z\text{-}(CO)_t\text{-}(CR^{20}R^{21})_s\text{-}$$

where:

s is an integer from 1 to 6,

t is either 0 or 1,

R^{20} and R^{21} are identical or different and each represents hydrogen, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkoxy, $(C_3\text{-}C_7)$-cycloalkyl, hydroxyl or fluorine,

Z represents a radical which is selected from the group consisting of cyano; $-C(NR^{22}R^{23})=NR^{24}$; $-CO(NH)_uNR^{22}R^{23}$; and $-NR^{25}R^{26}$,

where:

u is either 0 or 1, preferably 0, and

R^{22}, R^{23} and R^{24} are identical or different and independently of one another each represents hydrogen, $(C_1\text{-}C_4)$-alkyl or $(C_3\text{-}C_7)$-cycloalkyl, preferably hydrogen or methyl,
and/or

R^{22} and R^{23} together with the N atom to which they are attached form a 5- to 7-membered heterocycle which may optionally contain

up to 2 further heteroatoms and/or hetero chain members from the group consisting of N, O, S, SO and SO_2;

R^{25} and R^{26} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or (C_3-C_7)-cycloalkyl, preferably hydrogen, methyl or ethyl, where (C_1-C_4)-alkyl and (C_3-C_7)-cycloalkyl for their part may optionally be substituted by hydroxyl or (C_1-C_6)-alkoxy.

Furthermore, in the compounds of the general formula (I), the radical

R^2 may represent one of the following groups:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:

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

where

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; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (C_1-C_6)-alkyl and (C_3-C_7)-cycloalkyl,

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 $-C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1 and

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

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

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, (C_1-C_4)-alkanoyl, (C_6-C_{14})-arylcarbonyl, (C_5-C_{10})-heteroarylcarbonyl, (C_1-C_4)-alkylaminocarbonyl or $-CH_2C(NR^{27}R^{28})=NR^{29}$.

Preference is also given to compounds of the general formula (I) in which the radical

R^2 represents one of the groups below:

A-,

A-M-,

D-M-A-,

B-M-A-,

B-,

B-M-,

B-M-B-,

D-M-B-,

where:

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

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;

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;

the radical "M" represents –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or represents a covalent bond;

where

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,

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},

where:

v is either 0 or 1, preferably 0, and

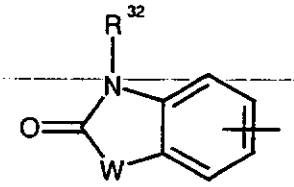
R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl
and/or

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

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.

Likewise, in the compounds of the general formula (I), the radical

R^2 may represent a group of the following formula:



,

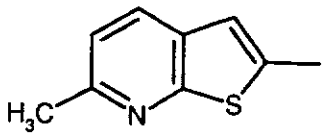
where

R^{32} represents hydrogen or (C_1-C_4)-alkyl, preferably hydrogen or methyl, and

W represents S, NH or O, preferably S.

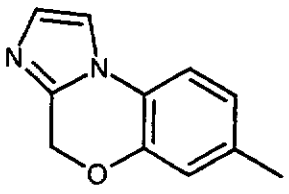
Moreover, in the compounds of the general formula (I), the radical

R^2 may be a group of the formula below



Finally, in the compounds of the general formula (I), the radical

R^2 may be a group of the formula below



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

Substituted aryl- and heteroarylphenyloxazolidinones in which a mono- or polysubstituted phenyl radical may be attached to the N atom of the oxazolidinone ring and which may have an unsubstituted N-methyl-2-thiophenecarboxamide radical in the 5-position of the oxazolidinone ring, and their use as antibacterial substances, are known from 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 and/or fibrinogen antagonists (WO-A-99/31092, EP-A-623615).

Depending on the substitution pattern, the compounds of the general formula (I) according to the invention may exist in stereoisomeric forms which are either like image and mirror image (enantiomers) or not like image and mirror image

(diastereomers). The invention relates both to the enantiomers or diastereomers and to their respective mixtures. The racemic forms, like the diastereomers, can be separated in a known manner into the stereoisomerically uniform components.

Furthermore, certain compounds of the general formula (I) can be present in tautomeric forms. This is known to the person skilled in the art, and such compounds are likewise within the scope of the invention.

Physiologically acceptable, i.e. pharmaceutically compatible, salts can be salts of the compounds according to the invention with inorganic or organic acids. Preference is given to salts with inorganic acids, such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or to salts with organic carboxylic or sulphonic acids, such as, for example, acetic acid, trifluoroacetic acid, propionic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid, or methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

Other pharmaceutically compatible salts which may be mentioned are salts with customary bases, such as, for example, alkali metal salts (for example sodium or potassium salts), alkaline earth metal salts (for example calcium or magnesium salts) or ammonium salts, derived from ammonia or organic amines, such as, for example, diethylamine, triethylamine, ethyldiisopropylamine, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine or methylpiperidine.

According to the invention, "hydrates" are forms of the compounds of the general formula (I) above which form a molecule compound (solvate) in the solid or liquid state by hydration with water. In the hydrates, the water molecules are attached through secondary valencies by intermolecular forces, in particular hydrogen bridges. Solid hydrates contain water as so-called crystal water in stoichiometric ratios, where the water molecules do not have to be equivalent with respect to their binding state. Examples of hydrates are sesquihydrates, monohydrates, dihydrates or trihydrates. Equally suitable are the hydrates of salts of the compounds according to the invention.

According to the invention, "prodrugs" are forms of the compounds of the general formula (I) above which for their part can be biologically active or inactive, but which

can be converted into the corresponding biologically active form (for example metabolically, solvolytically or in another way).

Halogen represents fluorine, chlorine, bromine and iodine. Preference is given to chlorine or fluorine.

(C_1-C_8)-Alkyl represents a straight-chain or branched alkyl radical having 1 to 8 carbon atoms. Examples which may be mentioned are: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl and n-hexyl. The corresponding alkyl groups with fewer carbon atoms, such as, for example, (C_1-C_6)-alkyl and (C_1-C_4)-alkyl, are derived analogously from this definition. In general, preference is given to (C_1-C_4)-alkyl.

The meaning of the corresponding component of other more complex substituents, such as, for example, alkylsulphonyl, hydroxyalkyl, hydroxyalkylcarbonyl, alkoxyalkyl, alkoxycarbonyl-alkyl, alkanoylalkyl, aminoalkyl or alkylaminoalkyl is likewise derived from this definition.

(C_3-C_7)-Cycloalkyl represents a cyclic alkyl radical having 3 to 7 carbon atoms. Examples which may be mentioned are: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. The corresponding cycloalkyl groups having fewer carbon atoms, such as, for example, (C_3-C_5)-cycloalkyl, are derived analogously from this definition. Preference is given to cyclopropyl, cyclopentyl and cyclohexyl.

The meaning of the corresponding component of other more complex substituents, such as, for example, cycloalkanoyl, is likewise derived from this definition.

In the context of the invention, (C_2-C_6)-alkenyl represents a straight-chain or branched alkenyl radical having 2 to 6 carbon atoms. Preference is given to a straight-chain or branched alkenyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are: vinyl, allyl, isopropenyl and n-but-2-en-1-yl.

(C_1-C_8)-Alkoxy represents a straight-chain or branched alkoxy radical having 1 to 8 carbon atoms. Examples which may be mentioned are: methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentoxy, n-hexoxy, n-heptoxy and n-octoxy. The corresponding alkoxy groups having fewer carbon atoms, such as, for

example, (C_1-C_6)-alkoxy and (C_1-C_4)-Alkoxy, are derived analogously from this definition. In general, preference is given to (C_1-C_4)-alkoxy.

The meaning of the corresponding component of other more complex substituents, such as, for example alkoxy-alkyl, alkoxycarbonyl-alkyl and alkoxycarbonyl, is likewise derived from this definition.

Mono- or di-(C_1-C_4)-alkylaminocarbonyl represents an amino group which is attached via a carbonyl group and which has a straight-chain or branched or two identical or different straight-chain or branched alkyl substitutents having in each case 1 to 4 carbon atoms. Examples which may be mentioned are: methylamino, ethylamino, n-propylamino, isopropylamino, t-butylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino and *N*-t-butyl-*N*-methylamino.

(C_1-C_6)-Alkanoyl represents a straight-chain or branched alkyl radical having 1 to 6 carbon atoms which carries a doubly attached oxygen atom in the 1-position and is attached via the 1-position. Examples which may be mentioned are: formyl, acetyl, propionyl, n-butyryl, i-butyryl, pivaloyl, n-hexanoyl. The corresponding alkanoyl groups with fewer carbon atoms, such as, for example, (C_1-C_5)-alkanoyl, (C_1-C_4)-alkanoyl and (C_1-C_3)-alkanoyl, are derived analogously from this definition. In general, preference is given to (C_1-C_3)-alkanoyl.

The meaning of the corresponding component of other more complex substituents, such as, for example, cycloalkanoyl and alkanoylalkyl, is likewise derived from this definition.

(C_3-C_7)-Cycloalkanoyl represents a cycloalkyl radical having 3 to 7 carbon atoms as defined above which is attached via a carbonyl group.

(C_1-C_6)-Alkanoyloxymethyloxy represents a straight-chain or branched alkanoyloxymethyloxy radical having 1 to 6 carbon atoms. Examples which may be mentioned are: acetoxymethyloxy, propionoxymethyloxy, n-butyroxymethyloxy, i-butyroxymethyloxy, pivaloyloxymethyloxy, n-hexanoyloxymethyloxy. The corresponding alkanoyloxymethyloxy groups having fewer carbon atoms, such as, for

example, (C_1-C_3)-alkanoyloxymethyloxy, are derived analogously from this definition. In general, preference is given to (C_1-C_3)-alkanoyloxymethyloxy.

(C_6-C_{14})-Aryl represents an aromatic radical having 6 to 14 carbon atoms. Examples which may be mentioned are: phenyl, naphthyl, phenanthrenyl and anthracenyl. The corresponding aryl groups with fewer carbon atoms, such as, for example, (C_6-C_{10})-aryl are derived analogously from this definition. In general, preference is given to (C_6-C_{10})-aryl.

The meaning of the corresponding component of other more complex substituents, such as, for example, arylcarbonyl, is likewise derived from this definition.

(C_5-C_{10})-Heteroaryl or a 5- to 10-membered aromatic heterocycle having up to 3 heteroatoms and/or hetero chain members from the group consisting of S, O, N and NO (N-oxide) represents a mono- or bicyclic heteroaromatic which is attached via a carbon ring atom of the heteroaromatic or, if appropriate, via a nitrogen ring atom of the heteroaromatic. Examples which may be mentioned are: pyridyl, pyridyl N-oxide, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl or isoxazolyl, indolinyl, indolyl, benzo[b]thienyl, benzo[b]furyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl, quinazolinyl. The corresponding heterocycles having a smaller ring size, such as, for example, 5- or 6-membered aromatic heterocycles, are derived analogously from this definition. In general, preference is given to 5- or 6-membered aromatic heterocycles, such as, for example, pyridyl, pyridyl N-oxide, pyrimidyl, pyridazinyl, furyl and thienyl.

The meaning of the corresponding component of other more complex substituents, such as, for example, (C_5-C_{10})-heteroarylcarbonyl, is likewise derived from this definition.

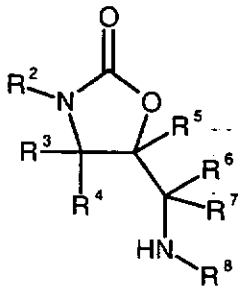
A 3- to 9-membered saturated or partially unsaturated, mono- or bicyclic, optionally benzo-fused heterocycle having up to 3 heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O represents a heterocycle which may contain one or more double bonds, which may be mono- or bicyclic, to which a benzene ring may be fused to two adjacent carbon ring atoms and which is attached via a carbon ring atom or a nitrogen ring atom. Examples which may be mentioned are: tetrahydrofuryl, pyrrolidinyl, pyrrolinyl, piperidinyl, 1,2-

dihydropyridinyl, 1,4-dihydropyridinyl, piperazinyl, morpholinyl, morpholinyl N-oxide, thiomorpholinyl, azepinyl, 1,4-diazepinyl and cyclohexyl. Preference is given to piperidinyl, morpholinyl and pyrrolidinyl.

The corresponding cycles having a smaller ring size, such as, for example, 5- to 7-membered cycles, are derived analogously from this definition.

The present invention also provides a process for preparing the compounds of the general formula (I) according to the invention where either, according to one process alternative

[A] compounds of the general formula (II)

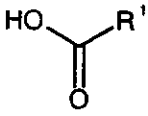


(II),

in which

the radicals R^2, R^3, R^4, R^5, R^6 and R^7 are each as defined above,

are reacted with carboxylic acids of the general formula (III)



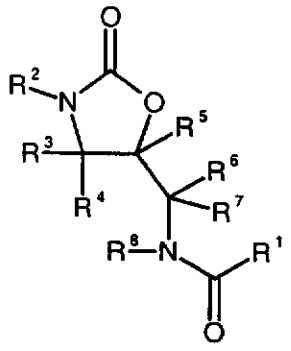
(III),

in which

the radical R^1 is as defined above,

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

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



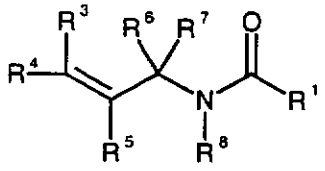
(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined above,

or else according to a process alternative

[B] compounds of the general formula (IV)

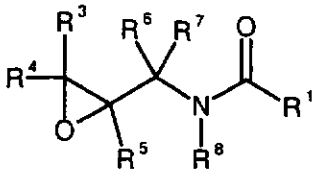


(IV),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined above,

are converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the general formula (V)



(V),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined above,

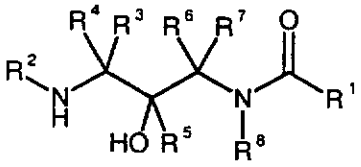
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the general formula (VI)

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

in which

the radical R^2 is as defined above,

the compounds of the general formula (VII)



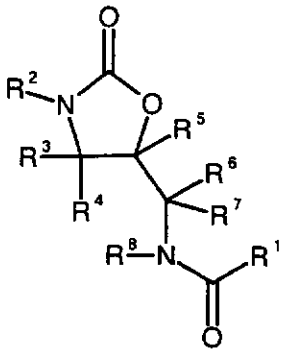
(VII),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined above,

are initially prepared and

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



(I)

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined above,

where - both for process alternative [A] and for process alternative [B] - in the case where R^2 contains a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical having one or more identical or different heteroatoms from the group consisting of N and S, an oxidation with a selective oxidizing agent to afford the corresponding sulphone, sulphoxide or N-oxide may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a cyano group in the molecule, an amidination of this cyano group by customary methods may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a BOC amino protective group in the molecule, removal of this BOC amino protective group by customary methods may follow

and/or

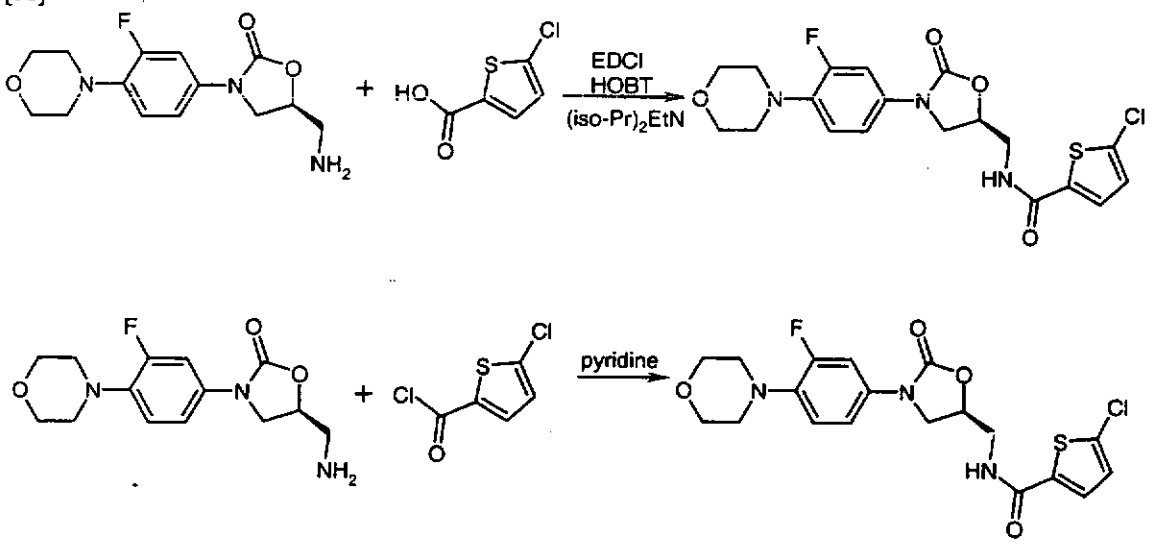
where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with various reagents such as carboxylic acids, carboxylic anhydrides, carbonyl chlorides, isocyanates, sulphonyl chlorides or alkyl halides to give the corresponding derivatives may follow

and/or

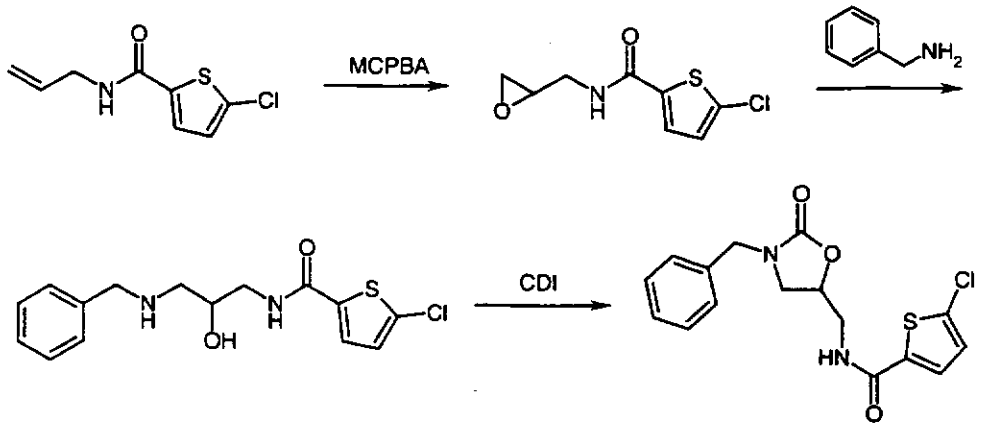
where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with amines to give the corresponding sulphonamides may follow.

The processes according to the invention can be illustrated in an exemplary manner by the equations below:

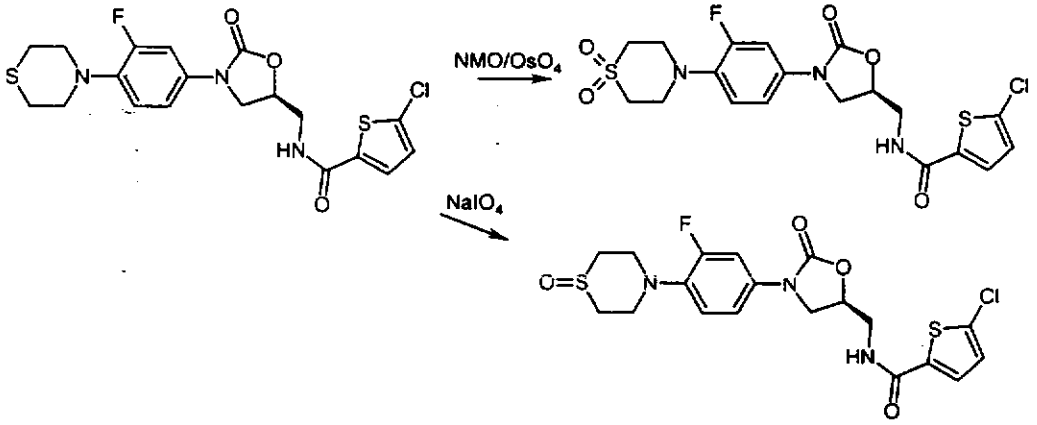
[A]



[B]



The oxidation step described above, which is optional, can be illustrated in an exemplary manner by the equation below:



Suitable solvents for the processes described above are organic solvents which are inert under the reaction conditions. These include halogenated hydrocarbons, such as dichloromethane, trichloromethane, carbon tetrachloride, 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 sulphoxide, acetonitrile, pyridine, hexamethylphosphoric triamide or water.

It is also possible to use solvent mixtures of the solvents mentioned above.

Suitable activating or coupling agents for the processes described above are the reagents which are customarily used for this purpose, for example *N'*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide · HCl, *N,N'*-dicyclohexylcarbodiimide, 1-hydroxy-1H-benzotriazole · H_2O and the like.

Suitable bases are the customary inorganic or organic bases. These preferably include alkali metal hydroxides, such as, for example, sodium hydroxide or potassium hydroxide, or alkali metal carbonates, such as sodium carbonate or potassium carbonate, or sodium methoxide or potassium methoxide or sodium ethoxide or potassium ethoxide or potassium-tert-butoxide, or amides, such as sodium amide, 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 here 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 are generally carried out in a temperature range of from –78°C to reflux temperature, preferably in the range from 0°C to reflux temperature.

The reactions can be carried out at atmospheric, elevated or reduced pressure (for example in the range from 0.5 to 5 bar). In general, the reactions are carried out at atmospheric pressure.

Suitable selective oxidizing agents, both for the preparation of the epoxides and for the optional oxidation to give the sulphone, sulphoxide or N-oxide, are m-chloroperbenzoic acid (MCPBA), sodium metaperiodate, N-methylmorpholine N-oxide (NMO), monoperoxyphthalic acid or osmium tetroxide.

With respect to the preparation of the epoxides, the preparation conditions which are customary for this purpose are employed.

With respect to more detailed process conditions for the optional oxidation to give the sulphone, sulphoxide or N-oxide, reference is made to the following literature: M. R. Barbachyn et al., J. Med. Chem. **1996**, *39*, 680 and WO-A-97/10223.

Furthermore, reference is made to Examples 14 to 16 given in the experimental part.

The optional amidation is carried out under customary conditions. For more details, reference is made to Examples 31 to 35 and 140 to 147.

The compounds of the general formulae (II), (III), (IV) and (VI) are known per se to the person skilled in the art or can be prepared by customary 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 compounds of the general formula (I) according to the invention have an unforeseeable useful pharmacological activity spectrum and are therefore particularly suitable for the prophylaxis and/or treatment of disorders.

The compounds of the general formula (I) according to the ivnention - including the compounds which are excluded by disclaimer from the chemical product protection - act in particular as anticoagulants and can therefore preferably be employed in medicaments for the prophylaxis and/or therapy of thromboembolic disorders. For the purpose of the present invention, "thromboembolic disorders" include, 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 occlusion disorders, pulmonary embolisms or deep venous thromboses.

Furthermore, the compounds of the general formula (I) according to the invention - including the compounds which are excluded by disclaimer from the chemical product protection - are also suitable for treating disseminated intravascular coagulation (DIC).

Finally, the compounds of the general formula (I) according to the invention - including the compounds which are excluded by disclaimer from the chemical product protection - are also suitable for the prophylaxis and/or treatment of atherosclerosis and arthritis, and additionally also for the prophylaxis and/or treatment of Alzheimer's disease and cancer.

The compounds of the general formula (I) according to the invention - including the compounds excluded by disclaimer from the chemical product protection - act in particular as selective inhibitors of the blood coagulation factor Xa and do not inhibit, or only inhibit at considerably higher concentrations, other serine proteases as well, such as thrombin, plasmin or trypsin.

In the context of the present invention, inhibitors of the blood coagulation factor Xa in which the IC_{50} values for the factor Xa inhibition are lower by a factor of 100, preferably by a factor of 500, in particular by a factor of 1000, than the IC_{50} values for the inhibition of other serine proteases, in particular thrombin, plasmin and trypsin, are referred to as being „selective", where with a view to the test methods for selectivity, reference is made to the test methods of Examples A-1) a.1) and a.2) described below.

The compounds of the general formula (I) according to the invention - including the compounds which are excluded by disclaimer from the chemical product protection - can furthermore be used for preventing coagulation *ex vivo*, for example for banked blood or biological samples which contain factor Xa.

The present invention thus provides oxazolidinones of the formula (I) effecting in particular an unexpected, strong and selective inhibition of factor Xa, and this also applies to the compounds excluded by disclaimer from the chemical product protection.

The present invention further provides medicaments and pharmaceutical compositions comprising at least one compound of the general 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.

Furthermore, the present invention relates to a method for the prophylaxis and/or treatment of disorders of the human or animal body, in particular of the abovementioned disorders, using the compounds of the general formula (I) according to the invention - including the compounds excluded by disclaimer from the chemical product protection.

Furthermore, the present invention also includes a method for preventing blood coagulation in vitro, in particular in banked blood or biological samples which contain factor Xa, which method is characterized in that compounds of the general formula (I) - including the compounds excluded by disclaimer from the chemical product protection - are added.

All customary administration forms are suitable for administration of the compounds according to the invention. Administration is preferably carried out orally, lingually, sublingually, buccally, rectally or parenterally (i.e. bypassing the intestinal tract, that is intravenously, intraarterially, intracardially, intracutaneously, subcutaneously, transdermally, intraperitoneally or intramuscularly). Particularly suitable are oral and intravenous administration. Very particular preference is given to oral administration, this being a further advantage with respect to the prior-art therapy of thromboembolic disorders.

The novel active compounds of the general formula (I) can be converted in a known manner into the customary formulations, such as tablets, sugar-coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert non-toxic pharmaceutically suitable excipients or solvents. Here, the therapeutically active compound should in each case be present in a concentration of from about 0.1 to 95% by weight, preferably from 0.5 to 90% by weight, in particular from 1 to 85% by weight, of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

In spite of this, if appropriate, it may be necessary to depart from the amounts mentioned, namely depending on the body weight or on the type of administration route, on the individual response to the medicament, on the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be adequate to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into several individual administrations over the course of the day.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, it

being possible, for example if the diluent used is water, optionally to use organic solvents as auxiliary solvents.

In general it has proved advantageous in the case of intravenous administration to administer amounts from approximately 0.001 to 10 mg/kg, preferably approximately 0.01 to 10 mg/kg, in particular approximately 0.1 to 8 mg/kg, of body weight to achieve effective results.

In general, it has proved advantageous in the case of oral administration to administer amounts from approximately 0.01 to 50 mg/kg, preferably approximately 0.1 to 10 mg/kg, in particular approximately 0.5 to 8 mg/kg, of body weight to achieve effective results.

In spite of this, if appropriate, it may be necessary in the case of intravenous or oral administration to depart from the amounts mentioned, namely depending on the body weight or on the type of administration route, on the individual response to the medicament, on the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be adequate to manage with less than the abovementioned mininum amount, while in other cases the upper limit mentioned must be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these over the course of the day, namely into several individual doses or as a continuous infusion.

Compared to the conventional preparations for treating thromboembolic disorders, the compounds of the general formula (I) according to the invention - including the compounds excluded by disclaimer from the chemical product protection - are distinguished in particular by the fact that a greater therapeutic range is achieved by the selective inhibition of factor Xa. For the patient, this means a lower risk of bleeding, and for the treating physician, this means that the patient is easier to adjust. Moreover - owing to the mechanism - the onset of action is more rapid. Above all, however, the compounds according to the invention permit an oral administration form, which is a further advantage of the therapy with the compounds according to the invention.

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

Examples

A Evaluation of the physiological activity

1. General test methods

The particularly advantageous biological properties of the compounds according to the invention can be determined by the following methods.

a) Test description (in vitro)

a.1) Determination of the factor Xa inhibition

The enzymatic activity of human factor Xa (FXa) was measured using the conversion of a chromogenic substrate specific for FXa. Factor Xa cleaves p-nitroaniline from the chromogenic substrate. The determinations were carried out in microtitre plates as follows.

The test substances, in various concentrations, were dissolved in DMSO and incubated at 25°C with human FXa (0.5 nmol/l dissolved in 50 mmol/l of tris buffer [C,C,C-tris(hydroxymethyl)-aminomethane], 150 mmol/l of NaCl, 0.1% BSA (bovine serum albumin), pH = 8.3) for 10 minutes. Pure DMSO was used as control. The chromogenic substrate (150 µmol/l of Pefachrome® FXa from Pentapharm) was then added. After an incubation time of 20 minutes at 25°C, the extinction at 405 nm was determined. The extinctions of the test mixtures containing test substance were compared with the control mixtures without test substance, and the IC_{50} values were calculated from these data.

a.2) Determination of the selectivity

To assess selective FXa inhibition, the test substances were examined for their inhibition of other human serine proteases such as thrombin, trypsin and plasmin. To determine the enzymatic activity of thrombin (75 mU/ml), trypsin (500 mU/ml) and plasmin (3.2 nmol/l), these enzymes were dissolved in tris buffer (100 mmol/l, 20 mmol/l $CaCl_2$, pH = 8.0) and incubated with test substance or solvent for 10 minutes. The enzymatic reaction was then started by adding the corresponding

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

a.3) Determination of the anticoagulant action

The anticoagulant action of the test substances was determined in vitro in human plasma. To this end, human blood was drawn off in a mixing ratio of sodium citrate/blood of 1/9 using a 0.11 molar sodium citrate solution as receiver. Immediately after the blood had been drawn off, it was mixed thoroughly and centrifuged at about 2000 g for 10 minutes. The supernatant was pipetted off. The prothrombin time (PT, synonyms: thromboplastin time, quick test) was determined in the presence of varying concentrations of test substance or the corresponding solvent using a commercial test kit (Neoplastin® from Boehringer Mannheim). The test compounds were incubated with the plasma at 37°C for 10 minutes. Coagulation was then started by addition of thromboplastin, and the time when coagulation occurred was determined. The concentration of test substance which effected a doubling of the prothrombin time was determined.

b) Determination of the antithrombotic activity (in vivo)

b.1) Arteriovenous shunt model (rat)

Fasting male rats (strain: HSD CPB:WU) having a weight of 200-250 g were anaesthetized using a Rompun/Ketavet solution (12 mg/kg/ 50 mg/kg). Thrombus formation was initiated in an arteriovenous shunt in accordance with the method described by Christopher N. Berry et al., Br. J. Pharmacol. (1994), 113, 1209-1214. To this end, the left jugular vein and the right carotid artery were exposed. The two vessels were connected by an extracorporeal shunt using a polyethylene tube (PE 60) of a length of 10 cm. In the middle, this polyethylene tube was attached to a further polyethylene tube (PE 160) of a length of 3 cm which contained a roughened nylon thread which had been arranged to form a loop, to form a thrombogenic surface. The extracorporeal circulation was maintained for 15 minutes. The shunt was then

removed and the nylon thread with the thrombus was weighed immediately. The weight of the nylon thread on its own had been determined before the experiment was started. Before the extracorporeal circulation was set up, the test substances were administered to the animals while awake either intravenously via the tail vein or orally using a pharyngeal tube.

The results are shown in Table 1:

Table 1: Antithrombotic activity in the arteriovenous shunt model (rat) after oral or intravenous administration

Example	ED_{50} [mg/kg] p.o.	ED_{50} [mg/kg] i.v.
1		10
17		6
44	3	
95		3
114		3
115		3
123	3	
162		3

b.2) Arterial thrombosis model (rat)

Male fasting rats (strain: HSD CPB: WU) were anaesthetized as described above. On average, the rats had a weight of about 200 g. The left carotid artery was exposed (about 2 cm). The formation of an arterial thrombus was induced by mechanical injury to the blood vessel in accordance with the method described by K. Meng et al., Naunyn-Schmiedeberg's Arch. Pharmacol. (1977), 301, 115-119. To this end, the exposed carotid artery was clamped from the blood flow, cooled to -12°C in a metal trough for 2 minutes and, to standardize the size of the thrombi, simultaneously compressed using a weight of 200 g. The blood flow was then additionally reduced by a clip which was placed around the carotid artery distally from the injured section of the vessel. The proximal clamp was removed, and the wound was closed and re-opened after 4 hours to remove the injured section of the vessel. The section of the vessel was opened longitudinally and the thrombus was removed from the injured section of the vessel. The moist weight of the thrombi was determined immediately. The test substances were administered to the animals while awake at the beginning of the experiment, either intravenously via the tail vein or orally using a pharyngeal tube.

b.3) Venous thrombosis model (rat)

Male fasting rats (strain: HSD CPB: WU) were anaesthetized as described above. On average, the rats had a weight of about 200 g. The left jugular vein was exposed (about 2 cm). The formation of a venous thrombus was induced by mechanical injury to the blood vessel in accordance with the method described by K. Meng et al., Naunyn-Schmiedeberg's Arch. Pharmacol. (1977), 301, 115-119. To this end, the jugular vein was clamped from the blood flow, cooled to -12°C in a metal trough for 2 minutes and, to standardize the size of the thrombi, simultaneously compressed using a weight of 200 g. The blood flow was re-opened and the wound was closed. After 4 hours, the wound was re-opened to remove the thrombi from the injured sections of the vessel. The moist weight of the thrombi was determined immediately. The test substances were administered to the animals while awake at the beginning of the experiment, either intravenously via the tail vein or orally using a pharyngeal tube.

B Preparation Examples

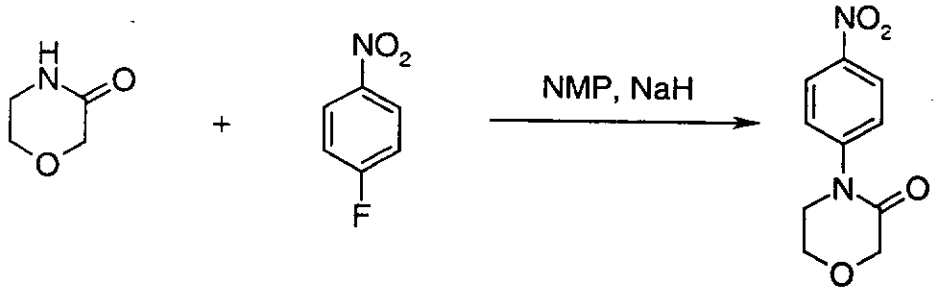
Starting materials

The preparation of 3-morpholinone is described in US 5 349 045.

The preparation of N-(2,3-epoxypropyl)phthalimide is described in J.-W. Chern et al. Tetrahedron Lett. **1998**,*39*,8483.

The substituted anilines can be obtained by reacting, for example, 4-fluoronitrobenzene, 2,4-difluoronitrobenzene or 4-chloronitrobenzene with the appropriate amines or amides in the presence of a base. This can also be carried out using Pd catalysts, such as $Pd(OAc)_2$/DPPF/NaOt-Bu (Tetrahedron Lett. **1999**,*40*,2035) or copper (Renger, Synthesis **1985**,856; Aebischer et al., Heterocycles **1998**,*48*,2225). Likewise, it is possible to initially convert halogenated aromatics without nitro group into the corresponding amides, followed by nitration in the 4-position (US3279880).

I. 4-(4-Morpholin-3-onyl)nitrobenzene



2 mol (202 g) of morpholin-3-one (E. Pfeil, U. Harder, Angew. Chem. 79, 1967, 188) are dissolved in 2 l of N-methylpyrrolidone (NMP). Over a period of 2 h, 88 g (2.2 mol) of sodium hydride (60% in paraffin) are then added a little at a time. After the evolution of hydrogen has ceased, 282 g (2 mol) of 4-fluoronitrobenzene are added dropwise with cooling at room temperature, over a period of 1 h, and the reaction mixture is then stirred overnight. At 12 mbar and 76°C, 1.7 l of the liquid volume are then distilled off, the residue is poured into 2 l of water and this mixture is extracted twice with in each case 1 l of ethyl acetate. After washing of the combined organic phases with water, the mixture is dried over sodium sulphate and the solvent is distilled off under reduced pressure. Purification is carried out by silica gel chromatography using hexane/ethyl acetate (1:1) and subsequent crystallization

from ethyl acetate. This gives 78 g of product as a colourless to brownish solid, in a yield of 17.6% of theory.

^{1}H-NMR (300 MHz, $CDCl_3$): 3.86 (m, 2 H, CH_2CH_2), 4.08 (m, 2 H, CH_2CH_2), 4.49 (s, 2 H, CH_2CO), 7.61 (d, 2 H, ^3J=8.95 Hz, CHCH), 8.28 (d, 2 H, ^3J=8.95 Hz, CHCH)

MS (r.I.%) = 222 (74, M^+), 193 (100), 164 (28), 150 (21), 136 (61), 117 (22), 106 (24), 90 (37), 76 (38), 63 (32), 50 (25)

The following compounds were synthesized analogously:

3-fluoro-4-(4-morpholin-3-onyl)nitrobenzene

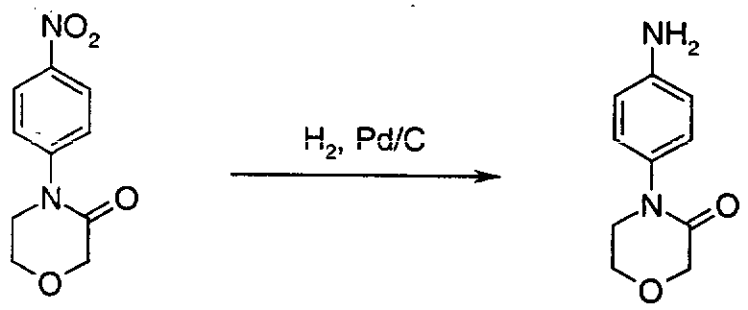
4-(N-piperidonyl)nitrobenzene

3-fluoro-4-(N-piperidonyl)nitrobenzene

4-(N-pyrrolidonyl)nitrobenzene

3-fluoro-4-(N-pyrrolidonyl)nitrobenzene

II. 4-(4-Morpholin-3-onyl)aniline



In an autoclave, 63 g (0.275 mol) of 4-(4-morpholin-3-onyl)nitrobenzene are dissolved in 200 ml of tetrahydrofuran, admixed with 3.1 g of Pd/C (5%ig) and hydrogenated at 70°C and a hydrogen pressure of 50 bar for 8 h. The catalyst is filtered off, the solvent is then distilled off under reduced pressure and the product is purified by crystallization from ethyl acetate. 20 g of product are obtained as a colourless to bluish solid, in a yield of 37.6% of theory.

Purification can also be carried out by silica gel chromatography using hexane/ethyl acetate.

^{1}H-NMR (300 MHz, $CDCl_3$): 3.67 (m, 2 H, CH_2CH_2), 3.99 (m, 2 H, CH_2CH_2), 4.27 (s, 2 H, CH_2CO), 6.68 (d, 2 H, ^3J=8.71 Hz, CHCH), 7.03 (d, 2 H, ^3J=8.71 Hz, CHCH)

MS (r.I.%) = 192 (100, M^+), 163 (48), 133 (26), 119 (76), 106 (49), 92 (38), 67 (27), 65 (45), 52 (22), 28 (22)

The following compounds were synthesized analogously:

3-fluoro-4-(4-morpholin-3-onyl)aniline

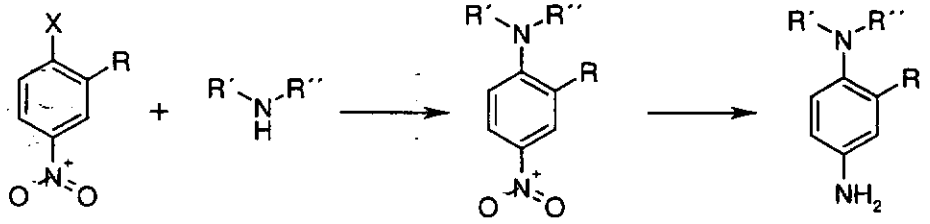
4-(N-piperidonyl)aniline

3-fluoro-4-(N-piperidonyl)aniline

4-(N-pyrrolidonyl)aniline

3-fluoro-4-(N-pyrrolidonyl)aniline

General method for preparing 4-substituted anilines by reacting 1-fluoro-4-nitrobenzenes and 1-chloro-4-nitrobenzenes with primary or secondary amines, followed by reduction



X = F, Cl

Equimolar amounts of the fluoronitrobenzene or chloronitrobenzene and the amine are dissolved in dimethyl sulphoxide or acetonitrile (0.1 M to 1 M solution), and the mixture is stirred at 100°C overnight. After cooling to RT, the reaction mixture is diluted with ether and washed with water. The organic phase is dried over $MgSO_4$, filtered and concentrated. If a precipitate forms in the reaction mixture, the precipitate is filtered off and washed with ether or acetonitrile. If the mother liquor also contains product, it is worked up as described using ether and water. The crude products can be purified by silica gel chromatography (dichloromethane/cyclohexane and dichloromethane/ethanol mixtures).

For the subsequent reduction, the nitro compound is dissolved in methanol, ethanol or ethanol/dichloromethane mixtures (0.01 M to 0.5 M solution) admixed with palladium on carbon (10%) and stirred under an atmospheric hydrogen pressure overnight. The mixture is then filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase HPLC (acetonitrile/water mixtures).

Alternatively, the reducing agent used can also be iron powder. To this end, the nitro compound is dissolved in acetic acid (0.1 M to 0.5 M solution) and, at 90°C, six equivalents of iron powder and water (0.3 to 0.5 times the volume of the acetic acid) are added a little at a time over a period of 10-15 min. After a further 30 min at 90°C, the mixture is filtered and the filtrate is concentrated. The residue is worked up by extraction with ethyl acetate and 2N aqueous sodium hydroxide solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase HPLC (acetonitrile/water mixtures).

The following starting materials were prepared in an analogous manner:

III-1. tert-butyl-1-(4-aminophenyl)-L-prolinate
MS (ESI): m/z (%) = 304 (M+H+MeCN, 100), 263 (M+H, 20);
HPLC (method 4): rt = 2.79 min.

III-2. 1-(4-aminophenyl)-3-piperidinecarboxamide
MS (ESI): m/z (%) = 220 (M+H, 100);
HPLC (method 4): rt = 0.59 min.

III-3. 1-(4-aminophenyl)-4-piperidincarboxamide
MS (ESI): m/z (%) = 220 (M+H, 100);
HPLC (method 4): rt = 0.57 min.

III-4. 1-(4-aminophenyl)-4-piperidinone
MS (ESI): m/z (%) = 191 (M+H, 100);
HPLC (method 4): rt = 0.64 min.

III-5. 1-(4-aminophenyl)-L-prolinamide
MS (ESI): m/z (%) = 206 (M+H, 100);
HPLC (method 4): rt = 0.72 min.

III-6. [1-(4-aminophenyl)-3-piperidinyl]methanol
MS (ESI): m/z (%) = 207 (M+H, 100);
HPLC (method 4): rt = 0.60 min.

III-7. [1-(4-aminophenyl)-2-piperidinyl]methanol

MS (ESI): m/z (%) = 207 (M+H, 100);

HPLC (method 4): rt = 0.59 min.

III-8. ethyl 1-(4-aminophenyl)-2-piperidinecarboxylate

MS (ESI): m/z (%) = 249 (M+H, 35), 175 (100);

HPLC (method 4): rt = 2.43 min.

III-9. [1-(4-aminophenyl)-2-pyrrolidinyl]methanol

MS (ESI): m/z (%) = 193 (M+H, 45);

HPLC (method 4): rt = 0.79 min.

III-10. 4-(2-methylhexahydro-5H-pyrrolo[3,4-d]isoxazol-5-yl)phenylamine

starting from 2-methylhexahydro-2H-pyrrolo[3,4-d]isoxazole (Ziegler, Carl B., et al.; J. Heterocycl. Chem.; 25; 2; 1988; 719-723)

MS (ESI): m/z (%) = 220 (M+H, 50), 171 (100);

HPLC (method 4): rt = 0.54 min.

III-11. 4-(1-pyrrolidinyl)-3-(trifluoromethyl)aniline

MS (ESI): m/z (%) = 231 (M+H, 100);

HPLC (method 7): rt = 3.40 min.

III-12. 3-chloro-4-(1-pyrrolidinyl)aniline

MS (ESI): m/z (%) = 197 (M+H, 100);

HPLC (method 4): rt = 0.78 min.

III.-13. 5-amino-2-(4-morpholinyl)benzamide

MS (ESI): m/z (%) = 222 (M+H, 100);

HPLC (method 4): rt = 0.77 min.

III-14. 3-methoxy-4-(4-morpholinyl)aniline

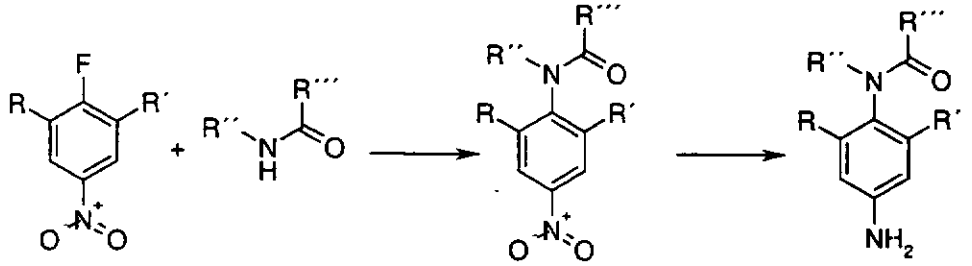
MS (ESI): m/z (%) = 209 (M+H, 100);

HPLC (method 4): rt = 0.67 min.

III-15. 1-[5-amino-2-(4-morpholinyl)phenyl]ethanone

MS (ESI): m/z (%) = 221 (M+H, 100);
HPLC (method 4): rt = 0.77 min.

General method for preparing 4-substituted anilines by reacting 1-fluoro-4-nitrobenzenes with amides, followed by reduction



The amide is dissolved in DMF and admixed with 1.5 equivalents of potassium tert-butoxide. The mixture is stirred at RT for 1 h, and 1.2 equivalents of the 1-fluoro-4-nitrobenzene are then added a little at a time. The reaction mixture is stirred at RT overnight, diluted with ether or ethyl acetate and washed with sat. aqu. sodium bicarbonate solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures).

For the subsequent reduction, the nitro compound is dissolved in ethanol (0.01 M to 0.5 M solution), admixed with palladium on carbon (10%) and stirred under atmospheric hydrogen pressure overnight. The mixture is then filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase HPLC (acetonitrile/water mixtures).

Alternatively, the reducing agent used can also be iron powder. To this end, the nitro compound is dissolved in acetic acid (0.1 M to 0.5 M solution) and, at 90°C, six equivalents of iron powder and water (0.3 to 0.5 times the volume of the acetic acid) are added a little at a time over a period of 10-15 min. After a further 30 min at 90°C, the mixture is filtered and the filtrate is concentrated. The residue is worked up by extraction with ethyl acetate and 2N aqueous sodium hydroxide solution. The organic phase is dried over magnesium sulphate, filtered and concentrated. The crude product can be purified by silica gel chromatography (dichloromethane/ethanol mixtures) or preparative reversed-phase HPLC (acetonitrile/water mixtures).

The following starting materials were prepared in an analogous manner:

IV-1. 1-[4-amino-2-(trifluoromethyl)phenyl]-2-pyrrolidinone
MS (ESI): m/z (%) = 245 (M+H, 100);
HPLC (method 4): rt = 2.98 min

IV-2. 4-[4-amino-2-(trifluoromethyl)phenyl]-3-morpholinone
MS (ESI): m/z (%) = 261 (M+H, 100);
HPLC (method 4): rt = 2.54 min.

IV-3. 4-(4-amino-2-chlorophenyl)-3-morpholinone
MS (ESI): m/z (%) = 227 (M+H, 100);
HPLC (method 4): rt = 1.96 min.

IV-4. 4-(4-amino-2-methylphenyl)-3-morpholinone
MS (ESI): m/z (%) = 207 (M+H, 100);
HPLC (method 4): rt = 0.71 min.

IV-5. 5-amino-2-(3-oxo-4-morpholinyl)benzonitrile
MS (ESI): m/z (%) = 218 (M+H, 100);
HPLC (method 4): rt = 1.85 min.

IV-6. 1-(4-amino-2-chlorophenyl)-2-pyrrolidinone
MS (ESI): m/z (%) = 211 (M+H, 100);
HPLC (method 4): rt = 2.27 min.

IV-7. 4-(4-amino-2,6-dimethylphenyl)-3-morpholinone
starting from 2-fluoro-1,3-dimethyl-5-nitrobenzene (Bartoli et al., J. Org. Chem. 1975, *40*, 872):
MS (ESI): m/z (%) = 221 (M+H, 100);
HPLC (method 4): rt = 0.77 min.

IV-8. 4-(2,4-diaminophenyl)-3-morpholinone
starting from 1-fluoro-2,4-dinitrobenzene:
MS (ESI): m/z (%) = 208 (M+H, 100);
HPLC (method 4): rt = 0.60 min.

IV-9. 4-(4-amino-2-chlorophenyl)-2-methyl-3-morpholinone

starting from 2-methyl-3-morpholinone (Pfeil, E.; Harder, U.; Angew. Chem. 1967, *79*, 188):

MS (ESI): m/z (%) = 241 (M+H, 100);

HPLC (method 4): rt = 2.27 min.

IV-10. 4-(4-amino-2-chlorophenyl)-6-methyl-3-morpholinone

starting from 6-methyl-3-morpholinone (EP 350 002):

MS (ESI): m/z (%) = 241 (M+H, 100);

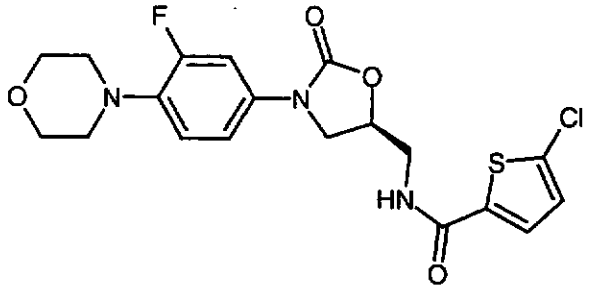
HPLC (method 4): rt = 2.43 min.

Synthesis Examples

The Examples 1 to 13, 17 to 19 and 36 to 57 below refer to process variant [A].

Example 1

Preparation of 5-chloro-N-{[(5S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



(5S)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)-1,3-oxazolidin-2-one (preparation see S. J. Brickner et al., J. Med. Chem. **1996**, *39*, 673) (0.45 g, 1.52 mmol), 5-chlorothiophene-2-carboxylic acid (0.25 g, 1.52 mmol) and 1-hydroxy-1H-benzotriazole hydrate (HOBT) (0.3 g, 1.3 equivalents) are dissolved in 9.9 ml of DMF. 0.31 g (1.98 mmol, 1.3 equivalents) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI) are added, and 0.39 g (0.53 ml, 3.05 mmol, 2 equivalents) of diisopropylethylamine (DIEA) are added dropwise at room temperature. The mixture is stirred at room temperature overnight. 2 g of silica gel are added, and the mixture is evaporated to dryness under reduced pressure. The residue is chromatographed on silica gel using a toluene/ethyl acetate gradient. This gives 0.412 g (61.5% of theory) of the target compound of melting point (m.p.) 197°C.

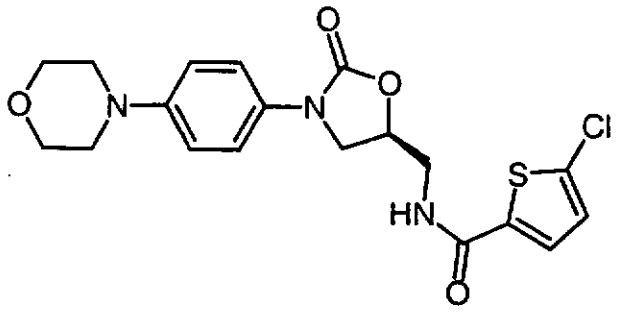
R_f (SiO_2, toluene/ethyl acetate 1:1) = 0.29 (starting material = 0.0);

MS (DCI) 440.2 (M+H), Cl pattern;

^{1}H-NMR (d_6-DMSO, 300 MHz) 2.95 (m, 4H), 3.6 (t, 2H), 3.72 (m, 4H), 3.8 (dd, 1H), 4.12 (t, 1H), 4.75-4.85 (m, 1H), 7.05 (t, 1H), 7.15-7.2 (m, 3H), 7.45 (dd, 1H), 7.68 (d, 1H), 8.95 (t, 1H).

Example 2

5-Chloro-N-{[(5S)-3-(4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



is obtained analogously from benzyl 4-morpholinophenylcarbamate via the (5S)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)-1,3-oxazolidin-2-one intermediate (see Example 1).

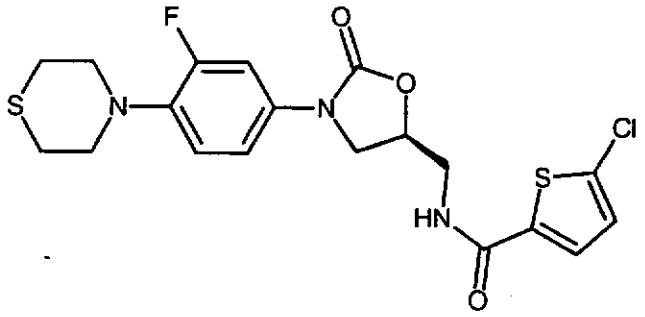
M.p.: 198°C;

IC_{50} value = 43 nM;

R_f (SiO_2, toluene/ethyl acetate 1:1) = 0.24.

Example 3

5-Chloro-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



is obtained analogously from (5S)-5-(aminomethyl)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-1,3-oxazolidin-2-one (preparation see M. R. Barbachyn et al., J. Med. Chem. **1996**, *39*, 680).

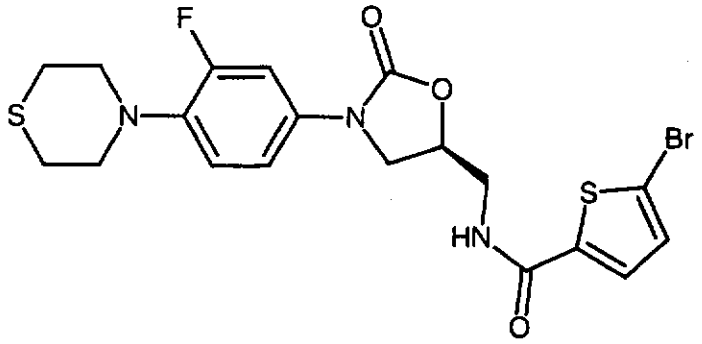
M.p.: 193°C;

Yield: 82%;

R_f (SiO_2, toluene/ethyl acetate 1:1) = 0.47 (starting material = 0.0).

Example 4

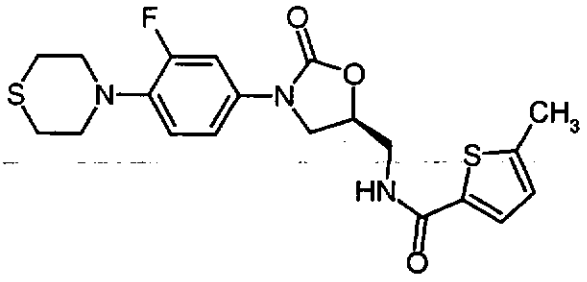
5-Bromo-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



is obtained analogously from 5-bromothiophene-2-carboxylic acid.
M.p.: 200°C.

Example 5

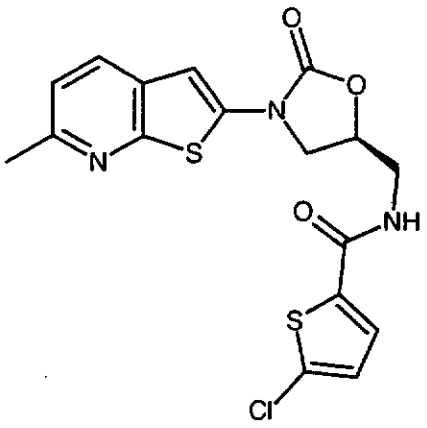
N-({(5S)-3-[3-Fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-methyl-2-thiophenecarboxamide



is obtained analogously from 5-methylthiophene-2-carboxylic acid.
M.p.: 167°C.

Example 6

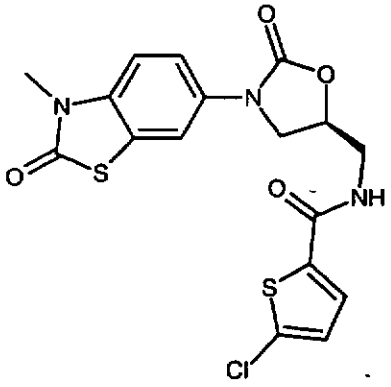
5-Chloro-N-{[(5S)-3-(6-methylthieno[2,3-b]pyridin-2-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



is obtained analogously from (5S)-5-(aminomethyl)-3-(6-methylthieno[2,3-b]pyridin-2-yl)-1,3-oxazolidin-2-one (preparation see EP-A-785 200).
M.p.: 247°C.

Example 7

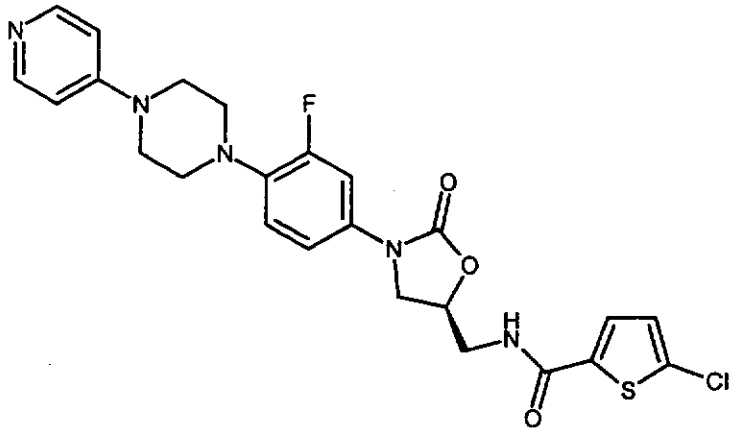
5-Chloro-N-{[(5S)-3-(3-methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



is obtained analogously from 6-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-3-methyl-1,3-benzothiazol-2(3H)-one (preparation see EP-A-738 726).
M.p.: 217°C.

Example 8

5-Chloro-N-[((5S)-3-{3-fluoro-4-[4-(4-pyridinyl)piperazino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

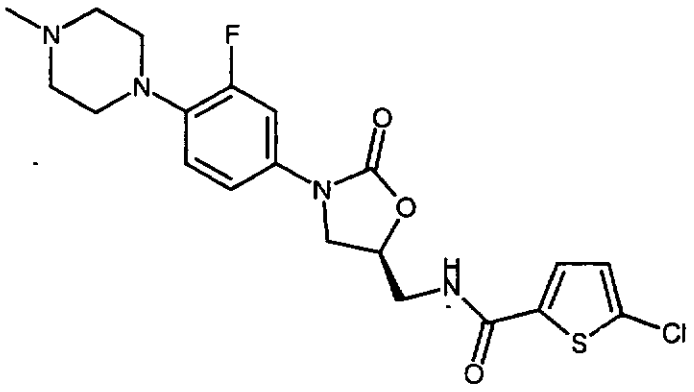


is obtained analogously from (5S)-5-(aminomethyl)-3-{3-fluoro-4-[4-(4-pyridinyl)piperazino]phenyl}-1,3-oxazolidin-2-one (preparation analogously to J. A. Tucker et al., J. Med. Chem. 1998, 41, 3727).

MS (ESI) 516 (M+H),Cl pattern.

Example 9

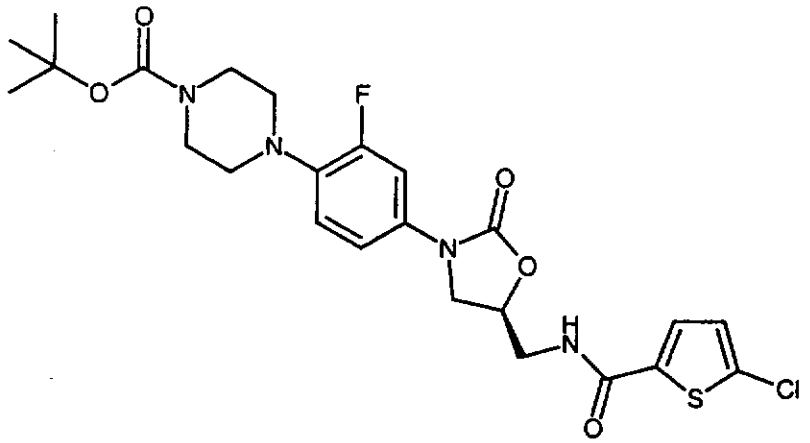
5-Chloro-N-({(5S)-3-[3-fluoro-4-(4-methylpiperazino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



is obtained analogously from (5S)-5-(aminomethyl)-3-[3-fluoro-4-(4-methylpiperazino)phenyl]-1,3-oxazolidin-2-one.

Example 10

5-Chloro-N-({(5S)-3-[3-fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



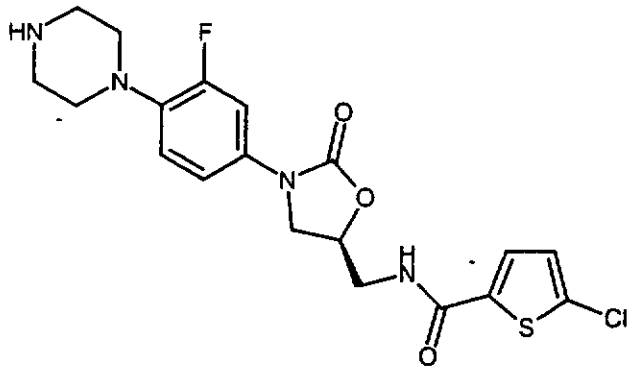
is obtained analogously from (5S)-5-(aminomethyl)-3-[3-fluoro-4-(4-tert-butoxycarbonylpiperazin-1-yl)phenyl]-1,3-oxazolidin-2-one (preparation see WO-A-93/23384, which has already been cited).

M.p.: 184°C;

R_f (SiO_2, toluene/ethyl acetate 1:1) = 0.42.

Example 11

5-Chloro-N-({(5S)-3-[3-fluoro-4-(piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



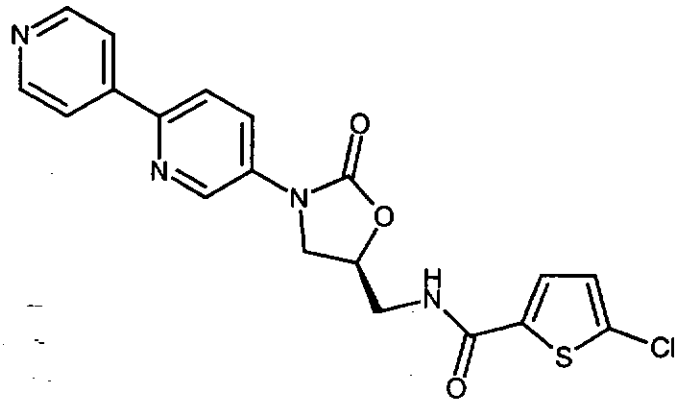
is obtained by reacting Example 12 with trifluoroacetic acid in methylene chloride.

IC_{50} value = 140 nM;

^{1}H-NMR [d_6-DMSO]: 3.01-3.25 (m, 8H), 3.5-3.65 (m, 2H), 3.7-3.9 (m, 1H), 4.05-4.2 (m, 1H), 4.75-4.9 (m, 1H), 7.05-7.25 (m, 3H), 7.5 (dd, 1H), 7.7 (d, 1H), 8.4 (broad s, 1H), 9.0 (t, 1H).

Example 12

5-Chloro-N-[((5S)-3-(2,4'-bipyridinyl-5-yl)-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



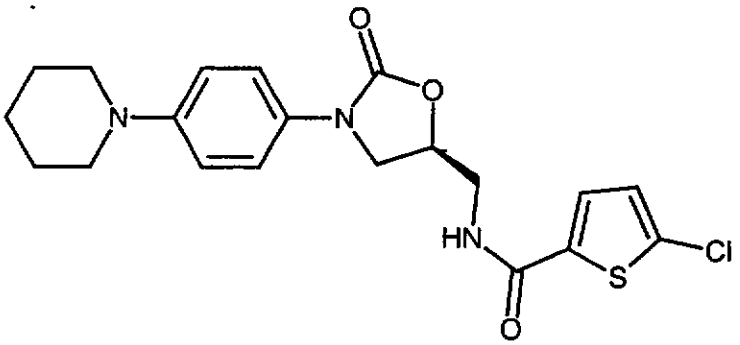
is obtained analogously from (5S)-5-aminomethyl-3-(2,4'-bipyridinyl-5-yl)-2-oxo-1,3-oxazolidin-2-one (preparation see EP-A-789 026).

R_f (SiO_2, ethyl acetate/ethanol 1:2) = 0.6;

MS (ESI) 515 (M+H), Cl pattern.

Example 13

5-Chloro-N-{[(5S)-2-oxo-3-(4-piperidinophenyl)-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



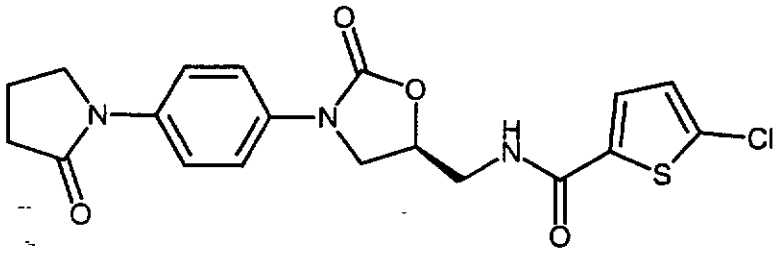
is obtained from 5-(hydroxymethyl)-3-(4-piperidinophenyl)-1,3-oxazolidin-2-one (preparation see DE 2708236) after mesylation, reaction with potassium phthalimide, hydrazinolysis and reaction with 5-chlorothiophene-2-carboxylic acid.

R_f (SiO_2, ethyl acetate/toluene 1:1) = 0.31;

m.p. 205°C.

Example 17

5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



Analogously to the known synthesis scheme (see S.J. Brickner et al., J. Med. Chem. **1996**, *39*, 673), 1-(4-aminophenyl)pyrrolidin-2-one (preparation see Reppe et al., Justus Liebigs Ann. Chem.; 596; 1955; 209) gives, after reaction with benzyloxycarbonyl chloride, followed by reaction with *R*-glycidyl butyrate, mesylation, reaction with potassium phthalimide, hydrazinolysis in methanol and reaction with 5-chlorothiophene-2-carboxylic acid, finally 5-chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The 5-chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)-phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide obtained in this manner has an IC_{50} value of 4 nM (test method for the IC_{50} value according to Example A-1.a.1 described above) "determination of the inhibition of factor Xa").

M.p.: 229°C;

R_f value (SiO_2, toluene/ethyl acetate 1:1) = 0.05 (starting material: = 0.0);

MS (ESI): 442.0 (21%, M+Na, Cl pattern), 420.0 (72%, M+H, Cl pattern), 302.3 (12%), 215(52%), 145 (100%);

^{1}H-NMR (d_6-DMSO, 300 MHz): 2.05 (m,2H), 2.45 (m,2H), 3.6 (t,2H), 3.77-3.85 (m,3H), 4.15(t,1H), 4.75-4.85 (m,1H), 7.2 (d,1H), 7.5 (d,2H), 7.65 (d,2H), 7.69 (d,1H), 8.96 (t,1H).

The individual steps of the synthesis of Example 17 described above with the respective precursors are as follows:

At -20°C, 4 g (22.7 mmol) of 1-(4-aminophenyl)pyrrolidin-2-one and 3.6 ml (28.4 mmol) of N,N-dimethylaniline in 107 ml of tetrahydrofuran are admixed slowly with 4.27 g (25.03 mmol) of benzyl chloroformate. The mixture is stirred at -20°C for 30 minutes and then allowed to warm to room temperature. 0.5 l of ethyl acetate are added, and the organic phase is washed with 0.5 l of saturated NaCl solution. The organic phase is separated off and dried with $MgSO_4$, and the solvent is evaporated under reduced pressure. The residue is triturated with diethyl ether and filtered off with suction. This gives 5.2 g (73.8% of theory) of benzyl 4-(2-oxo-1-pyrrolidinyl)phenylcarbamate as light-beige crystals of melting point 174°C.

At −10°C and under argon, 1.47 g (16.66 mmol) of isoamyl alcohol in 200 ml of tetrahydrofuran are admixed dropwise with 7.27 ml of a 2.5 M solution of n-butyllithium (BuLi) in hexane, a further 8 ml of BuLi solution being required for the added indicator N-benzylidenebenzylamine to change colour. The mixture is stirred at -10°C for 10 minutes and cooled to -78°C, and a solution of 4.7 g (15.14 mmol) of benzyl 4-(2-oxo-1-pyrrolidinyl)phenylcarbamate is added slowly. Another 4 ml of n-BuLi solution are then added until the colour of the indicator changes to pink. The mixture is stirred at -78°C for 10 minutes, 2.62 g (18.17 mmol) of *R*-glycidyl butyrate are added and the mixture is stirred at -78°C for another 30 minutes.

Overnight, the mixture is allowed to warm to room temperature, 200 ml of water are added and the THF fraction is evaporated under reduced pressure. The aqueous residue is extracted with ethyl acetate and the organic phase is dried with $MgSO_4$ and evaporated under reduced pressure. The residue is triturated with 500 ml of diethyl ether and the precipitated crystals are filtered off with suction under reduced pressure.

This gives 3.76 g (90% of theory) of (5R)-5-(hydroxymethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one of melting point 148°C, with an R_f value (SiO_2, toluene/ethyl acetate 1:1) of 0.04 (starting material = 0.3).

At 0°C, 3.6 g (13.03 mmol) of (5R)-5-(hydroxymethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one and 2.9 g (28.67 mmol) of triethylamine are initially charged with stirring in 160 ml of dichloromethane. 1.79 g (15.64 mmol) of methanesulphonyl chloride are added with stirring, and the mixture is stirred at 0°C for 1.5 hours and then at room temperature for 3 h.

The reaction mixture is washed with water and the aqueous phase is reextracted with methylene chloride. The combined organic extracts are dried with $MgSO_4$ and concentrated. The residue (1.67 g) is then dissolved in 70 ml of acetonitrile, admixed with 2.62 g (14.16 mmol) of potassium phthalimide and stirred in a closed vessel at 180°C in a microwave oven for 45 minutes.

The mixture is filtered off from insoluble residues, the filtrate is evaporated under reduced pressure and the residue (1.9 g) is dissolved in methanol and admixed with 0.47 g (9.37 mmol) of hydrazine hydrate. The mixture is boiled for 2 hours, cooled, admixed with saturated sodium bicarbonate solution and extracted six times with a total of 2 l of methylene chloride. The combined organic extracts of the crude (5S)-5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one are dried with $MgSO_4$ and concentrated under reduced pressure.

The end product, 5-chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, is prepared by dissolving 0.32 g (1.16 mmol) of the (5S)-5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one prepared above, 5-chlorothiophene-2-carboxylic acid (0.19 g; 1.16 mmol) and 1-hydroxy-1H-benzotriazole hydrate (HOBT) (0.23 g, 1.51 mmol) in 7.6 ml of DMF. 0.29 g (1.51 mmol) of N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI) are added, and 0.3 g (0.4 ml; 2.32 mmol, 2 equivalents) of diisopropylethylamine (DIEA) are added dropwise at room temperature. The mixture is stirred at room temperature overnight.

The mixture is evaporated to dryness under reduced pressure and the residue is dissolved in 3 ml of DMSO and chromatographed on an RP-MPLC using an acetonitrile/water/0.5% TFA gradient. From the appropriate fractions, the acetonitrile fraction is evaporated and the precipitated compound is filtered off with suction. This gives 0.19 g (39% of theory) of the target compound.

The following compounds were prepared in an analogous manner:

Example 18

5-Chloro-N-({(5S)-2-oxo-3-[4-(1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

Analogously to Example 17, 4-pyrrolidin-1-yl-aniline (Reppe et al., Justus Liebigs Ann. Chem.; 596; 1955; 151) gives the compound 5-chloro-N-({(5S)-2-oxo-3-[4-(1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.
IC_{50}=40 nM;
m.p.: 216°C;
R_f value (SiO_2, toluene/ethyl acetate 1:1) = 0.31 [starting material: = 0.0].

Example 19

5-Chloro-N-({(5S)-2-oxo-3-[4-(diethylamino)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

Analogously, N,N-diethylphenyl-1,4-diamine (US-A-2 811 555; 1955) gives the compound 5-chloro-N-({(5S)-2-oxo-3-[4-(diethylamino)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.
IC_{50}=270 nM;
m.p.: 181°C;
R_f value (SiO_2, toluene/ethyl acetate 1:1) = 0.25 [starting material: = 0.0].

Example 36

5-Chloro-*N*-({(5*S*)-3-[2-methyl-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
starting from 2-methyl-4-(4-morpholinyl)aniline (J.E.LuValle *et al. J.Am.Chem.Soc.* **1948**, *70*, 2223):
MS (ESI): m/z (%) = 436 ($[M+H]^+$, 100), Cl pattern;
HPLC (method 1): rt (%) = 3.77 (98).
IC_{50}: 1.26 μM

Example 37

5-Chloro-*N*-{[(5*S*)-3-(3-chloro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

starting from 3-chloro-4-(4-morpholinyl)aniline (H.R.Snyder *et al. J.Pharm.Sci.* **1977**, *66*, 1204):

MS (ESI): m/z (%) = 456 ($[M+H]^+$, 100), Cl_2 pattern;

HPLC (method 2): rt (%) = 4.31 (100).

IC_{50}: 33 nM

Example 38

5-Chloro-*N*-({(5*S*)-3-[4-(4-morpholinylsulphonyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

starting from 4-(4-morpholinylsulphonyl)aniline (Adams *et al. J.Am.Chem.Soc.* **1939**, *61*, 2342):

MS (ESI): m/z (%) = 486 ($[M+H]^+$, 100), Cl pattern;

HPLC (method 3): rt (%) = 4.07 (100).

IC_{50}: 2 μM

Example 39

5-Chloro-*N*-({(5*S*)-3-[4-(1-azetidinylsulphonyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

starting from 4-(1-azetidinylsulphonyl)aniline:

MS (DCI, NH_3): m/z (%) = 473 ($[M+NH_4]^+$, 100), Cl pattern;

HPLC (method 3): rt (%) = 4.10 (100).

IC_{50}: 0.84 μM

Example 40

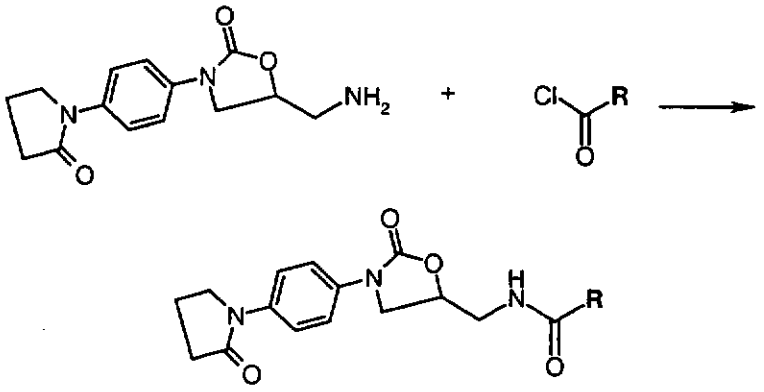
5-Chloro-*N*-[((5*S*)-3-{4-[(dimethylamino)sulphonyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

starting from 4-amino-*N*,*N*-dimethylbenzenesulphonamide (I.K.Khanna *et al. J.Med.Chem.* **1997**, *40*, 1619):

MS (ESI): m/z (%) = 444 ($[M+H]^+$, 100), Cl pattern;

HPLC (method 3): rt (%) = 4.22 (100).
IC_{50}: 90 nM

General method for the acylation of 5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one with carbonyl chlorides.



Under argon and at room temperature, an about 0.1 molar solution of 5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one (from Example 45) (1.0 eq.) and absolute pyridine (about 6 eq.) in absolute dichloromethane is added dropwise to the appropriate acid chloride (2.5 eq.). The mixture is stirred at room temperature for about 4 h, and about 5.5 eq of PS-trisamine (Argonaut Technologies) are then added. The suspension is stirred gently for 2 h, diluted with dichloromethane/DMF (3:1) and then filtered (the resin is washed with dichloromethane/DMF) and the filtrate is concentrated. If appropriate, the product that is obtained is purified by preparative RP-HPLC.

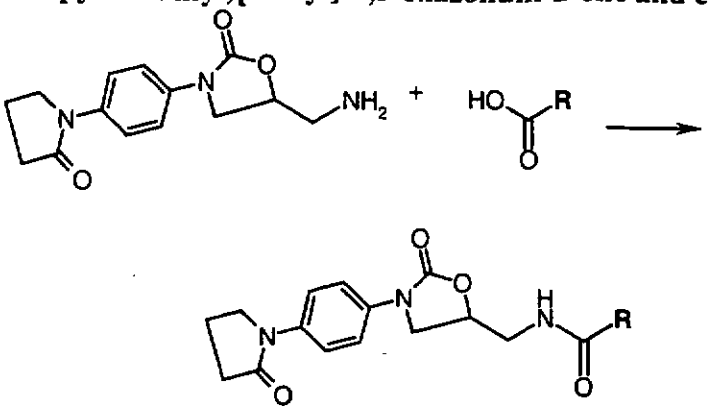
The following compounds were prepared in an analogous manner:

Example 41

***N*-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide**

LC-MS (method 6): m/z (%) = 386 (M+H, 100);
LC-MS: rt (%) = 3.04 (100).
IC_{50}: 1.3 μM

General method for preparing acyl derivatives starting from 5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one and carboxylic acids



The appropriate carboxylic acid (about 2 eq.) and a mixture of absolute dichloromethane/DMF (about 9:1) are added to 2.9 eq. of resin-bonded carbodiimide (PS-carbodiimide, Argonaut Technologies). The mixture is shaken gently at room temperature for about 15 min, 5-(aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one (from Example 45) (1.0 eq.) is then added and the mixture is shaken overnight, after which the resin is filtered off (and washed with dichloromethane), and the filtrate is concentrated. If appropriate, the resulting product is purified by preparative RP-HPLC.

The following compounds were prepared in an analogous manner:

Example 42

5-Methyl-*N*-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

LC-MS: m/z (%) = 400 (M+H, 100);

LC-MS (method 6): rt (%) = 3.23 (100).

IC_{50}: 0.16 μM

Example 43

5-Bromo-*N*-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

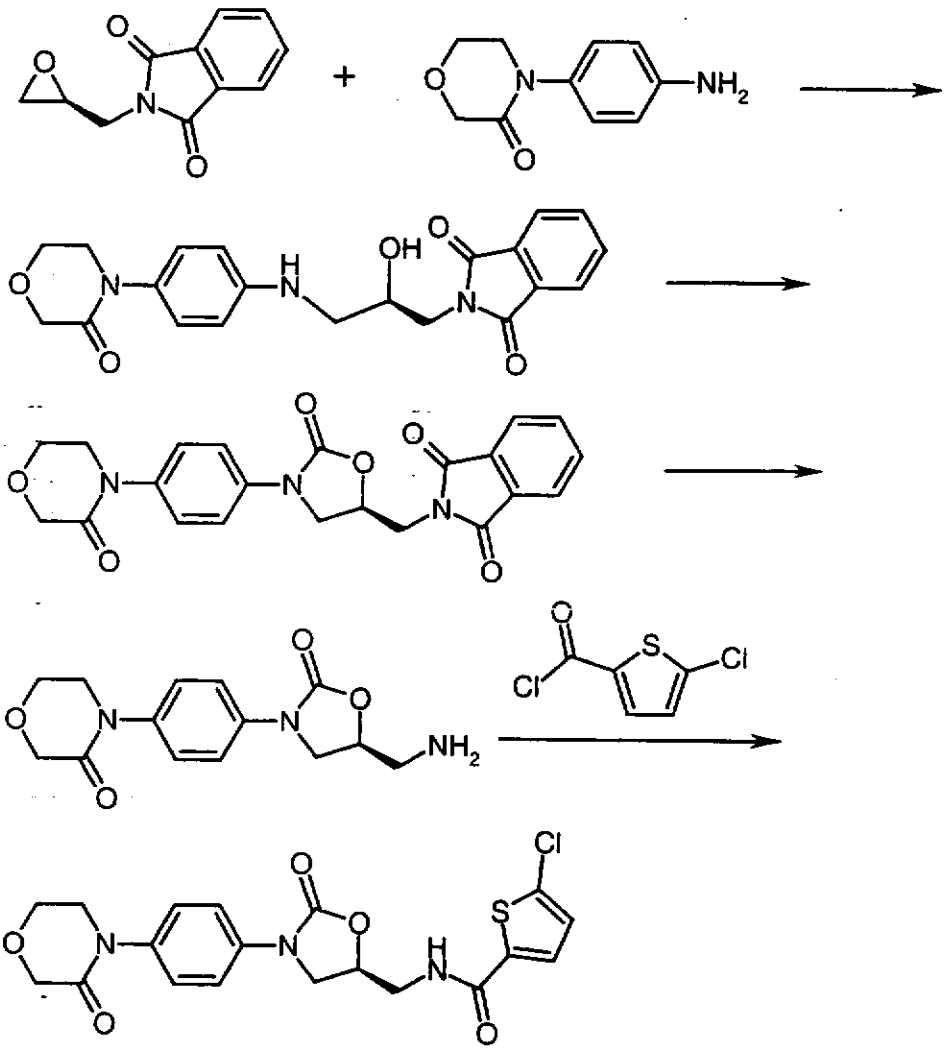
LC-MS : m/z (%) = 466 (M+H, 100);

LC-MS (method 5): rt (%) = 3.48 (78).

IC_{50}: 0.014 μM

Example 44

5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



a) 2-((2*R*)-2-Hydroxy-3-{[4-(3-oxo-4-morpholinyl)phenyl]amino}propyl)-1*H*-isoindole-1,3(2*H*)-dione:

A suspension of 2-[(2*S*)-2-oxiranylmethyl]-1*H*-isoindole-1,3(2*H*)-dione (A. Gutcait *et al. Tetrahedron Asym.* **1996**, *7*, 1641) (5.68 g, 27.9 mmol) and 4-(4-aminophenyl)-3-morpholinone (5.37 g, 27.9 mmol) in ethanol/water (9:1, 140 ml) is refluxed for

14 h (the precipitate dissolves, after some time again formation of a precipitate). The precipitate (desired product) is filtered off, washed three times with diethyl ether and dried. The combined mother liquors are concentrated under reduced pressure and, after addition of a second portion of 2-[(2*S*)-2-oxiranylmethyl]-1*H*-isoindole-1,3(2*H*)-dione (2.84 g, 14.0 mmol), suspended in ethanol/water (9:1, 70 ml) and refluxed for 13 h (the precipitate dissolves, after some time again formation of a precipitate). The precipitate (desired product) is filtered off, washed three times with diethyl ether and dried. Total yield: 10.14 g, 92% of theory.

MS (ESI): m/z (%) = 418 ($[M+Na]^+$, 84), 396 ($[M+H]^+$, 93);

HPLC (method 3): rt (%) = 3.34 (100).

b) 2-({(5*S*)-2-Oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindole-1,3(2*H*)-dione:

Under argon and at room temperature, *N*,*N*′-carbonyldiimidazole (2.94 g, 18.1 mmol) and dimethylaminopyridine (a catalytic amount) are added to a suspension of the amino alcohol (3.58 g, 9.05 mmol) in tetrahydrofuran (90 ml). The reaction suspension is stirred at 60°C for 12 h (the precipitate dissolves, after some time again formation of a precipitate), admixed with a second portion of *N*,*N*′-carbonyldiimidazole (2.94 g, 18.1 mmol) and stirred at 60°C for another 12 h. The precipitate (desired product) is filtered off, washed with tetrahydrofuran and dried. The filtrate is concentrated under reduced pressure and further product is purified by flash chromatography (dichloromethane/methanol mixtures). Total yield: 3.32 g, 87% of theory.

MS (ESI): m/z (%) = 422 ($[M+H]^+$, 100);

HPLC (method 4): rt (%) = 3.37 (100).

c) 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide:

At room temperature, methylamine (40% strength in water, 10.2 ml, 0.142 mol) is added dropwise to a suspension of the oxazolidinone (4.45 g, 10.6 mmol) in ethanol (102 ml). The reaction mixture is refluxed for 1 h and concentrated under reduced pressure. The crude product is used without further purification for the next reaction.

Under argon and at 0°C, 5-chlorothiophene-2-carbonyl chloride (2.29 g, 12.7 mmol) is added dropwise to a solution of the amine in pyridine (90 ml). Ice-cooling is removed and the reaction mixture is stirred at room temperature for 1 h and admixed with water. Dichloromethane is added and the phases are separated, and the aqueous phase is then extracted with dichloromethane. The combined organic phases are dried (sodium sulphate), filtered and concentrated under reduced pressure. The desired product is purified by flash chromatography (dichloromethane/methanol mixtures). Total yield: 3.92 g, 86% of theory.

M.p: 232-233°C;

^{1}H NMR (DMSO-d^6, 200 MHz): 9.05-8.90 (t, J = 5.8 Hz, 1H), 7.70 (d, J = 4.1 Hz, 1H), 7.56 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 4.1 Hz, 1H), 4.93-4.75 (m, 1H), 4.27-4.12 (m, 3H), 4.02-3.91 (m, 2H), 3.91-3.79 (dd, J = 6.1 Hz, 9.2 Hz, 1H), 3.76-3.66 (m, 2H), 3.66-3.54 (m, 2H);

MS (ESI): m/z (%) = 436 ($[M+H]^+$, 100, Cl pattern);

HPLC (method 2): rt (%) = 3.60 (100);

$[\alpha]^{21}_D$ = -38° (c 0.2985, DMSO); ee: 99%.

IC_{50}: 0.7 nM

The following compounds were prepared in an analogous manner:

Example 45

5-Methyl-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 831 ($[2M+H]^+$, 100), 416 ($[M+H]^+$, 66);

HPLC (method 3): rt (%) = 3.65 (100).

IC_{50}: 4.2 nM

Example 46

5-Bromo-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

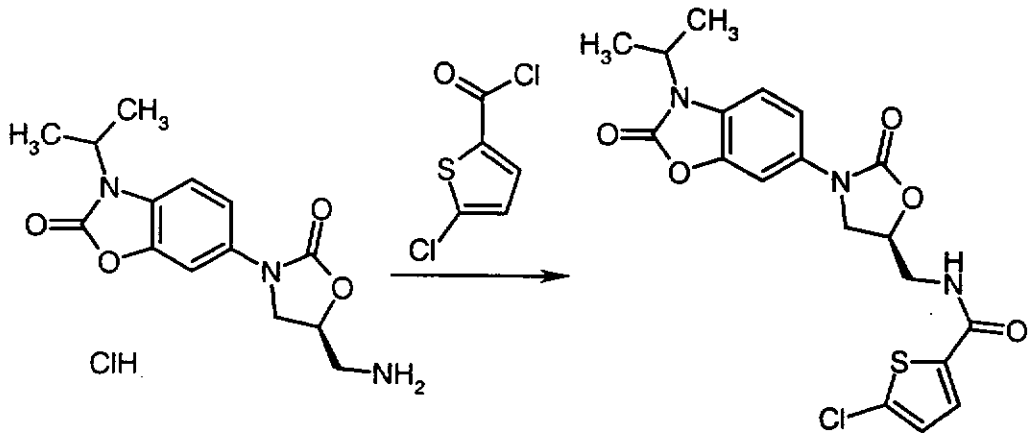
MS (ESI): m/z (%) = 480 ($[M+H]^+$, 100, Br pattern);

HPLC (method 3): rt (%) = 3.87 (100).

IC_{50}: 0.3 nM

Example 47

5-Chloro-N-{[(5S)-3-(3-isopropyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

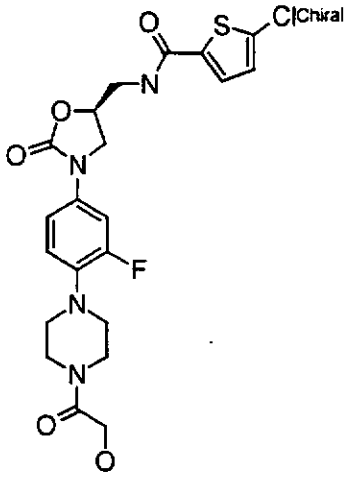
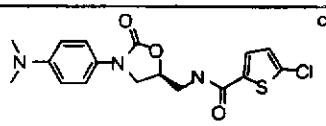
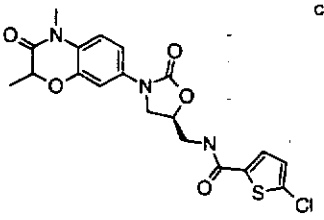
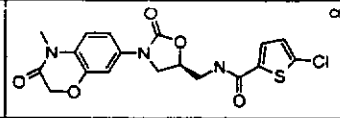
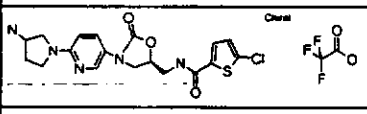
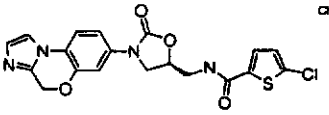


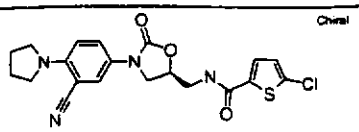
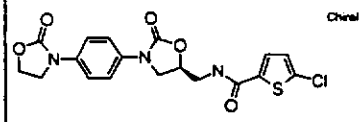
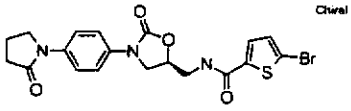
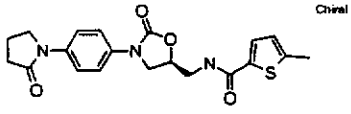
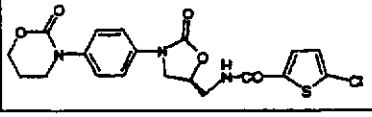
200 mg (0.61 mmol) of 6-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-3-isopropyl-1,3-benzoxazol-2(3H)-one hydrochloride (EP 738726) are suspended in 5 ml of tetrahydrofuran and admixed with 0.26 ml (1.83 mmol) of triethylamine and 132 mg (0.73 mmol) of 5-chlorothiophene-2-carbonyl chloride. The reaction mixture is stirred at room temperature overnight and then concentrated. The product is isolated by column chromatography (silica gel, methylene chloride/ethanol = 50/1 to 20/1). This gives 115 mg (43% of theory) of the desired compound.

MS (ESI): m/z (%) = 436 (M+H, 100);

HPLC (method 4): rt = 3.78 min.

The following compounds were prepared in an analogous manner:

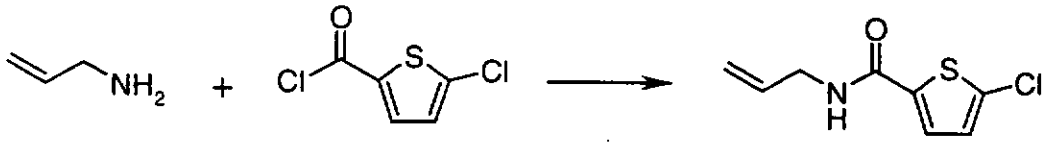
Example No.	Structure	M.p. [°C]	IC_{50} [μM]
48		210	0.12
49		234	0.074
50		195	1.15
51		212	1.19
52		160	0.19
53		MS (ESI): m/z (%) = 431 ([M+H]$^+$, 100), Cl pattern	0.74

Example No.	Structure	M.p. [°C]	IC_{50} [μM]
54	 from 5-amino-2-pyrrolidino-benzonitrile (Grell, W., Humaus, R.; Griss, G., Sauter, R.; Rupprecht, E. et al.; J.Med.Chem.1998, 41; 5219)	221	0.13
55	 from 3-(4-amino-phenyl)-oxazolidin-2-one (Artico, M. et al.; Farmaco Ed.Sci. 1969, 24; 179)	256	0.04
56		218	0.004
57		226	0.58
58		228-230	

Examples 20 to 30 and 58 to 139 below refer to process variant [B], and Examples 20 and 21 describe the preparation of precursors.

Example 20

Preparation of *N*-allyl-5-chloro-2-thiophenecarboxamide



An ice-cooled solution of 2.63 ml (35 mmol) of allylamine in 14.2 ml of absolute pyridine and 14.2 ml of absolute THF is admixed dropwise with 5-chloro-thiophene-2-carbonyl chloride (7.61 g, 42 mmol). Ice-cooling is removed and the mixture is stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue is admixed with water and the solid is filtered off. The crude product is purified by flash chromatography over silica gel (dichloromethane).

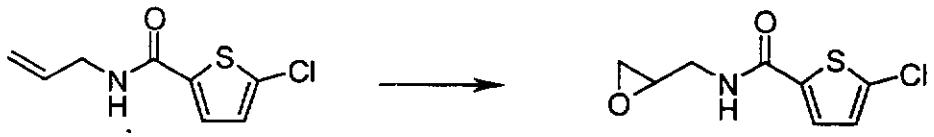
Yield: 7.20 g (99% of theory);

MS (DCI, NH_4): m/z (%) = 219 ($M+NH_4$, 100), 202 (M+H, 32);

HPLC (method 1): rt (%) = 3.96 min (98.9).

Example 21

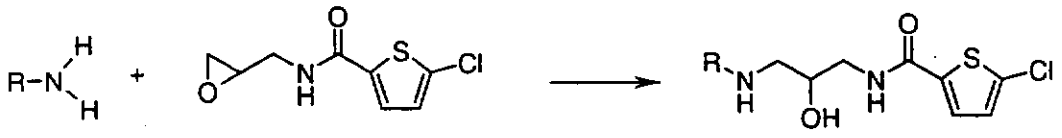
Preparation of 5-chloro-*N*-(2-oxiranylmethyl)-2-thiophenecarboxamide



An ice-cooled solution of 2.0 g (9.92 mmol) of *N*-allyl-5-chloro-2-thiophenecarboxamide in 10 ml of dichloromethane is admixed with meta-chloroperbenzoic acid (3.83 g, about 60% strength). The mixture is stirred overnight, during which it is allowed to warm to room temperature, and is then washed with 10% sodium hydrogen sulphate solution (three times). The organic phase is washed with saturated sodium bicarbonate solution (twice) and with saturated sodium

chloride solution, dried over magnesium sulphate and concentrated. The product is purified by silica gel chromatography (cyclohexane/ethyl acetate 1:1).
Yield: 837 mg (39% of theory);
MS (DCI, NH_4): m/z (%) =253 ($M+NH_4$, 100), 218 (M+H, 80);
HPLC (method 1): rt (%) = 3.69 min (about 80).

General method for preparing substituted *N*-(3-amino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide derivatives starting from 5-chloro-*N*-(2-oxiranylmethyl)-2-thiophenecarboxamide



At room temperature or at temperatures up to 80°C, 5-chloro-*N*-(2-oxiranylmethyl)-2-thiophenecarboxamide (1.0 eq.) is added a little at a time to a solution of the primary amine or aniline derivative (1.5 to 2.5 eq.) in 1,4-dioxane, 1,4-dioxane/water mixtures or ethanol, ethanol/water mixtures (about 0.3 to 1.0 mol/l). The mixture is stirred for 2 to 6 hours and then concentrated. From the reaction mixture, the product can be isolated by silica gel chromatography (cyclohexane/ethyl acetate mixtures, dichloromethane/methanol mixtures or dichloromethane/methanol/triethylamine mixtures).

The following compounds were prepared in an analogous manner:

Example 22

***N*-[3-(Benzylamino)-2-hydroxypropyl]-5-chloro-2-thiophenecarboxamide**
MS (ESI): m/z (%) = 325 (M+H, 100);
HPLC (method 1): rt (%) = 3.87 min (97.9).

Example 23

5-Chloro-*N*-[3-(3-cyanoanilino)-2-hydroxypropyl]-2-thiophenecarboxamide
MS (ESI): m/z (%) = 336 (M+H, 100);
HPLC (method 2): rt (%) = 4.04 min (100).

Example 24

5-Chloro-*N*-[3-(4-cyanoanilino)-2-hydroxypropyl]-2-thiophenecarboxamide
MS (ESI): m/z (%) = 336 (M+H, 100);
HPLC (method 1): rt (%) = 4.12 min (100).

Example 25

5-Chloro-N-{3-[4-(cyanomethyl)anilino]-2-hydroxypropyl}-2-thiophenecarboxamide
MS (ESI): m/z (%) = 350 (M+H, 100);
HPLC (method 4): rt (%) = 3.60 min (95.4).

Example 26

5-Chloro-N-{3-[3-(cyanomethyl)anilino]-2-hydroxypropyl}-2-thiophenecarboxamide
MS (ESI): m/z (%) = 350 (M+H, 100);
HPLC (method 4): rt (%) = 3.76 min (94.2).

Example 58

***tert*-Butyl 4-[(3-{[(5-chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]-benzylcarbamate**

starting from *tert*-butyl 4-aminobenzylcarbamate (*Bioorg. Med. Chem. Lett.*; **1997**; 1921-1926):
MS (ES-pos): m/z (%) = 440 (M+H, 100), (ES-neg): m/z (%) = 438 (M-H, 100);
HPLC (method 1): rt (%) = 4.08 (100).

Example 59

***tert*-Butyl 4-[(3-{[(5-chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]-phenyl-carbamate**

starting from *N-tert*-butyloxycarbonyl-1,4-phenylenediamine:
MS (ESI): m/z (%) = 426 (M+H, 45), 370 (100);

HPLC (method 1): rt (%) = 4.06 (100).

Example 60

***tert*-Butyl 2-hydroxy-3-{[4-(2-oxo-1-pyrrolidinyl)phenyl]amino}propyl-carbamate**

starting from 1-(4-aminophenyl)-2-pyrrolidinone (*Justus Liebigs Ann. Chem.*; **1955**; *596*; 204):
MS (DCI, NH_3): m/z (%) = 350 (M+H, 100);
HPLC (method 1): rt (%) = 3.57 (97).

Example 61

5-Chloro-N-(3-{[3-fluoro-4-(3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

800 mg (3.8 mmol) of 4-(4-amino-2-fluorophenyl)-3-morpholinone and 700 mg (3.22 mmol) of 5-chloro-N-(2-oxiranylmethyl)-2-thiophenecarboxamide in 15 ml of ethanol and 1 ml of water are heated under reflux for 6 hours. The mixture is concentrated under reduced pressure and treated with ethyl acetate, precipitated crystals are filtered off with suction and the mother liquor is chromatographed giving 276 mg (17% of theory) of the target compound.
R_f (ethyl acetate): 0.25.

Example 62

(*N*-(3-Anilino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide
starting from aniline:
MS (DCI, NH_3): m/z (%) = 311 ($[M+H]^+$, 100), Cl pattern;
HPLC (method 3): rt (%) = 3.79 (100).

Example 63

5-Chloro-*N*-(2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)phenyl]amino}propyl)-2-thiophenecarboxamide

starting from 4-(4-aminophenyl)-3-morpholinone:
MS (ESI): m/z (%) = 410 ($[M+H]^+$, 50), Cl pattern;
HPLC (method 3): rt (%) = 3.58 (100).

Example 64

***N*-[3-({4-[Acetyl(cyclopropyl)amino]phenyl}amino)-2-hydroxypropyl]-5-chloro-2-thiophenecarboxamide**
starting from *N*-(4-aminophenyl)-*N*-cyclopropylacetamide:
MS (ESI): m/z (%) = 408 ($[M+H]^+$, 100), Cl pattern;
HPLC (method 3): rt (%) = 3.77 (100).

Example 65

N-[3-({4-[Acetyl(methyl)amino]phenyl}amino)-2-hydroxypropyl]-5-chloro-2-thiophenecarboxamide
starting from N-(4-aminophenyl)-N-methylacetamide:
MS (ESI): m/z (%) = 382 (M+H, 100);
HPLC (method 4): rt = 3.31 min.

Example 66

5-Chloro-N-(2-hydroxy-3-{[4-(1H-1,2,3-triazol-1-yl)phenyl]amino}propyl)-2-thiophenecarboxamide
starting from 4-(1H-1,2,3-triazol-1-yl)aniline (Bouchet et al.; J.Chem.Soc.Perkin Trans.2; 1974; 449):
MS (ESI): m/z (%) = 378 (M+H, 100);
HPLC (method 4): rt = 3.55 min.

Example 67

tert-butyl 1-{4-[(3-{[(5-chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)-amino]phenyl}-L-prolinate
MS (ESI): m/z (%) = 480 (M+H, 100);
HPLC (method 4): rt = 3.40 min.

Example 68

1-{4-[(3-{[(5-Chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]phenyl}-4-piperidinecarboxamide

MS (ESI): m/z (%) = 437 (M+H, 100);

HPLC (method 4): rt = 2.39 min.

Example 69

1-{4-[(3-{[(5-Chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)-amino]phenyl}-3-piperidinecarboxamide

MS (ESI): m/z (%) = 437 (M+H, 100);

HPLC (method 4): rt = 2.43 min.

Example 70

5-Chloro-N-(2-hydroxy-3-{[4-(4-oxo-1-piperidinyl)phenyl]amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 408 (M+H, 100);

HPLC (method 4): rt = 2.43 min.

Example 71

1-{4-[(3-{[(5-Chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)amino]phenyl}-L-prolinamide

MS (ESI): m/z (%) = 423 (M+H, 100);

HPLC (method 4): rt = 2.51 min.

Example 72

5-Chloro-N-[2-hydroxy-3-({4-[3-(hydroxymethyl)-1-piperidinyl]phenyl}-amino)propyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 424 (M+H, 100);

HPLC (method 4): rt = 2.43 min.

Example 73

5-Chloro-N-[2-hydroxy-3-({4-[2-(hydroxymethyl)-1-piperidinyl]phenyl}-amino)propyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 424 (M+H, 100);

HPLC (method 4): rt = 2.49 min.

Example 74

Ethyl 1-{4-[(3-{[(5-chloro-2-thienyl)carbonyl]amino}-2-hydroxypropyl)-amino]phenyl}-2-piperidinecarboxylate

MS (ESI): m/z (%) = 466 (M+H, 100);

HPLC (method 4): rt = 3.02 min.

Example 75

5-Chloro-N-[2-hydroxy-3-({4-[2-(hydroxymethyl)-1-pyrrolidinyl]phenyl}amino)-propyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 410 (M+H, 100);

HPLC (method 4): rt = 2.48 min.

Example 76

5-Chloro-N-(2-hydroxy-3-{[4-(2-methylhexahydro-5H-pyrrolo[3,4-d]isoxazol-5-yl)phenyl]amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 437 (M+H, 100).

HPLC (method 5): rt = 1.74 min.

Example 77

5-Chloro-N-(2-hydroxy-3-{[4-(1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 448 (M+H, 100);

HPLC (method 4): rt = 3.30 min.

Example 78

5-Chloro-N-(2-hydroxy-3-{[4-(2-oxo-1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-amino}propyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 462 (M+H, 100);
HPLC (method 4): rt = 3.50 min.

Example 79

5-Chloro-N-(3-{[3-chloro-4-(3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxy-propyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 444 (M+H, 100);
HPLC (method 4): rt = 3.26 min.

Example 80

5-Chloro-N-(2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-3-(trifluoromethyl)phenyl]-amino}propyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 478 (M+H, 100);
HPLC (method 4): rt = 3.37 min.

Example 81

5-Chloro-N-(2-hydroxy-3-{[3-methyl-4-(3-oxo-4-morpholinyl)phenyl]amino}-propyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 424 (M+H, 100);
HPLC (method 4): rt = 2.86 min.

Example 82

5-Chloro-N-(3-{[3-cyano-4-(3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypro-pyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 435 (M+H, 100);
HPLC (method 4): rt = 3.10 min.

Example 83

5-Chloro-N-(3-{[3-chloro-4-(1-pyrrolidinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 414 (M+H, 100);

HPLC (method 4): rt = 2.49 min.

Example 84

5-Chloro-N-(3-{[3-chloro-4-(2-oxo-1-pyrrolidinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 428 (M+H, 100);

HPLC (method 4): rt = 3.39 min.

Example 85

5-Chloro-N-(3-{[3,5-dimethyl-4-(3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 438 (M+H, 100);

HPLC (method 4): rt = 2.84 min.

Example 86

N-(3-{[3-(Aminocarbonyl)-4-(4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 439 (M+H, 100);

HPLC (method 4): rt = 2.32 min.

Example 87

5-Chloro-N-(2-hydroxy-3-{[3-methoxy-4-(4-morpholinyl)phenyl]amino}propyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 426 (M+H, 100);

HPLC (method 4): rt = 2.32 min.

Example 88

N-(3-{[3-Acetyl-4-(4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 438 (M+H, 100);
HPLC (method 4): rt = 2.46 min.

Example 89

N-(3-{[3-Amino-4-(3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 425 (M+H, 100);
HPLC (method 4): rt = 2.45 min.

Example 90

5-Chloro-N-(3-{[3-chloro-4-(2-methyl-3-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 458 (M+H, 100);
HPLC (method 4): rt = 3.44 min.

Example 91

5-Chloro-N-(3-{[3-chloro-4-(2-methyl-5-oxo-4-morpholinyl)phenyl]amino}-2-hydroxypropyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 458 (M+H, 100);
HPLC (method 4): rt = 3.48 min.

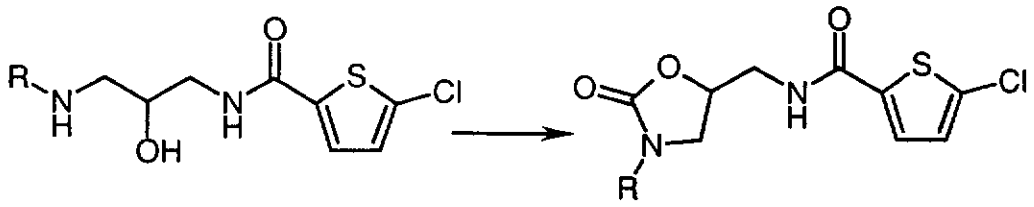
Example 91a

5-Chloro-N-[2-hydroxy-3-({4-[(3-oxo-4-morpholinyl)methyl]phenyl}amino)-propyl]-2-thiophenecarboxamide

starting from 4-(4-amino-benzyl)-3-morpholinone (Surrey et al.; J. Amer. Chem. Soc.; 77; 1955; 633):
MS (ESI): m/z (%) = 424 (M+H, 100);

HPLC (method 4): rt = 2.66 min.

General method for preparing 3-substituted 5-chloro-*N*-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide derivatives starting from substituted *N*-(3-amino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide derivatives



At room temperature, carbodiimidazole (1.2 to 1.8 eq.) or a similar phosgene equivalent are added to a solution of the substituted *N*-(3-amino-2-hydroxypropyl)-5-chloro-2-thiophenecarboxamide derivative (1.0 eq.) in absolute THF (about 0.1 mol/l). At room temperature or, if appropriate, at elevated temperature (up to 70°C), the mixture is stirred for 2 to 18 h and then concentrated under reduced pressure. The product can be purified by silica gel chromatography (dichloromethane/methanol mixtures or cyclohexane/ethyl acetate mixtures).

The following compounds were prepared in an analogous manner:

Example 27

***N*-[(3-Benzyl-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide**

MS (DCI, NH_4): m/z (%) = 372 (M+Na, 100), 351 (M+H, 45);
HPLC (method 1): rt (%) = 4.33 min (100).

Example 28

5-Chloro-*N*-{[3-(3-cyanophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

MS (DCI, NH_4): m/z (%) = 362 (M+H, 42), 145 (100);
HPLC (method 2): rt (%) = 4.13 min (100).

Example 29

5-Chloro-N-({3-[4-(cyanomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 376 (M+H, 100);
HPLC (method 4): rt = 4.12 min

Example 30

5-Chloro-N-({3-[3-(cyanomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 376 (M+H, 100);
HPLC (method 4): rt = 4.17 min

Example 92

***tert*-Butyl 4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]benzylcarbamate**

starting from Example 58:
MS (ESI): m/z (%) = 488 (M+Na, 23), 349 (100);
HPLC (method 1): rt (%) = 4.51 (98.5).

Example 93

***tert*-Butyl 4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenylcarbamate**

starting from Example 59:
MS (ESI): m/z (%) = 493 (M+Na, 70), 452 (M+H, 10), 395 (100);
HPLC (method 1): rt (%) = 4.41 (100).

Example 94

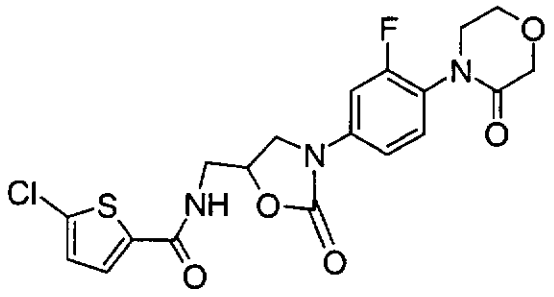
***tert*-Butyl 2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methylcarbamate**

starting from Example 60:
MS (DCI, NH_3): m/z (%) = 393 ($M+NH_4$, 100);

HPLC (method 3): rt (%) = 3.97 (100).

Example 95

5-Chloro-N-({3-[3-fluoro-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



260 mg (0.608 mmol) of 5-chloro-N-(3-{[3-fluoro-4-(3-oxo-4-morpholinyl)phenyl]-amino}-2-hydroxypropyl)-2-thiophenecarboxamide (from Example 61), 197 mg (1.22 mmol) of carbonylimidazole and 7 mg of dimethylaminopyridine in 20 ml of dioxane are boiled under reflux for 5 hours. 20 ml of acetonitrile are then added, and the mixture is stirred in a closed vessel in a microwave oven at 180°C for 30 minutes. The solution is concentrated using a rotary evaporator and chromatographed on an RP-HPLC column. This gives 53 mg (19% of theory) of the target compound.

NMR (300 MHz, d_6-DMSO): δ= 3.6-3.7 (m,4H), 3.85 (dd,1H), 3.95 (m,2H), 4.2 (m,1H), 4.21 (s,2H), 4.85 (m,1H), 4.18 (s,2H), 7.19 (d,1H,thiophene), 7.35 (dd,1H), 7.45 (t,1H), 7.55 (dd,1H), 7.67 (d,1H,thiophene), 8.95 (t,1H,CONH).

Example 96

5-Chloro-*N*-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

starting from Example 62:

MS (ESI): m/z (%) = 359 ($[M+Na]^+$, 71), 337 ($[M+H]^+$, 100), Cl pattern;

HPLC (method 3): rt (%) = 4.39 (100).

IC_{50}: 2 μM

Example 97

5-Chloro-*N*-({2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

starting from Example 63:

MS (ESI): m/z (%) = 458 ($[M+Na]^+$, 66), 436 ($[M+H]^+$, 100), Cl pattern;

HPLC (method 3): rt (%) = 3.89 (100).

IC_{50}: 1.4 nM

Example 98

***N*-[(3-{4-[Acetyl(cyclopropyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide**

starting from Example 64:

MS (ESI): m/z (%) = 456 ($[M+Na]^+$, 55), 434 ($[M+H]^+$, 100), Cl pattern;

HPLC (method 3): rt (%) = 4.05 (100).

IC_{50}: 50 nM

Example 99

N-[(3-{4-[Acetyl(methyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 408 (M+H, 30), 449 (M+H+MeCN, 100);

HPLC (method 4): rt = 3.66 min.

Example 100

5-Chloro-N-({2-oxo-3-[4-(1H-1,2,3-triazol-1-yl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 404 (M+H, 45), 445 (M+H+MeCN, 100);

HPLC (method 4): rt = 3.77 min.

Example 101

Tert-butyl 1-{4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-L-prolinate

MS (ESI): m/z (%) = 450 (M+H-56, 25), 506 (M+H, 100);
HPLC (method 4): rt = 5.13 min.

Example 102

1-{4-[5-({[(5-Chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-4-piperidinecarboxamide
MS (ESI): m/z (%) = 463 (M+H, 100);
HPLC (method 4): rt = 2.51 min.

Example 103

1-{4-[5-({[(5-Chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3-piperidinecarboxamide
MS (ESI): m/z (%) = 463 (M+H, 100);
HPLC (method 4): rt = 2.67 min.

Example 104

5-Chloro-N-({2-oxo-3-[4-(4-oxo-1-piperidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 434 (M+H, 40), 452 (M+H+H_2O, 100), 475 (M+H+MeCN, 60);
HPLC (method 4): rt = 3.44 min.

Example 105

1-{4-[5-({[(5-Chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-L-prolinamide
MS (ESI): m/z (%) = 449 (M+H, 100);
HPLC (method 4): rt = 3.54 min.

Example 106

5-Chloro-N-[(3-{4-[3-(hydroxymethyl)-1-piperidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 450 (M+H, 100);

HPLC (method 5): rt = 2.53 min.

Example 107

5-Chloro-N-[(3-{4-[2-(hydroxymethyl)-1-piperidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 450 (M+H, 100);

HPLC (method 5): rt = 2.32 min.

Example 108

Ethyl 1-{4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-piperidinecarboxylate

MS (ESI): m/z (%) = 492 (M+H, 100);

HPLC (method 5): rt = 4.35 min.

Example 109

5-Chloro-N-[(3-{4-[2-(hydroxymethyl)-1-pyrrolidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 436 (M+H, 100);

HPLC (method 4): rt = 2.98 min.

Example 110

5-Chloro-N-({2-oxo-3-[4-(1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 474 (M+H, 100);

HPLC (method 4): rt = 4.63 min.

Example 111

5-Chloro-N-({3-[4-(2-methylhexahydro-5H-pyrrolo[3,4-d]isoxazol-5-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 463 (M+H, 100);

HPLC (method 4): rt = 2.56 min.

Example 112

5-Chloro-N-({2-oxo-3-[4-(2-oxo-1-pyrrolidinyl)-3-(trifluoromethyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 488 (M+H, 100);

HPLC (method 4): rt = 3.64 min.

Example 113

5-Chloro-N-({3-[3-chloro-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 470 (M+H, 100);

HPLC (method 4): rt = 3.41 min.

Example 114

5-Chloro-N-({2-oxo-3-[4-(3-oxo-4-morpholinyl)-3-(trifluoromethyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 504 (M+H, 100);

HPLC (method 4): rt = 3.55 min.

Example 115

5-Chloro-N-({3-[3-methyl-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 450 (M+H, 100);

HPLC (method 4): rt = 3.23 min.

Example 116

5-Chloro-N-({3-[3-cyano-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 461 (M+H, 100);

HPLC (method 4): rt = 3.27 min.

Example 117

5-Chloro-N-({3-[3-chloro-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 440 (M+H, 100);

HPLC (method 4): rt = 3.72 min.

Example 118

5-Chloro-N-({3-[3-chloro-4-(2-oxo-1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 454 (M+H, 100);

HPLC (method 4): rt = 3.49 min.

Example 119

5-Chloro-N-({3-[3,5-dimethyl-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 464 (M+H, 100);

HPLC (method 4): rt = 3.39 min.

Example 120

N-({3-[3-(Aminocarbonyl)-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 465 (M+H, 100);

HPLC (method 4): rt = 3.07 min.

Example 121

5-Chloro-N-({3-[3-methoxy-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 452 (M+H, 100);

HPLC (method 4): rt = 2.86 min.

Example 122

N-({3-[3-Acetyl-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 464 (M+H, 100);

HPLC (method 4): rt = 3.52 min.

Example 123

N-({3-[3-Amino-4-(3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 451 (M+H, 100);

HPLC (method 6): rt = 3.16 min.

Example 124

5-Chloro-N-({3-[3-chloro-4-(2-methyl-3-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 484 (M+H, 100);

HPLC (method 4): rt = 3.59 min.

Example 125

5-Chloro-N-({3-[3-chloro-4-(2-methyl-5-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 484 (M+H, 100);

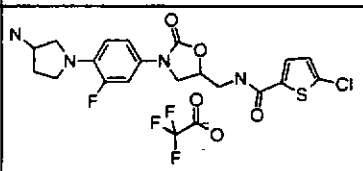
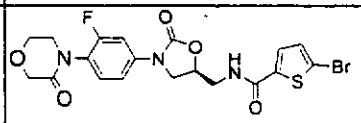
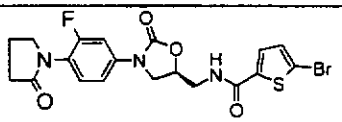
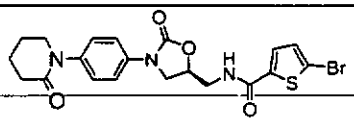
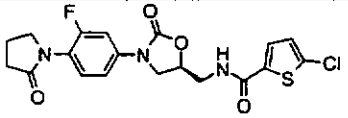
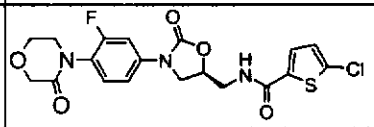
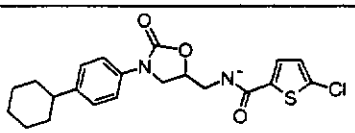
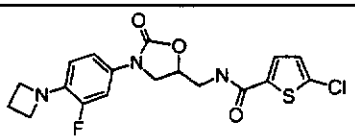
HPLC (method 4): rt = 3.63 min.

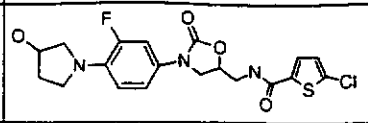
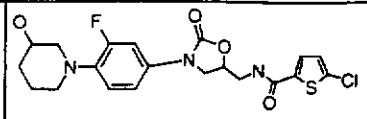
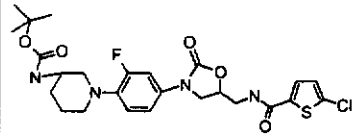
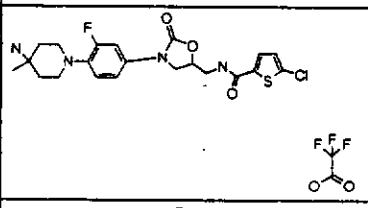
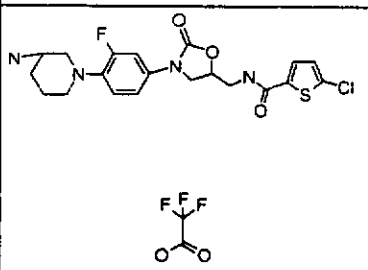
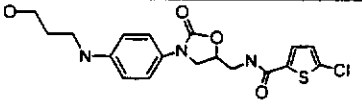
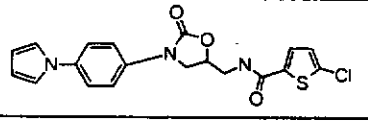
Example 125a

5-Chloro-N-[(2-oxo-3-{4-[(3-oxo-4-morpholinyl)methyl]phenyl}-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 450 (M+H, 100);
HPLC (method 4): rt = 3.25 min.

Via epoxide opening with an amine and subsequent cyclization to give the corresponding oxazolidinone, it was also possible to prepare the following compounds:

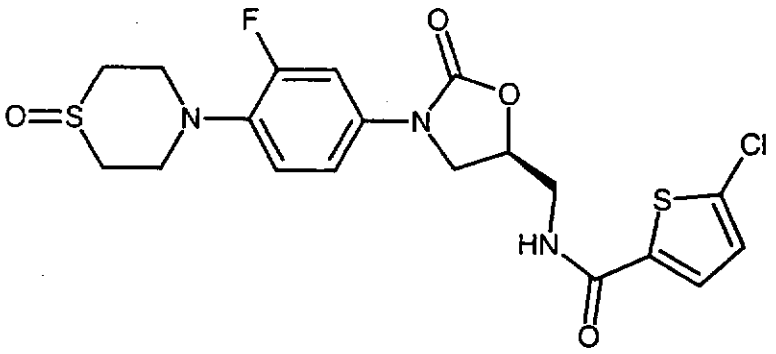
Example No.	Structure	M.p. [°C]	IC_{50} [μM]
126		229Z	0.013
127		159	0.0007
		198	0.002
129		196	0.001
130		206	0.0033
130a		194	
131		195	0.85
132		206	0.12

Example No.	Structure	M.p. [°C]	IC_{50} [μM]
133		217	0.062
134	 from 1-(4-amino-phenyl)-piperidin-3-ol (Tong, L.K.J. et al.; J.Amer.Chem.Soc 1960; 82, 1988).	207	0.48
135		202	1.1
136		239	1.2
137		219	0.044
138		95	0.42
139		217	1.7

Examples 14 to 16 below are working examples for the optional oxidation step.

Example 14

5-Chloro-N-({(5S)-3-[3-fluoro-4-(1-oxo-1[lambda]^4,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



At 0°C, 5-chloro-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (0.1 g, 0.22 mmol) from Example 3 in methanol (0.77 ml) is added to a solution of sodium periodate (0.05 g, 0.23 mmol) in water (0.54 ml), and the mixture is stirred at 0°C for 3 h. 1 ml of DMF is then added, and the mixture is stirred at RT for 8 h. After addition of a further 50 mg of sodium periodate, the mixture is once more stirred at RT overnight. The mixture is then admixed with 50 ml of water, and the insoluble product is filtered off with suction. Washing with water and drying gives 60 mg (58% of theory) of crystals.

M.p.: 257°C;

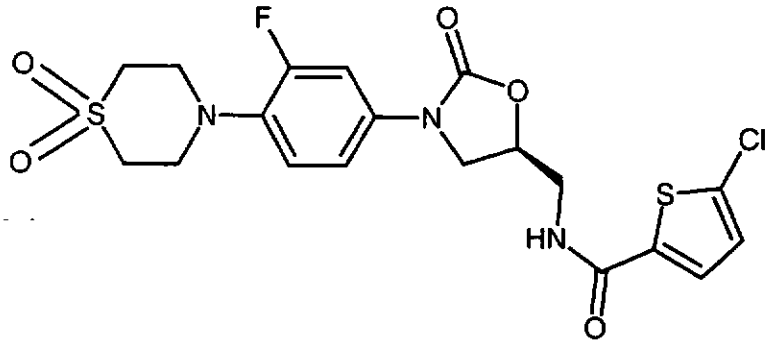
R_f (silica gel, toluene/ethyl acetate 1:1) = 0.54 (starting material = 0.46);

IC_{50} value = 1.1 μM;

MS (DCI) 489 ($M+NH_4$), Cl pattern.

Example 15

Preparation of 5-chloro-N-({(5S)-3-[4-(1,1-dioxo-1[lambda]^6,4-thiazinan-4-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



5-Chloro-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide from Example 3 (0.1 g, 0.22 mmol) in 3.32 ml of a mixture of 1 part of water and 3 parts of acetone is admixed with 80 mg (0.66 mmol) of N-methylmorpholine N-oxide (NMO) and 0.1 ml of a 2.5% strength solution of osmium tetroxide in 2-methyl-2-propanol. The mixture is stirred at room temperature overnight, and another 40 mg of NMO are added. The mixture is stirred for a further night and then poured into 50 ml of water and extracted three times with ethyl acetate. The organic phase gives, after drying and concentrating, 23 mg and the aqueous phase, after removal of the insoluble solid by filtration with suction, 19 mg (in total 39% of theory) of the target compound.

M.p.: 238°C;

R_f (toluene/ethyl acetate 1:1) = 0.14 (starting material = 0.46);

IC_{50} value = 210 nM;

MS (DCI): 505 ($M+NH_4$), Cl pattern.

Example 16

5-Chloro-N-{[(5S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide N-oxide

is obtained by treating 5-chloro-N-{[(5S)-3-(3-fluoro-4-morpholinophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide from Example 1 with the magnesium salt of monoperoxyphthalic acid.

MS (ESI): 456 (M+H, 21%, Cl pattern), 439 (100%).

The Examples 31 to 35 and 140 to 147 below refer to the optional amidination step.

General method for preparing amidines and amidine derivatives starting from cyanomethylphenyl-substituted 5-chloro-N-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide derivatives

The cyanomethylphenyl-substituted 5-chloro-N-[(2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide derivative in question (1.0 eq.) is, together with triethylamine (8.0 eq.), stirred at RT in a saturated solution of hydrogen sulphide in pyridine (about 0.05 – 0.1 mol/l) for one to two days. The reaction mixture is diluted with ethyl acetate (EtOAc) and washed with 2 N hydrochloric acid. The organic phase is dried with $MgSO_4$, filtered and concentrated under reduced pressure.

The crude product is dissolved in acetone (0.01-0.1 mol/l) and admixed with methyl iodide (40 eq.). The reaction mixture is stirred at room temperature (RT) for 2 to 5 h and then concentrated under reduced pressure.

The residue is dissolved in methanol (0.01-0.1 mol/l) and, to prepare the unsubstituted amidines, admixed with ammonium acetate (3 eq.) and ammonium chloride (2 eq.). To prepare the substituted amidine derivatives, primary or secondary amines (1.5 eq.) and acetic acid (2 eq.) are added to the methanolic solution. After 5-30 h, the solvent is removed under reduced pressure and the residue is purified by chromatography over an RP8 silica gel column (water/acetonitrile 9/1-1/1 + 0.1% trifluoroacetic acid).

The following compounds were prepared in an analogous manner:

Example 31:

N-({3-[4-(2-Amino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 393 (M+H, 100);

HPLC (method 4): rt = 2.63 min

Example 32:

5-Chloro-N-({3-[3-(4,5-dihydro-1H-imidazol-2-ylmethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 419 (M+H, 100);

HPLC (method 4): rt = 2.61 min

Example 33:

5-Chloro-N-[(3-{3-[2-imino-2-(4-morpholinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 463 (M+H, 100);

HPLC (method 4): rt = 2.70 min

Example 34:

5-Chloro-N-[(3-{3-[2-imino-2-(1-pyrrolidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 447 (M+H, 100);

HPLC (method 4): rt = 2.82 min

Example 35:

N-({3-[3-(2-Amino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 393 (M+H, 100);

HPLC (method 4): rt = 2.60 min

Example 140

5-Chloro-N-({3-[4-(4,5-dihydro-1H-imidazol-2-ylmethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 419 (M+H, 100);

HPLC (method 4): rt = 2.65 min

Example 141

5-Chloro-N-[(3-{4-[2-imino-2-(4-morpholinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 463 (M+H, 100);

HPLC (method 4): rt = 2.65 min

Example 142

5-Chloro-N-[(3-{4-[2-imino-2-(1-piperidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 461 (M+H, 100);

HPLC (method 4): rt = 2.83 min

Example 143

5-Chloro-N-[(3-{4-[2-imino-2-(1-pyrrolidinyl)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 447 (M+H, 100);

HPLC (method 4): rt = 2.76 min

Example 144

5-Chloro-N-[(3-{4-[2-(cyclopentylamino)-2-iminoethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 461 (M+H, 100);

HPLC (method 4): rt = 2.89 min

Example 145

5-Chloro-N-{[3-(4-{2-imino-2-[(2,2,2-trifluoroethyl)amino]ethyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide

MS (ESI): m/z (%) = 475 (M+H, 100);

HPLC (method 4): rt = 2.79 min

Example 146

N-({3-[4-(2-Anilino-2-iminoethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

MS (ESI): m/z (%) = 469 (M+H, 100);
HPLC (method 4): rt = 2.83 min

Example 147

5-Chloro-N-[(3-{4-[2-imino-2-(2-pyridinylamino)ethyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide

MS (ESI): m/z (%) = 470 (M+H, 100);
HPLC (method 4): rt = 2.84 min

Examples 148 to 151 below refer to the removal of BOC amino protective groups:

General method for removing Boc protective groups (*tert*-butyloxycarbonyl):



Aqueous trifluoroacetic acid (TFA, about 90%) is added dropwise to an ice-cooled solution of a *tert*-butyloxycarbonyl-(Boc) protected compound in chloroform or dichloromethane (about 0.1 to 0.3 mol/l). After about 15 min, ice-cooling is removed and the mixture is stirred at room temperature for approximately 2-3 h, and the solution is then concentrated and dried under high vacuum. The residue is taken up in dichloromethane or dichloromethane/methanol and washed with saturated sodium bicarbonate or 1N sodium hydroxide solution. The organic phase is washed with saturated sodium chloride solution, dried over a little magnesium sulphate and concentrated. If appropriate, purification is carried out by crystallization from ether or ether/dichloromethane mixtures.

The following compounds were prepared in an analogous manner from the corresponding Boc-protected precursors:

Example 148

***N*-({3-[4-(Aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide**

starting from Example 92:

MS (ESI): m/z (%) = 349 ($M-NH_2$, 25), 305 (100);

HPLC (method 1): rt (%) = 3.68 (98).

IC_{50}: 2.2 μM

Example 149

***N*-{[3-(4-Aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide**

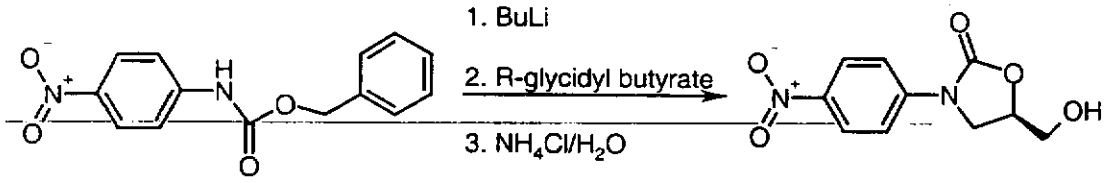
starting from Example 93:

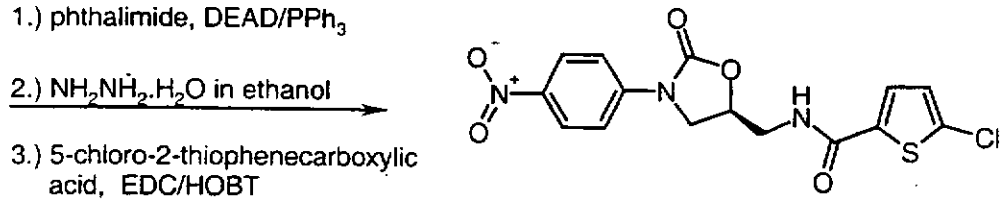
MS (ESI): m/z (%) = 352 (M+H, 25);

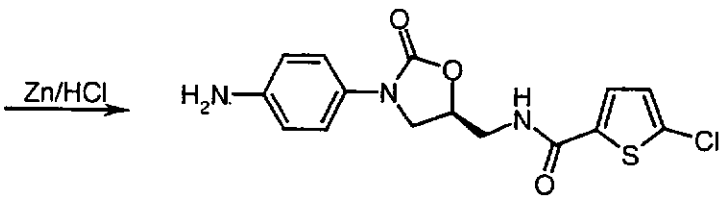
HPLC (method 1): rt (%) = 3.50 (100).

IC_{50}: 2 μM

An alternative enantiomerically pure synthesis of this compound is shown in the scheme below (cf. also Delalande S.A., DE 2836305,1979; Chem.Abstr. 90, 186926):







Example 150

5-Chloro-*N*-({3-[4-(glycylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

starting from Example 152:

MS (ES-pos): m/z (%) = 408 (100);

HPLC (method 3): rt (%) = 3.56 (97).

IC_{50}: 2 μM

Example 151

5-(Aminomethyl)-3-[4-(2-oxo-1-pyrrolidinyl)phenyl]-1,3-oxazolidin-2-one

starting from Example 60:

MS (ESI): m/z (%) = 276 (M+H, 100);

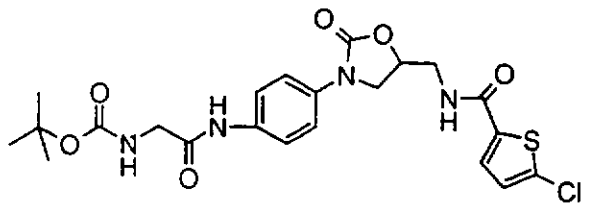
HPLC (method 3): rt (%) = 2.99 (100).

IC_{50}: 2 μM

The Examples 152 to 166 below refer to the amino group derivatization of aniline- or benzylamine-substituted oxazolidinones using various reagents:

Example 152

5-Chloro-*N*-({3-[4-(N-*tert*-butyloxycarbonyl-glycylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

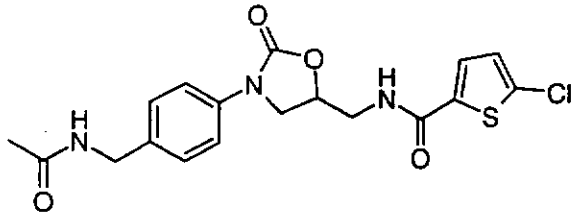


At 0°C, 754 mg (2.1 mmol) of *N*-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide (from Example 149) are added to a solution of 751 mg (4.3 mmol) of Boc-glycine, 870 mg (6.4 mmol) of HOBT (1-hydroxy-1H-benzotriazole x H_2O), 1790 mg (4.7 mmol) of HBTU [O-(benzotriazol-1-yl)-N,N,N´,N´-tetramethyluronium hexafluorophosphate] and 1.41 ml (12.9 mmol) of *N*-methylmorpholine in 15 ml of DMF/CH_2Cl_2 (1:1). The

mixture is stirred at room temperature overnight and then diluted with water. The precipitated solid is filtered off and dried. Yield: 894 mg (79.7% of theory);
MS (DCI, NH_3): m/z (%) = 526 ($M+NH_4$, 100);
HPLC (method 3): rt (%) = 4.17 (97).

Example 153

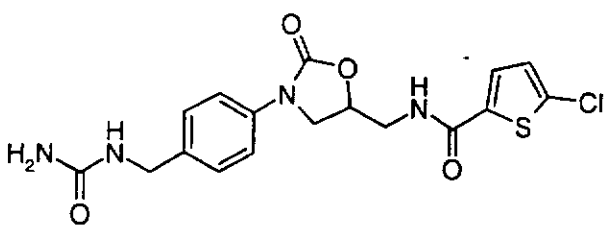
***N*-[(3-{4-[(Acetylamino)methyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide**



At 0°C, a mixture of 30 mg (0.082 mmol) of *N*-({3-[4-(aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide (from Example 148) in 1.5 ml of absolute THF and 1.0 ml of absolute dichloromethane, and 0.02 ml of absolute pyridine is mixed with acetic anhydride (0.015 ml, 0.164 mmol). The mixture is stirred at room temperature overnight. Addition of ether and crystallization affords the product. Yield: 30 mg (87% of theory),
MS (ESI): m/z (%) = 408 (M+H, 18), 305 (85);
HPLC (method 1): rt (%) = 3.78 (97).
IC_{50}: 0.6 μM

Example 154

***N*-{[3-(4-{[(Aminocarbonyl)amino]methyl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl}-5-chloro-2-thiophenecarboxamide**



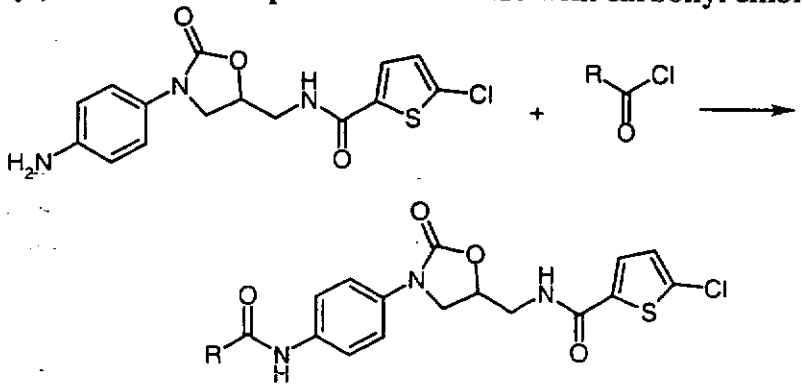
At room temperature, 0.19 ml (0.82 mmol) of trimethylsilylisocyanate are added dropwise to a mixture of 30 mg (0.082 mmol) of *N*-({3-[4-(aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide (from Example 148) in 1.0 ml of dichloromethane. The mixture is stirred overnight and, after addition of ether, the product is then obtained by filtration. Yield: 21.1 mg (52% of theory),

MS (ESI): m/z (%) = 409 (M+H, 5), 305 (72);

HPLC (method 1): rt (%) = 3.67 (83).

IC_{50}: 1.3 μM

General method for acylating *N*-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide with carbonyl chlorides:



Under argon, an approximately 0.1 molar solution of *N*-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide (from Example 149) (1.0 eq.) in absolute dichloromethane/pyridine (19:1) is added dropwise to the appropriate acid chloride (2.5 eq.). The mixture is stirred overnight and then admixed with about 5 eq. of PS trisamine (Argonaut Technologies) and 2 ml of absolute dichloromethane. The mixture is stirred gently for 1 h and then filtered off, and the filtrate is concentrated. If appropriate, the products are purified by preparative RP-HPLC.

The following compounds were prepared in an analogous manner:

Example 155

***N*-({3-[4-(Acetylamino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide**

LC-MS: m/z (%) = 394 (M+H, 100);

LC-MS (method 6): rt (%) = 3.25 (100).
IC_{50}: 1.2 μM

Example 156

5-Chloro-*N*-[(2-oxo-3-{4-[(2-thienylcarbonyl)amino]phenyl}-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide
LC-MS: m/z (%) = 462 (M+H, 100);
LC-MS (method 6): rt (%) = 3.87 (100).
IC_{50}: 1.3 μM

Example 157

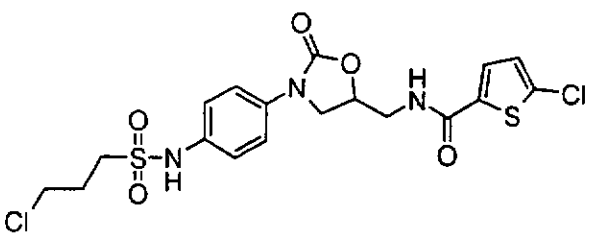
5-Chloro-*N*-[(3-{4-[(methoxyacetyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)-methyl]-2-thiophenecarboxamide
LC-MS: m/z (%) = 424 (M+H, 100);
LC-MS (method 6): rt (%) = 3.39 (100).
IC_{50}: 0.73 μM

Example 158

***N*-{4-[5-({[(5-Chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3,5-dimethyl-4-isoxazolecarboxamide**
LC-MS: m/z (%) = 475 (M+H, 100).
IC_{50}: 0.46 μM

Example 159

5-Chloro-*N*-{[3-(4-{[(3-chloropropyl)sulphonyl]amino}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



An ice-cooled solution of 26.4 mg (0.15 mmol) of 3-chloro-1-propanesulphonyl chloride and 0.03 ml (0.2 mmol) of triethylamine in 3.5 ml of absolute dichloromethane is admixed with 35 mg (0.1 mmol) of *N*-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl}-5-chloro-2-thiophene-carboxamide (from Example 149). After 30 min, ice-cooling is removed and the mixture is stirred at room temperature overnight, and 150 mg (about 5.5 eq.) of PS-trisamine (Argonaut Technologies) and 0.5 ml of dichloromethane are then added. The suspension is stirred gently for 2 h and filtered (the resin is washed with dichloromethane/methanol), and the filtrate is concentrated. The product is purified by preparative RP-HPLC. Yield: 19.6 mg (40% of theory),

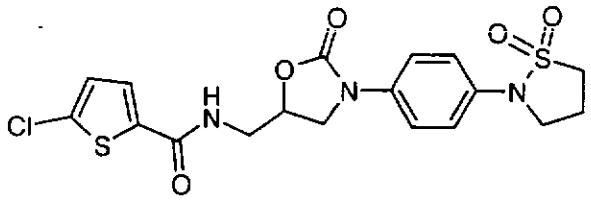
LC-MS: m/z (%) = 492 (M+H, 100);

LC-MS (method 5): rt (%) = 3.82 (91).

IC_{50}: 1.7 μM

Example 160

5-Chloro-*N*-({3-[4-(1,1-dioxido-2-isothiazolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



A mixture of 13.5 mg (0.027 mmol) of 5-chloro-*N*-{[3-(4-{[(3-chloropropyl)sulphonyl]amino}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophene-carboxamide (from Example 159) and 7.6 mg (0.055 mmol) of potassium carbonate in 0.2 ml of DMF is heated at 100°C for 2 h. After cooling, the mixture is diluted with dichloromethane and washed with water. The organic phase is dried and concentrated. The residue is purified by preparative thin-layer chromatography (silica gel, dichloromethane/methanol, 95:5). Yield: 1.8 mg (14.4% of theory),

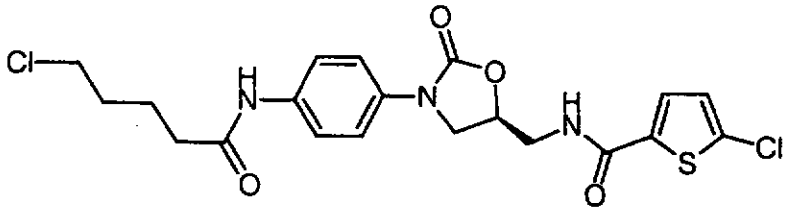
MS (ESI): m/z (%) = 456 (M+H, 15), 412 (100);

LC-MS (method 4): rt (%) = 3.81 (90).

IC_{50}: 0.14 μM

Example 161

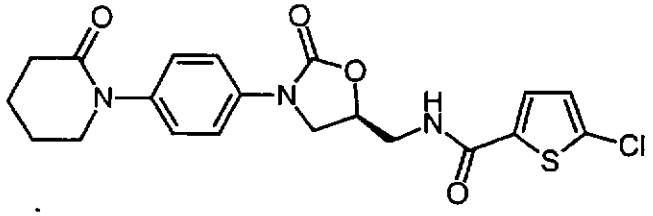
5-Chloro-N-[((5S)-3-{4-[(5-chloropentanoyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



0.5 g (1.29 mmol) of N-{[(5S)-3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide (from Example 149) is dissolved in 27 ml of tetrahydrofuran and admixed with 0.2 g (1.29 mmol) of 5-chlorovaleryl chloride and 0.395 ml (2.83 mmol) of triethylamine. The mixture is concentrated under reduced pressure and chromatographed over silica gel using a toluene/ethyl acetate=1:1 -> ethyl acetate gradient. This gives 315 mg (52% of theory) of a solid.
M.p.: 211°C.

Example 162

5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-piperidinyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide



Under inert conditions, 5 ml of DMSO are admixed with 30 mg of NaH (60% in paraffin oil), and the mixture is heated at 75°C for 30 min, until the evolution of gas has ceased. A solution of 290 mg (0.617 mmol) of 5-chloro-N-[((5S)-3-{4-[(5-chloropentanoyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide (from Example 161) in 5 ml of methylene chloride is then added dropwise, and the mixture is stirred at room temperature overnight. The reaction is terminated and the mixture is poured into 100 ml of water and extracted with ethyl

acetate. The evaporated organic phase is chromatographed on an RP-8 column and the product is eluted with acetonitrile/water. This gives 20 mg (7.5% of theory) of the target compound.

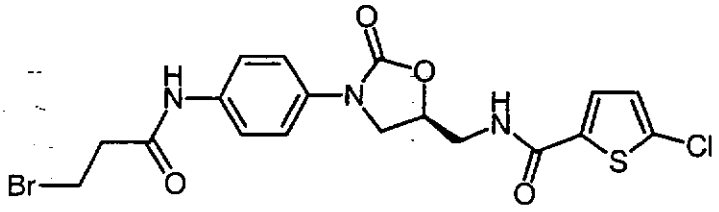
M.p.: 205°C;

NMR (300 MHz, d_6-DMSO): δ = 1.85 (m,4H), 2.35 (m,2H), 3.58 (m,4H), 3.85 (m,1H), 4.2 (t,1H), 4.82 (m,1H), 7.18 (d,1H,thiophene), 7.26 (d,2H), 7.5 (d,2H), 2.68 (d,1H,thiophene), 9.0 (t,1H,CONH).

IC_{50}: 2.8 nM

Example 163

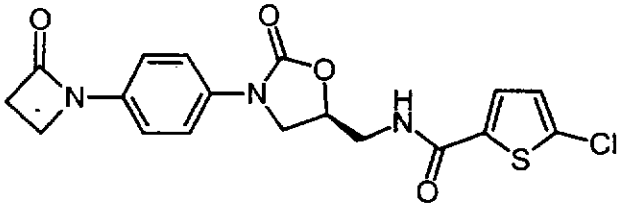
5-Chloro-N-[((5S)-3-{4-[(3-bromopropionyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



is obtained in an analogous manner from Example 149.

Example 164

5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-azetidinyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide



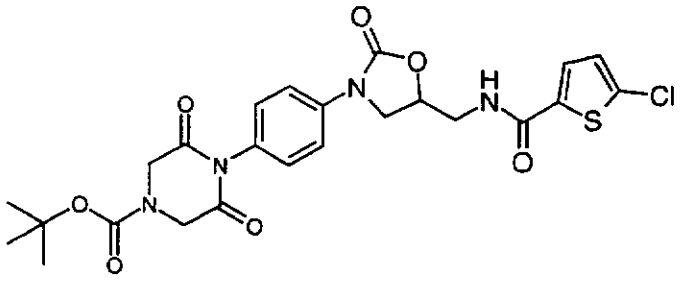
is obtained in an analogous manner by cyclization of the open-chain bromopropionyl compound from Example 163 using NaH/DMSO.

MS (ESI): m/z (%) = 406 ($[M+H]^+$, 100), Cl pattern.

IC_{50}: 380 nM

Example 165

***tert*-Butyl 4-{4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-3,5-dioxo-1-piperazinecarboxylate**



A solution of 199 mg (0.85 mmol) of Boc-iminodiacetic acid, 300 mg (2.2 mmol) of HOBT, 0.66 ml (6 mmol) of *N*-methylmorpholine and 647 mg (1.7 mmol) of HBTU is admixed with 300 mg (0.85 mmol) of *N*-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]-methyl}-5-chloro-2-thiophene-carboxamide in 6 ml of a mixture of DMF and dichloromethane (1:1). The mixture is stirred overnight, diluted with dichloromethane and then washed with water, saturated ammonium chloride solution, saturated sodium bicarbonate solution, water and saturated sodium chloride solution. The organic phase is dried over magnesium sulphate and concentrated. The crude product is purified by silica gel chromatography (dichloromethane/methanol 98:2). Yield: 134 mg (29% of theory);

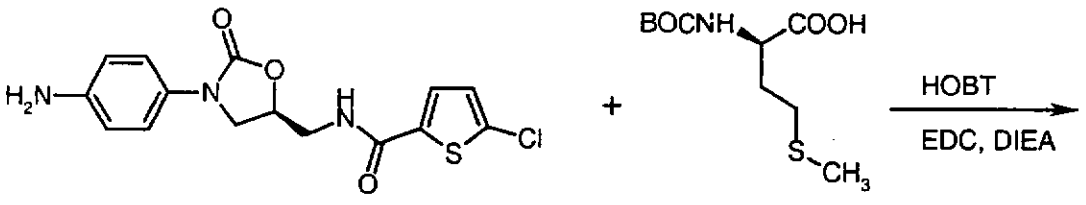
MS (ESI): m/z (%) = 571 (M+Na, 82), 493 (100);

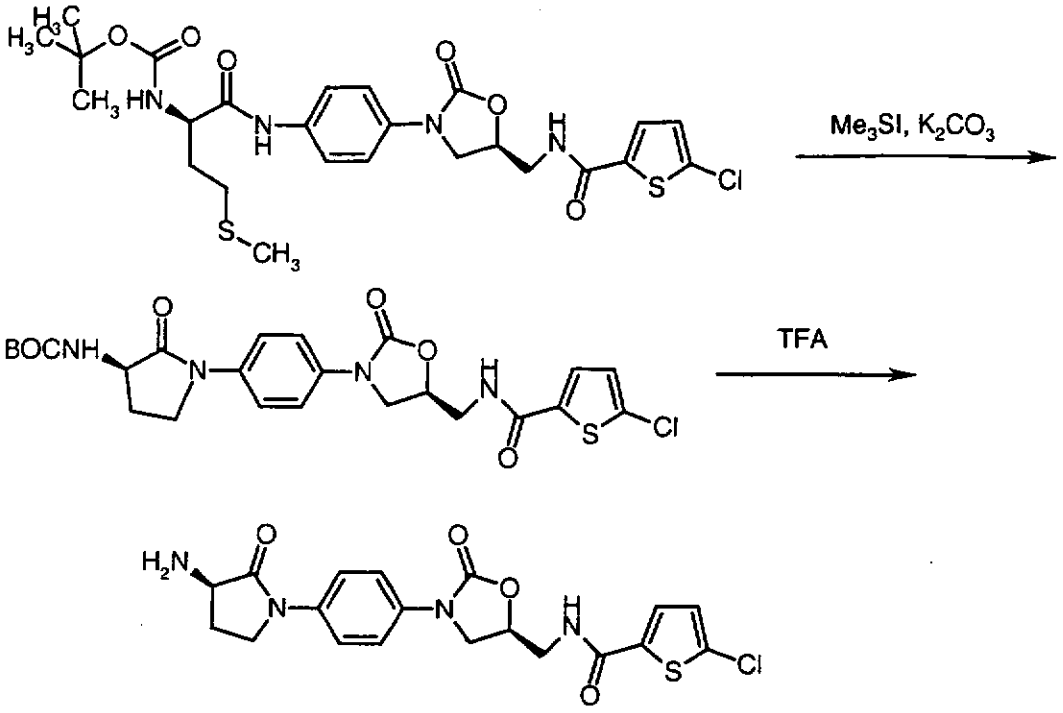
HPLC (method 3): rt (%) = 4.39 (90).

IC_{50}: 2 μM

Example 166

N-[((5S)-3-{4-[(3R)-3-Amino-2-oxo-1-pyrrolidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide trifluoroacetate





N2-(tert-Butoxycarbonyl)-N1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-D-methionineamide

429 mg (1.72 mmol) of N-BOC-D-methionine, 605 mg (1.72 mmol) of N-{[(5S)-3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide, and 527 mg (3.44 mmol) of HOBT hydrate are dissolved in 35 ml of DMF and admixed with 660 mg (3.441 mmol) of EDCI hydrochloride and then dropwise with 689 mg (5.334 mmol) of N-ethyl-diisopropylamine. The mixture is stirred at room temperature for two days. The resulting suspension is filtered off with suction and the residue is washed with DMF. The combined filtrates are admixed with a little silica gel, concentrated under reduced pressure and chromatographed over silica gel using a toluene -> T10EA7 gradient. This gives 170 mg (17% of theory) of the target compound of melting point 183°C.

R_f (SiO_2, toluene/ethyl acetate=1:1):0.2.

^{1}H-NMR (300 MHz, d_6-DMSO): δ=1.4 (s,1H,BOC), 1.88-1.95 (m,2H), 2.08 (s,3H,SMe), 2.4-2.5 (m,2H, partially obscurbed by DMSO), 3.6 (m,2H), 3.8 (m,1H), 4.15 (m,2H), 4.8 (m,1H), 7.2 (1H, thiophene), 7.42 (d, part of an AB system, 2H), 7.6 (d, part of an AB system, 2H), 7.7 (d, 1H, thiophene), 8.95 (t,1H, $CH_2N\underline{H}CO$), 9.93 (bs,1H,NH).

tert-Butyl (3R)-1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-oxo-3-pyrrolidinylcarbamate

170 mg (0.292 mmol) of N2-(tert-butoxycarbonyl)-N1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-D-methionine-amide are dissolved in 2 ml of DMSO and admixed with 178.5 mg (0.875 mmol) of trimethylsulphonium iodide and 60.4 mg (0.437 mmol) of potassium carbonate, and the mixture is stirred at 80°C for 3.5 hours. The mixture is then concentrated under high vacuum and the residue is washed with ethanol. 99 mg of the target compound remain.

^{1}H-NMR (300 MHz, d_6-DMSO): δ =1.4 (s,1H,BOC), 1.88-2.05 (m,1H), 2.3-2.4 (m,1H), 3.7-3.8 (m,3H), 3.8-3.9 (m,1H), 4.1-4.25 (m,1H), 4.25-4.45 (m,1H), 4.75-4.95 (m,1H), 7.15 (1H, thiophene), 7.25 (d,1H), 7.52 (d, part of an AB system, 2H), 7.65 (d, part of an AB system, 2H), 7.65 (d, 1H, thiophene), 9.0 (broad s,1H).

N-[((5S)-3-{4-[(3R)-3-Amino-2-oxo-1-pyrrolidinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide trifluoroacetate

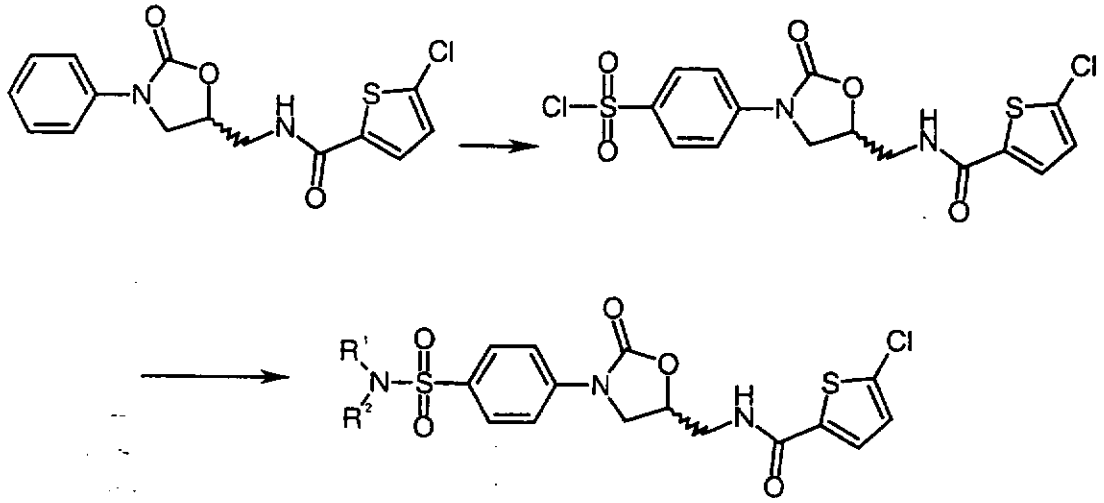
97 mg (0.181 mmol) of tert-butyl (3R)-1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-oxo-3-pyrrolidinylcarbamate are suspended in 4 ml of methylene chloride, 1.5 ml of trifluoroacetic acid are added and the mixture is stirred at room temperature for 1 hour. The mixture is then concentrated under reduced pressure and the residue is purified on an RP-HPLC (acetonitrile/water/0.1% TFA gradient). Evaporation of the appropriate fraction gives 29 mg (37% of theory) of the target compound of melting point 241°C (decomp.).

R_f (SiO_2,EtOH/TEA=17:1) 0.19.

^{1}H-NMR (300 MHz, d_6-DMSO): δ =1.92-2.2 (m,1H), 2.4-2.55 (m,1H, partially obscured by DMSO peak), 3.55-3.65 (m,2H), 3.75-3.95 (m,3H), 4.1-4.3 (m,2H), 4.75-4.9 (m,1H), 7.2 (1H, thiophene), 7.58 (d, part of an AB system, 2H), 7.7 (d, part of an AB system, 2H), 7.68 (d, 1H, thiophene), 8.4 (broad s,3H, NH3), 8.9 (t,1H,NHCO).

The Examples 167 to 170 below refer to the introduction of sulphonamide groups in phenyl-substituted oxazolidinones:

General method for preparing substituted sulphonamides starting from 5-chloro-*N*-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



Under argon and at 5°C, 5-chloro-*N*-[(2-oxo-3-phenyl-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide (from Example 96) is added to chlorosulphonic acid (12 eq.). The reaction mixture is stirred at room temperature for 2 h and then poured into ice-water. The resulting precipitate is filtered off, washed with water and dried.

Under argon and at room temperature, the precipitate is then dissolved in tetrahydrofuran (0.1 mol/l) and admixed with the appropriate amine (3 eq.), triethylamine (1.1 eq.) and dimethylaminopyridine (0.1 eq.). The reaction mixture is stirred for 1-2 h and then concentrated under reduced pressure. The desired product is purified by flash chromatography (dichloromethane/methanol mixtures).

The following compounds were prepared in an analogous manner:

Example 167

5-Chloro-*N*-({2-oxo-3-[4-(1-pyrrolidinylsulphonyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide

MS (ESI): m/z (%) = 492 ($[M+Na]^+$, 100), 470 ($[M+H]^+$, 68), Cl pattern;

HPLC (method 3): rt (%) = 4.34 (100).
IC_{50}: 0.5 μM

Example 168

5-Chloro-*N*-[(3-{4-[(4-methyl-1-piperazinyl)sulphonyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide
MS (ESI): m/z (%) = 499 ($[M+H]^+$, 100), Cl pattern;
HPLC (method 2): rt (%) = 3.3 (100).

Example 169

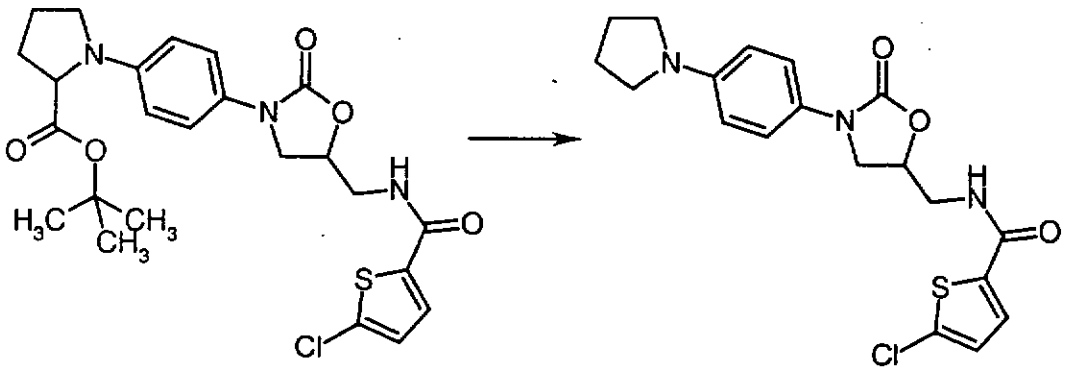
5-Chloro-*N*-({2-oxo-3-[4-(1-piperidinylsulphonyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 484 ($[M+H]^+$, 100), Cl pattern;
HPLC (method 2): rt (%) = 4.4 (100).

Example 170

5-Chloro-*N*-[(3-{4-[(4-hydroxy-1-piperidinyl)sulphonyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide
MS (ESI): m/z (%) = 500 ($[M+H]^+$, 100), Cl pattern;
HPLC (method 3): rt (%) = 3.9 (100).

Example 171

5-Chloro-N-({2-oxo-3-[4-(1-pyrrolidinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



780 mg (1.54 mmol) of tert-butyl 1-{4-[5-({[(5-chloro-2-thienyl)carbonyl]amino}-methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}prolinate are dissolved in 6 ml of dichloromethane and 9 ml of trifluoroacetic acid, and the mixture is stirred at 40°C for two days. The reaction mixture is then concentrated and stirred with ether and 2N aqueous sodium hydroxide solution. The aqueous phase is concentrated and stirred with ether and 2N hydrochloric acid. The organic phase of this extraction is dried over $MgSO_4$, filtered and concentrated. The crude product is chromatographed over silica gel (CH_2Cl_2/EtOH/conc. aqu. NH_3 sol. = 100/1/0.1 to 20/1/0.1).
This gives 280 mg (40% of theory) of the product.
MS (ESI): m/z (%) = 406 (M+H, 100);
HPLC (method 4): rt = 3.81 min.

HPLC parameter and LC-MS parameter for the HPLC and LC-MS data given in the examples above (the unit of the retention time (rt) is minutes):

[1] Column: Kromasil C18, L-R temperature: 30°C, flow rate = 0.75 ml min^{-1}, eluent: A = 0.01 M $HClO_4$, B = CH_3CN, gradient: -> 0.5 min 98%A -> 4.5 min 10%A ->6.5 min 10%A

[2] Column: Kromasil C18 60*2, L-R temperature: 30°C, flow rate = 0.75 ml min^{-1}, eluent: A = 0.01 M H_3PO_4, B = CH_3CN, gradient: -> 0.5 min 90%A -> 4.5 min 10%A ->6.5 min 10%A

[3] Column: Kromasil C18 60*2, L-R temperature: 30°C, flow rate = 0.75 ml min^{-1}, eluent: A = 0.005 M $HClO_4$, B = CH_3CN, gradient: -> 0.5 min 98%A -> 4.5 min 10%A ->6.5 min 10%A

[4] Column: Symmetry C18 2.1x150 mm, column oven: 50°C, flow rate = 0.6 ml min^{-1}, eluent: A = 0.6 g 30% strength HCl/ l of water, B = CH_3CN, gradient: 0.0 min 90%A -> 4.0 min 10%A ->9 min 10%A

[5] MHZ-2Q, Instrument Micromass Quattro LCZ
Column Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, temperature: 40°C, flow rate = 0.5 ml min^{-1}, eluent A = CH_3CN + 0.1% formic acid, eluent B = water + 0.1% formic acid, gradient: 0.0 min 10% A -> 4 min 90% A -> 6 min 90% A

[6] MHZ-2P, Instrument Micromass Platform LCZ
Column Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, temperature: 40°C, flow rate = 0.5 ml min^{-1}, eluent A = CH_3CN + 0.1% formic acid, eluent B = water + 0.1% formic acid, gradient: 0.0 min 10% A -> 4 min 90% A -> 6 min 90% A

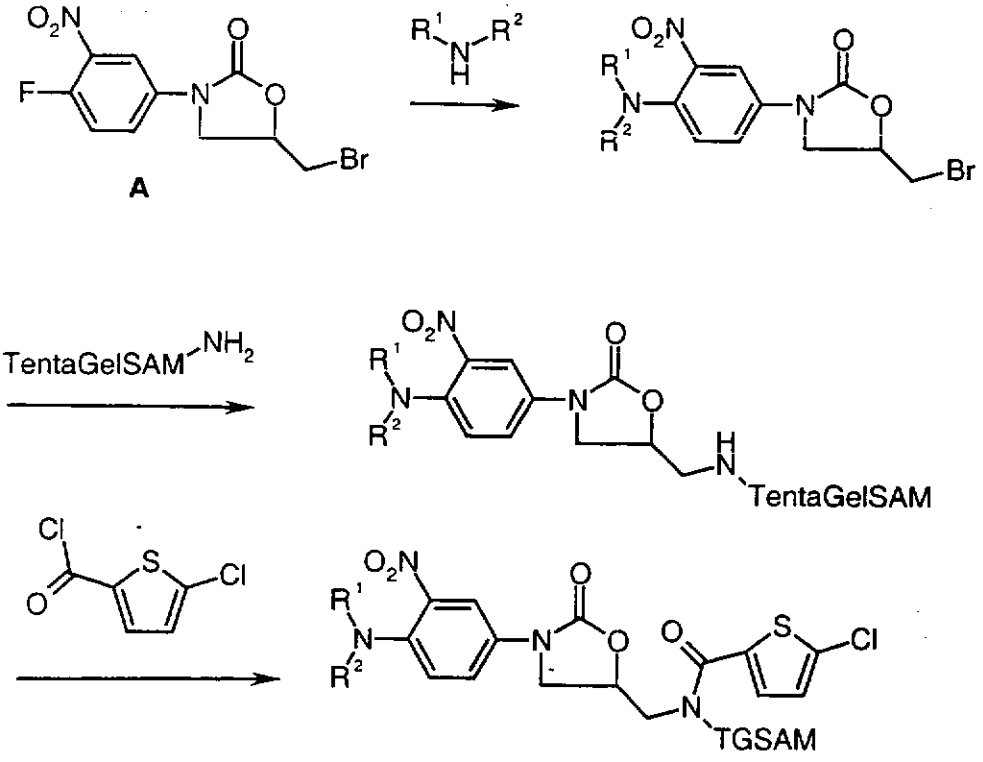
[7] MHZ-7Q, Instrument Micromass Quattro LCZ
Column Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, temperature: 40°C, flow rate = 0.5 ml min^{-1}, eluent A = CH_3CN + 0.1% formic acid, eluent B = water + 0.1% formic acid, gradient: 0.0 min 5% A -> 1 min 5% A -> 5 min 90% A -> 6 min 90% A

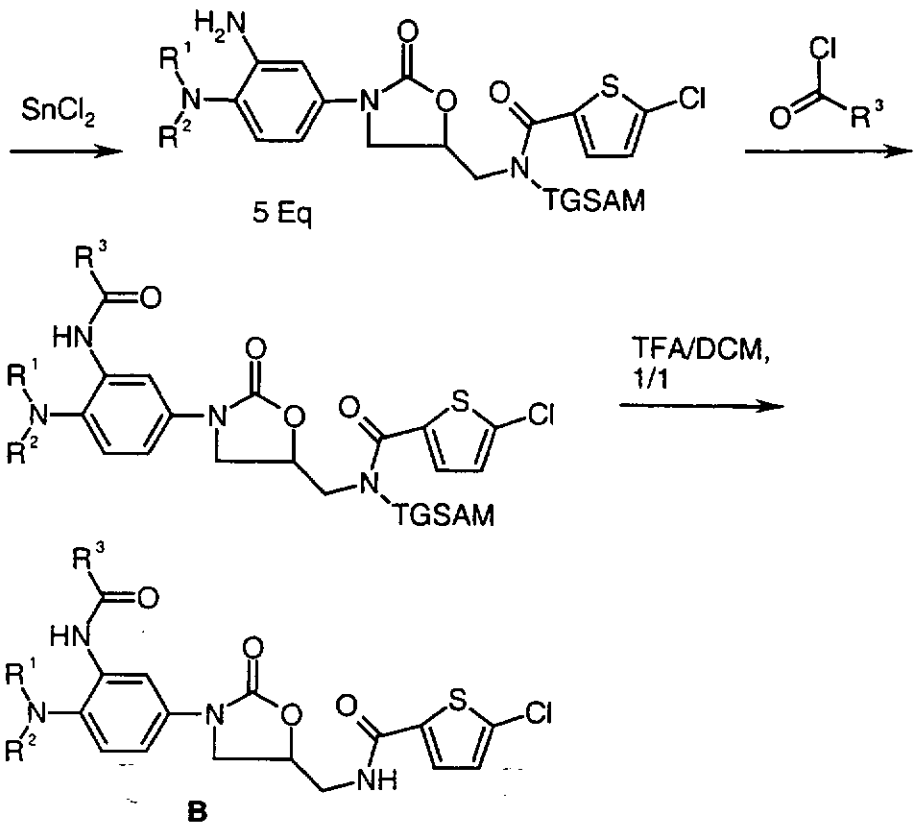
General method for preparing oxazolidinones of the general formula B by solid-phase-supported synthesis

Reactions with different resin-bonded products were carried out in a set of separated reaction vessels.

5-(Bromomethyl)-3-(4-fluoro-3-nitrophenyl)-1,3-oxazolidin-2-one **A** (prepared from epibromohydrin and 4-fluoro-3-nitrophenyl isocyanate using LiBr/Bu_3PO in xylene analogously to US 4128654, Ex.2) (1.20 g, 3.75 mmol) and ethyldiisopropylamine (DIEA, 1.91 ml, 4.13 mmol) were dissolved in DMSO (70 ml), admixed with a secondary amine (1.1 eq., amine component 1) and reacted at 55°C for 5 h. TentaGel SAM resin (5.00 g, 0.25 mmol/g) was added to this solution, and the mixture was reacted at 75°C for 48 h. The resin was filtered, washed repeatedly with methanol (MeOH), dimethylformamide (DMF), MeOH, dichloromethane (DCM) and diethyl ether and dried. The resin (5.00 g) was suspended in dichloromethane (80 ml), admixed with DIEA (10 eq.) and 5-chlorothiophene-2-carbonyl chloride [prepared by reacting 5-chlorothiophene-2-carboxylic acid (5 eq.) and 1-chloro-1-dimethylamino-2-methylpropene (5 eq.) in DCM (20 ml) at room temperature for 15 minutes] and the mixture was reacted at room temperature for 5 h. The resulting resin was filtered, washed repeatedly with MeOH, DCM and diethyl ether and dried. The resin was then

suspended in DMF/water (v/v 9:2, 80 ml), admixed with $SnCl_2*2H_2O$ (5 eq.) and reacted at room temperture for 18 h. The resin was washed repeatedly with MeOH, DMF, water, MeOH, DCM and diethyl ether and dried. This resin was suspended in DCM, admixed with DIEA (10 eq.) and, at 0°C, with an acid chloride (5 eq. of acid derivative 1), and the mixture was reacted at room temperature overnight. Prior to the reaction, carboxylic acids were converted into the corresponding acid chlorides by reaction with 1-dimethylamino-1-chloro-2-methylpropene (1 eq., based on the carboxylic acid) in DCM at room temperature for 15 min. The resin was washed repeatedly with DMF, water, DMF, MeOH, DCM and diethyl ether and dried. If the acid derivative 1 used was an Fmoc-protected amino acid, the Fmoc protective group was removed in the last reaction step by reaction with piperidine/DMF (v/v, 1/4) at room temperature for 15 minutes, and the resin was washed with DMF, MeOH, DCM and diethyl ether and dried. The products were then removed from the solid phase using trifluoroacetic acid (TFA)/DCM (v/v, 1/1), the resin was filtered off and the reaction solutions were concentrated. The crude products were filtered over silica gel (DCM/MeOH, 9:1) and evaporated, giving a set of products **B**.

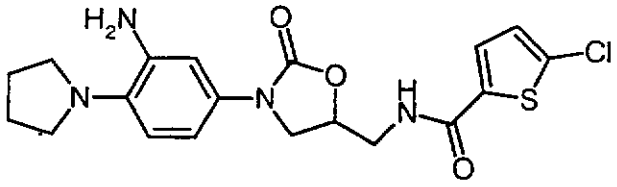




Compounds which were prepared by solid-phase-supported synthesis:

Example 172

N-({3-[3-Amino-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide



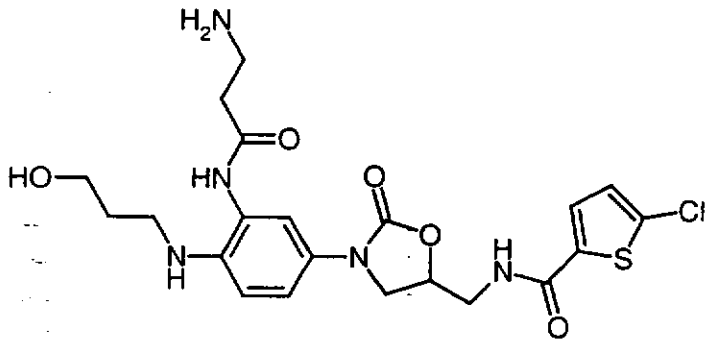
Analogously to the general procedure for preparing the derivatives **B**, 5 g (1.25 mmol) of TentaGel SAM resin were reacted with pyrrolidine as amine derivative 1. The aniline obtained after reduction with $SnCl_2*2H_2O$ was, without any further acylation step, removed from the solid phase and concentrated. The crude product was partitioned between ethyl acetate and $NaHCO_3$ solution and the organic phase was salted out using NaCl, decanted and evaporated to dryness. This crude

product was purified by vacuum flash chromatography over silica gel (dichloromethane/ethyl acetate, 3:1 – 1:2).

^{1}H-NMR (300 MHz, $CDCl_3$): 1.95 – 2.08, br, 4 H; 3.15-3.30, br, 4 H; 3.65-3.81, m, 2 H; 3.89, ddd, 1H; 4.05, dd, 1 H; 4.81, dddd, 1 H; 6.46, dd, 1 H; 6.72, dd, 1 H; 6.90, dd, 1 H; 6.99, dd, 1 H; 7.03, dd, 1 H; 7.29, d, 1 H.

Example 173

N-[(3-{3-(ß-Alanylamino)-4-[(3-hydroxypropyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide

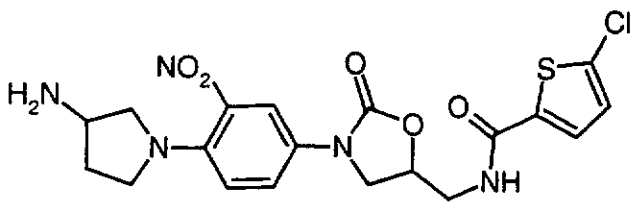


Analogously to the general procedure for preparing the derivatives **B**, 5 g (1.25 mmol) of TentaGel SAM resin were reacted with azetidine as amine derivative 1 and Fmoc-ß-alanine as acid derivative 1. The crude product obtained after the removal was stirred in methanol at room temperature for 48 h and evaporated to dryness. This crude product was purified by reversed phase HPLC using a water/TFA/acetonitrile gradient.

^{1}H-NMR (400 MHz, CD_3OD): 2.31, tt, 2 H; 3.36, t, 2 H; 3.54, t, 2 H; 3.62, t, 2 H; 3.72, dd, 1 H; 3.79, dd, 1 H; 4.01, dd, 1 H; 4.29, dd, 2 H; 4.43, t, 2 H; 4.85–4.95, m, 1 H; 7.01, d, 1 H; 4.48 – 7.55, m, 2 H; 7.61, d, 1 H; 7.84, d, 1 H.

Example 174

N-({3-[4-(3-Amino-1-pyrrolidinyl)-3-nitrophenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chloro-2-thiophenecarboxamide

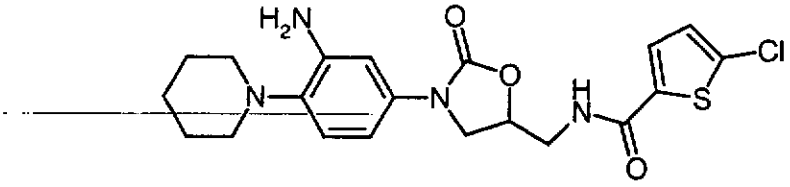


Analogously to the general procedure for preparing the derivatives **B**, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted with *tert*-butyl 3-pyrrolidinylcarbamate as amine derivative 1. The nitrobenzene derivative obtained after the acylation with 5-chlorothiophenecarboxylic acid was removed from the solid phase and concentrated. This crude product was purified by reversed phase HPLC using a water/TFA/acetonitrile gradient.

^{1}H-NMR (400 MHz, CD_3OH): 2.07-2.17, m, 1 H; 2.39-2.49, m, 1 H; 3.21-3.40, m, 2 H; 3.45, dd, 1 H; 3.50–3.60, m, 1 H; 3.67, dd, 1 H; 3.76, dd, 1 H; 3.88–4.00, m, 2 H; 4.14 – 4.21, t, 1 H; 4.85 – 4.95, m, 1 H; 7.01, d, 1 H; 7.11, d, 1 H; 7.52, d, 1 H; 7.66, dd, 1 H; 7.93, d, 1 H.

Example 175

N-({3-[3-Amino-4-(1-piperidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophenecarboxamide

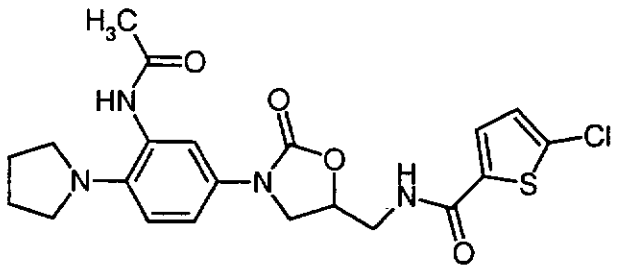


Analogously to the general procedure for preparing the derivatives **B**, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted with piperidine as amine derivative 1. The aniline obtained after the reduction was, without any further acylation step, removed from the solid phase and concentrated. This crude product was purified by reversed phase HPLC using a water/TFA/acetonitrile gradient.

^{1}H-NMR (400 MHz, CD_3OH): 1.65–1.75, m, 2 H; 1.84-1.95, m, 4 H; 3.20-3.28, m, 4 H; 3.68, dd, 1 H; 3.73, dd, 1H; 3.90, dd, 1 H; 4.17, dd, 1 H; 4.80-4.90, m, 1 H; 7.00, d, 1 H; 7.05, dd, 1 H; 7.30-7.38, m, 2H; 7.50, d, 1 H.

Example 176

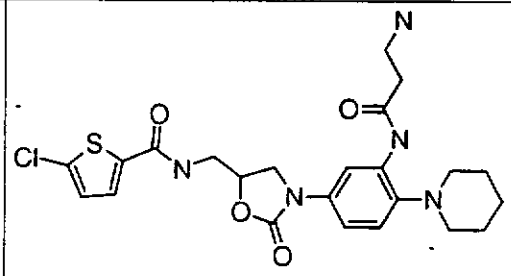
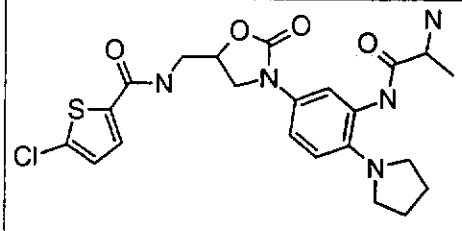
N-({3-[3-(Acetylamino)-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chloro-2-thiophenecarboxamide

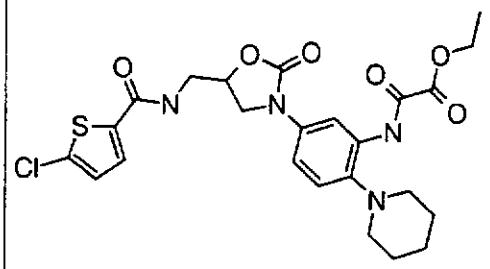
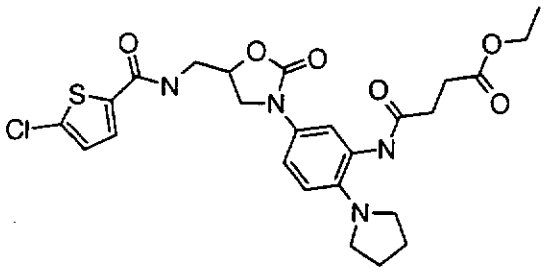
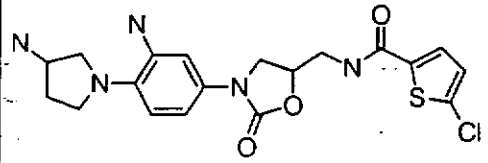
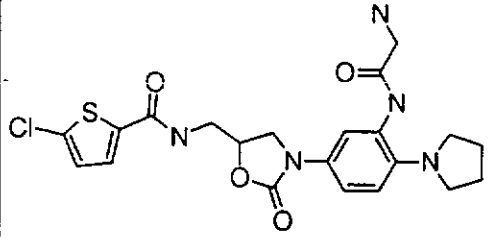
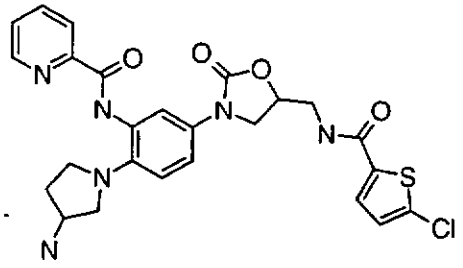
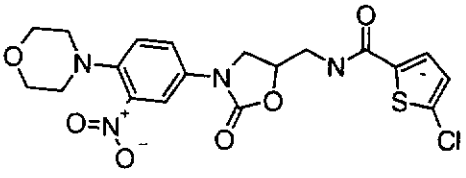


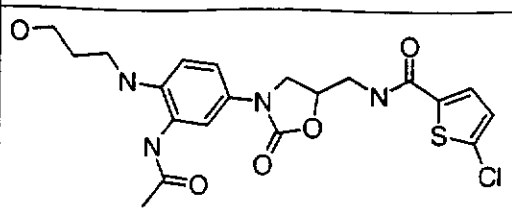
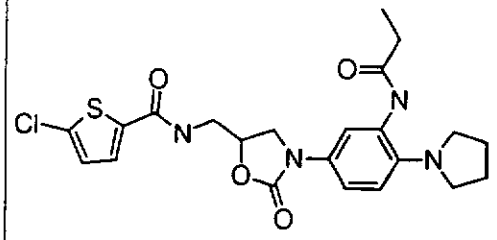
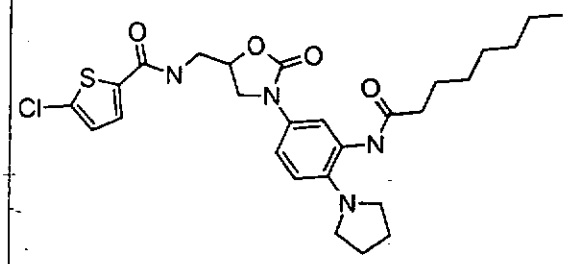
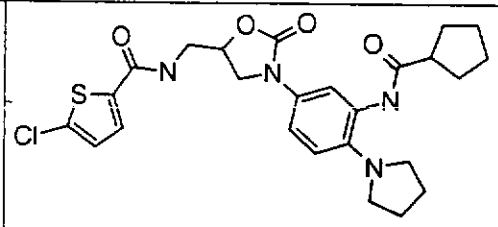
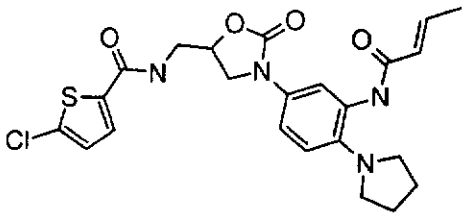
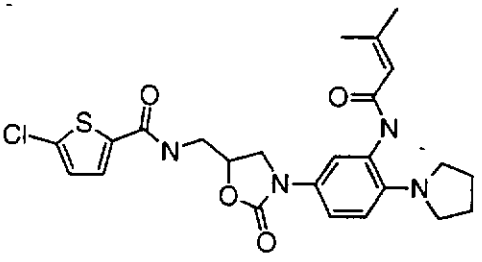
Analogously to the general procedure for preparing the derivatives **B**, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted pyrrolidine as amine derivative 1 and acetyl chloride as acid derivative 1. The crude product was partitioned between ethyl acetate $NaHCO_3$ solution and the organic phase was salted out using NaCl, decanted and evaporated to dryness. This crude product was purified by vacuum flash chromatography over silica gel (dichloromethane/ethyl acetate, 1:1-0:1).

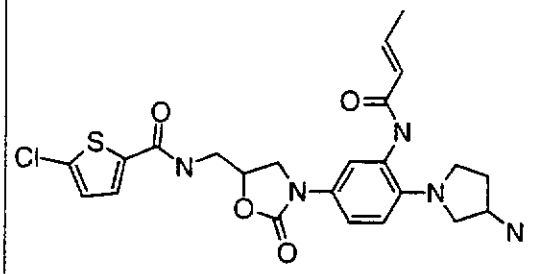
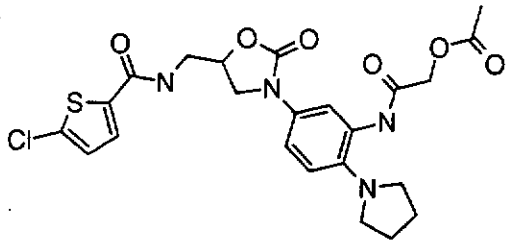
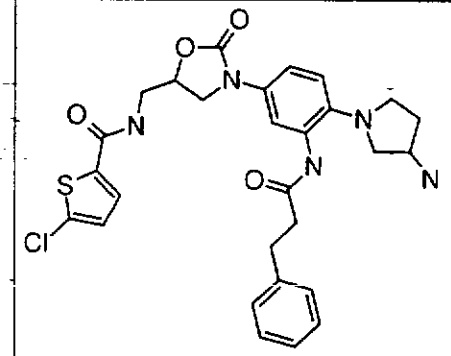
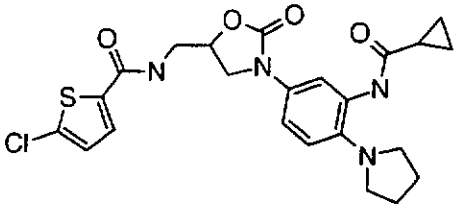
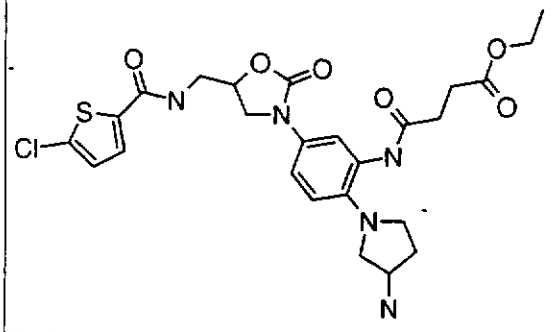
^{1}H-NMR (400 MHz, CD_3OH): 1.93 – 2.03, br, 4 H; 2.16, s, 3 H; 3.20-3.30, br, 4 H; 3.70, d, 2 H; 3.86, dd, 1H; 4.10, dd, 1 H; 4.14, dd, 1 H; 4.80-4.90, m, 1 H; 7.00, d, 1 H; 7.07, d, 1 H; 7.31, dd, 1 H; 7.51, d, 1 H; 7.60, d, 1 H.

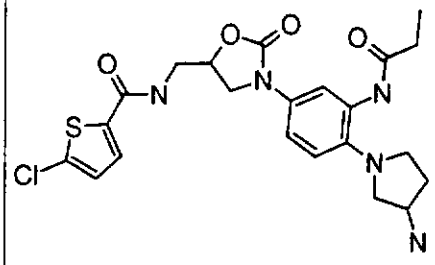
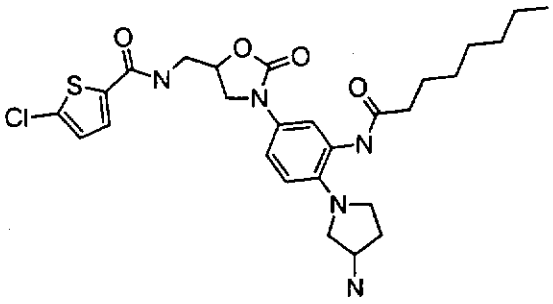
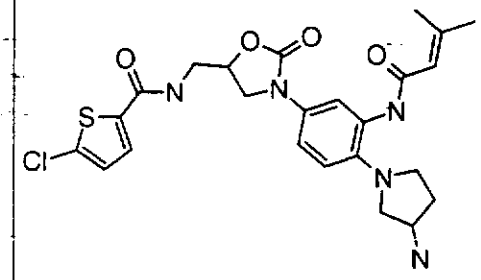
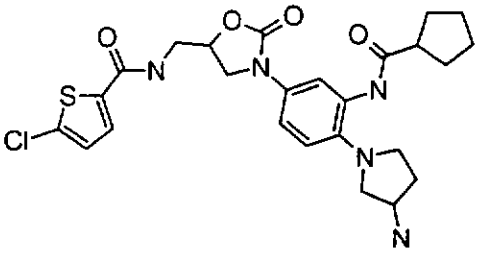
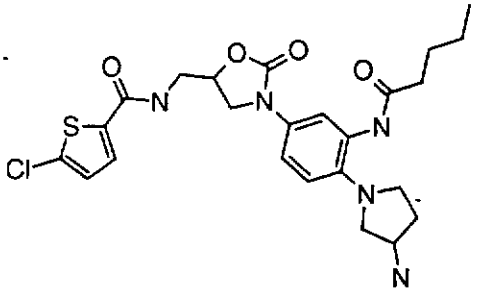
The following compounds were prepared analogously to the general procedure.

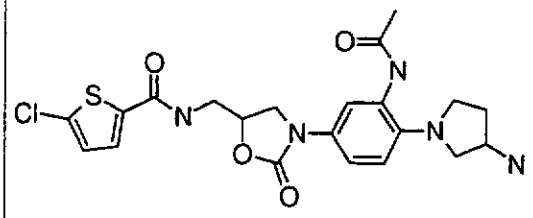
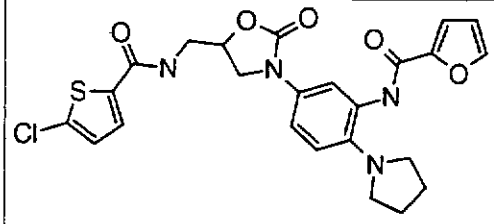
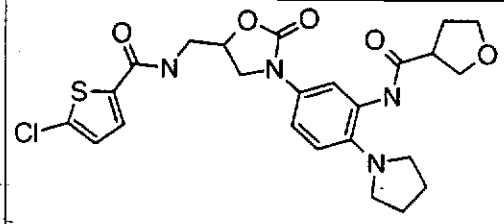
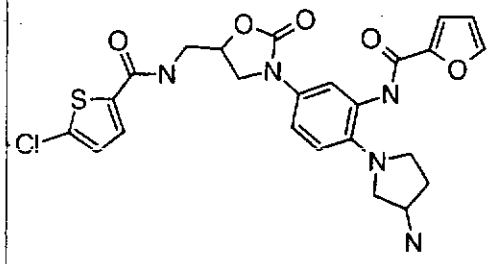
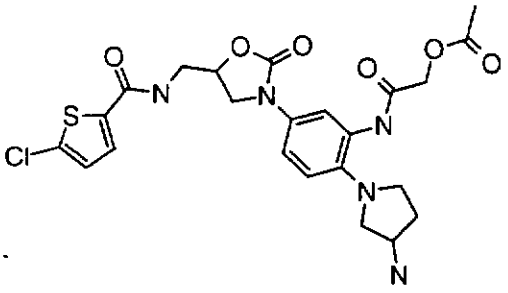
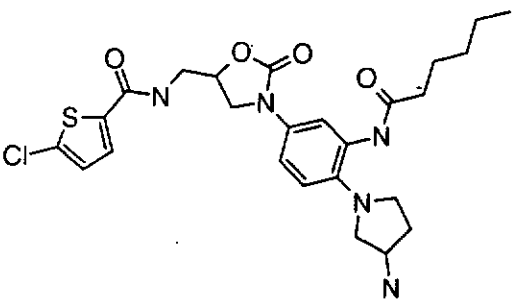
Example	Structure	Ret. time	HPLC [%]
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178		2.49	33.7

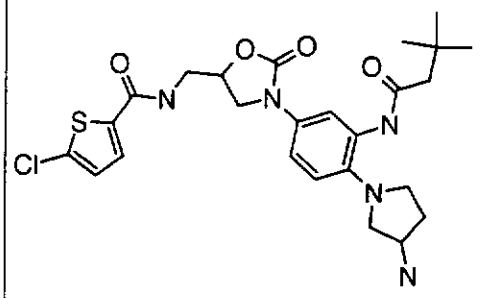
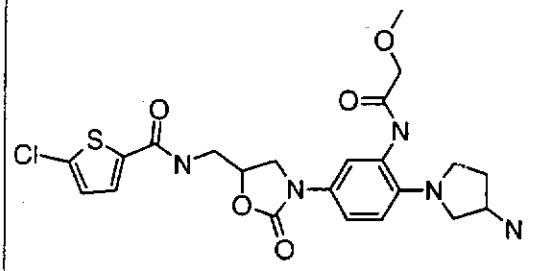
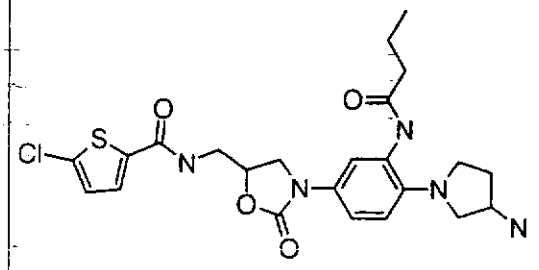
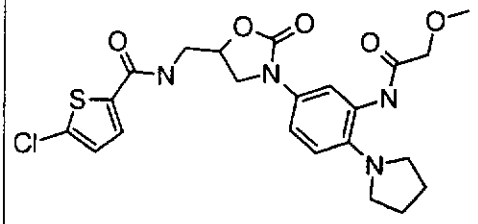
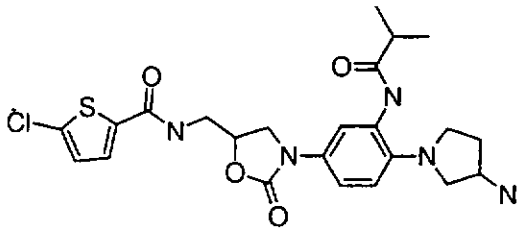
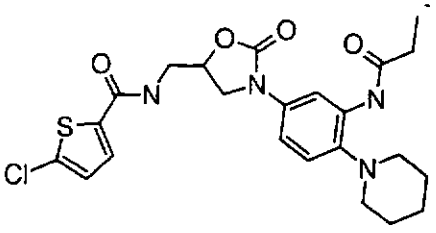
Example	Structure	Ret. time	HPLC [%]
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180		3.37	44.8
181		2.16	83
182		2.31	93.3
183		2.7	100
184		3.91	51

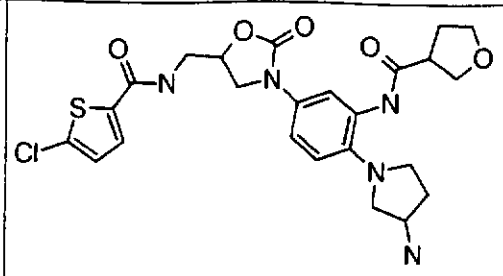
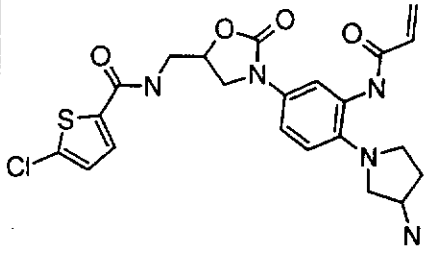
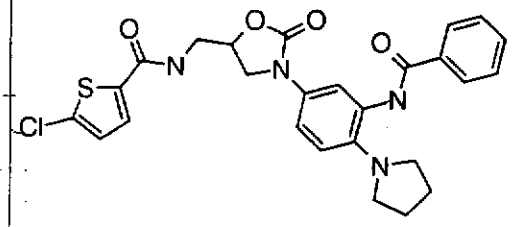
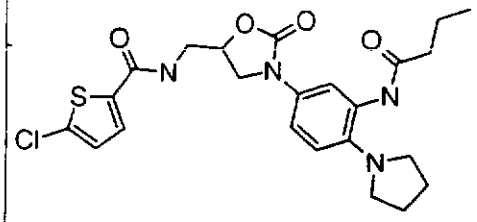
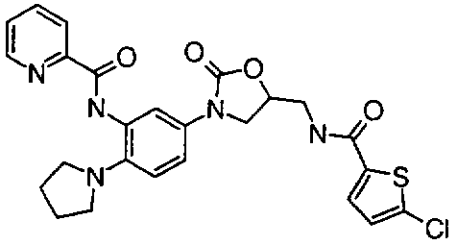
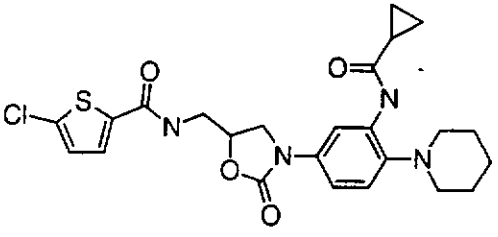
Example	Structure	Ret. time	HPLC [%]
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187		4.61	50.2
188		3.89	56.6
189		3.37	52.9
190		3.6	63.9

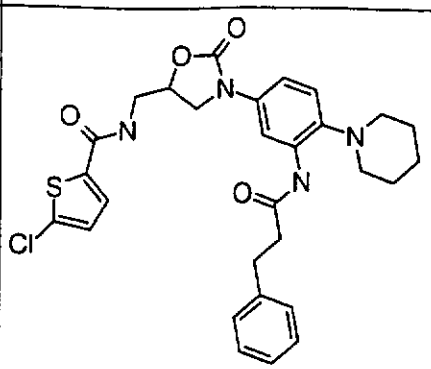
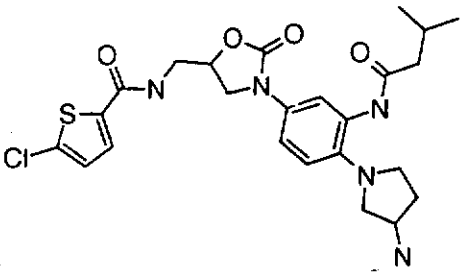
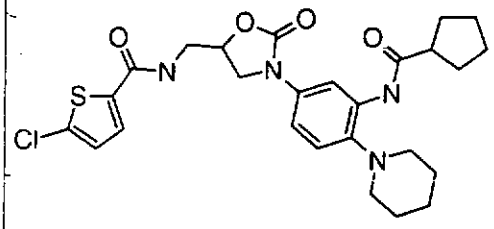
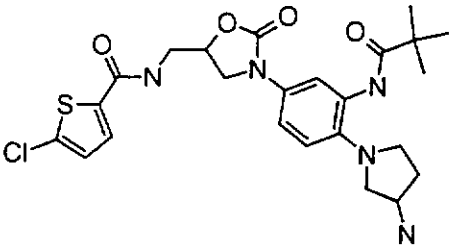
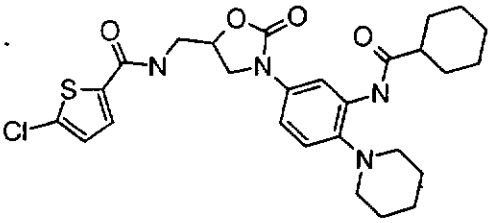
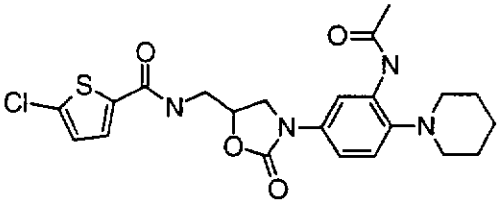
Example	Structure	Ret. time	HPLC [%]
191		2.52	70.1
192		3.52	46.6
193		2.87	50.1
194		3.25	71.1
195		2.66	67

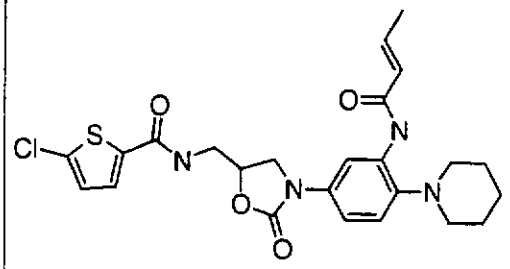
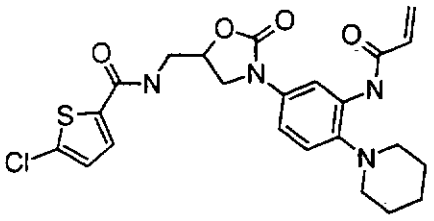
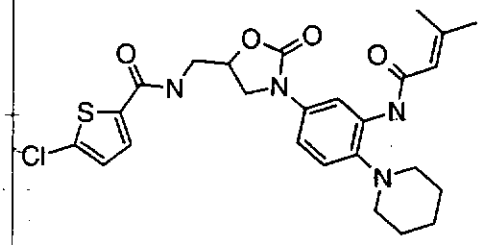
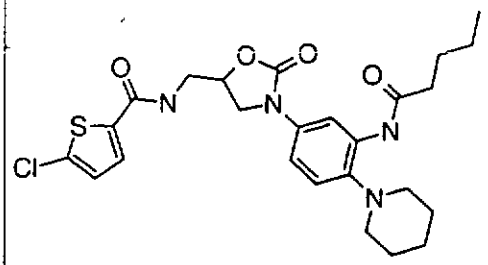
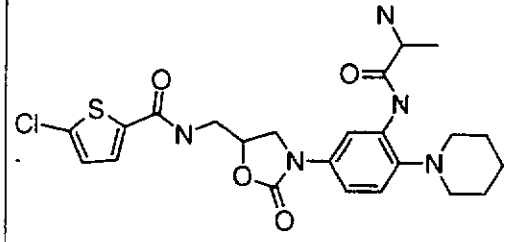
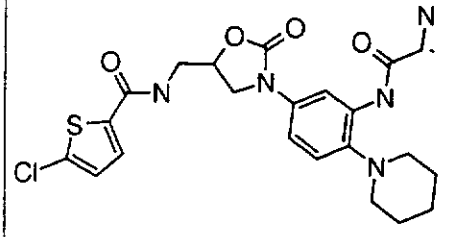
Example	Structure	Ret. time	HPLC [%]
196		2.4	52.1
197		3.13	48.9
198		2.67	75.5
199		2.72	65.7
200		2.71	57.3

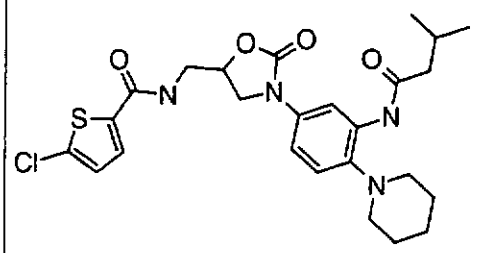
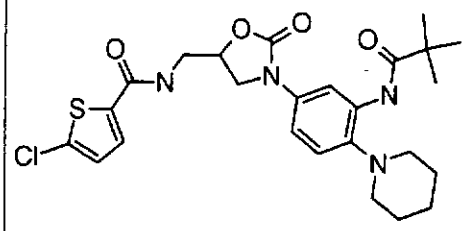
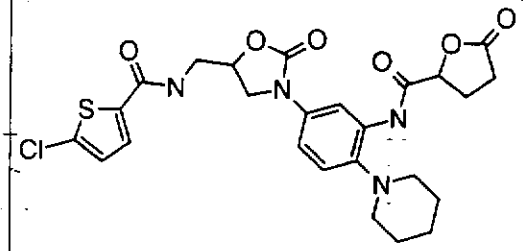
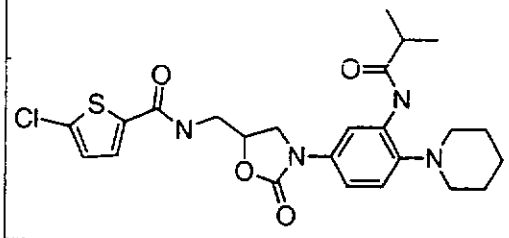
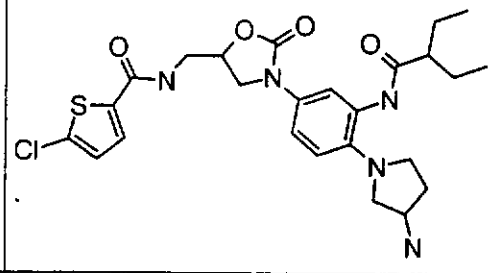
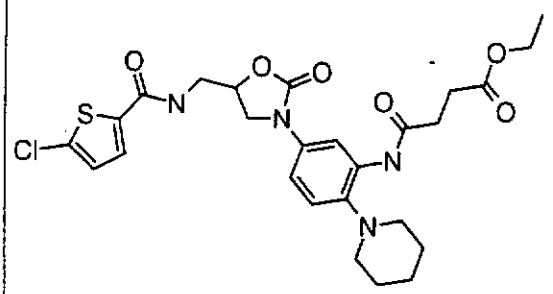
Example	Structure	Ret. time	HPLC [%]
201		2.22	100
202		3.89	75.7
203		3.19	49.6
204		2.55	88.2
205		2.44	68.6
206		2.86	71.8

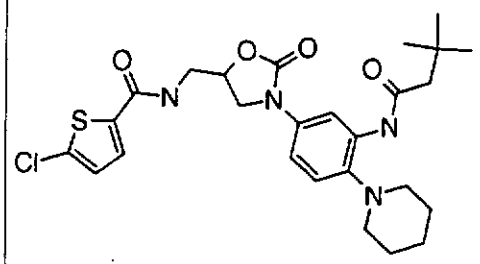
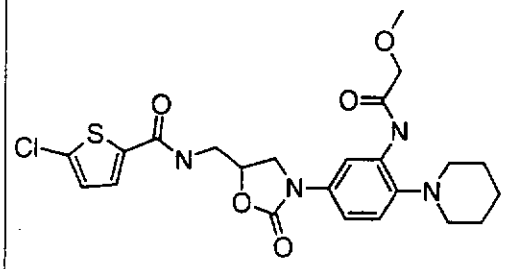
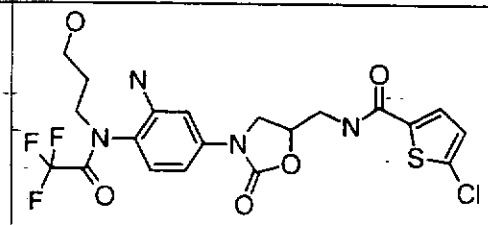
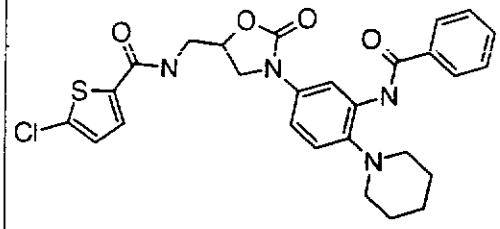
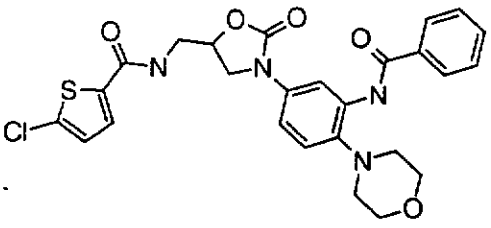
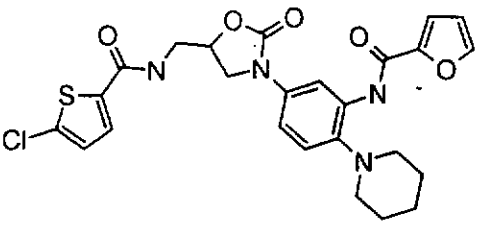
Example	Structure	Ret. time	HPLC [%]
207		2.8	63.6
208		2.41	77
209		2.56	67.9
210		3.67	78.4
211		2.54	69.8
212		3.84	59.2

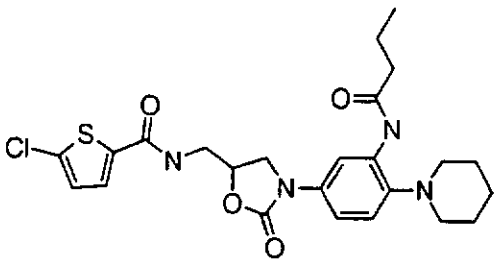
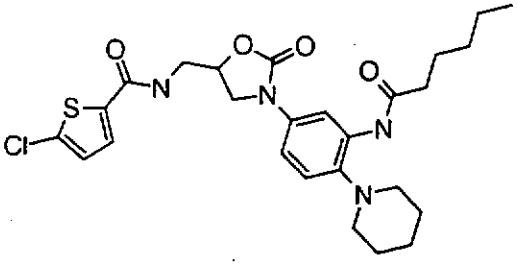
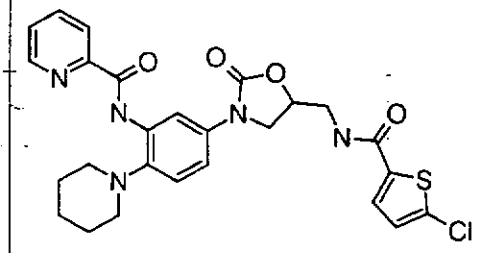
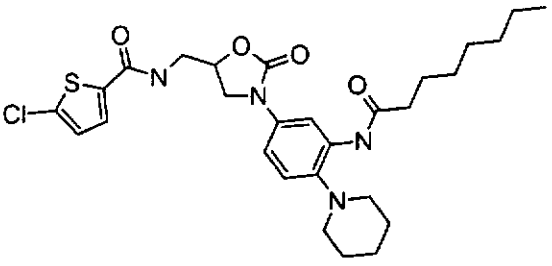
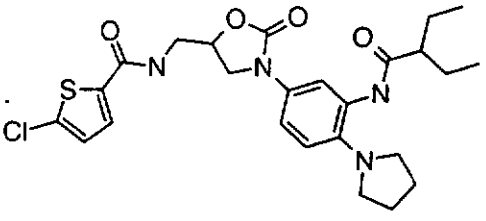
Example	Structure	Ret. time	HPLC [%]
213		2.41	67.8
214		2.41	75.4
215		4.01	81.3
216		3.46	49.5
217		4.4	60.2
218		3.79	70.9

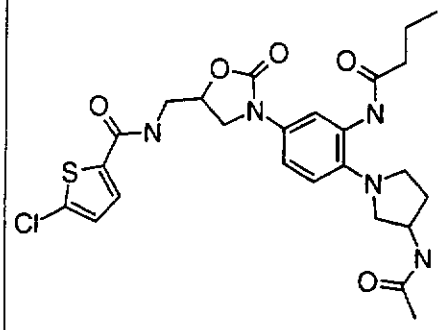
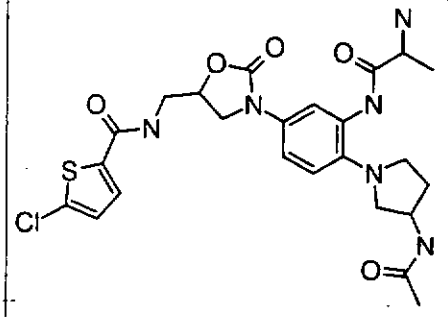
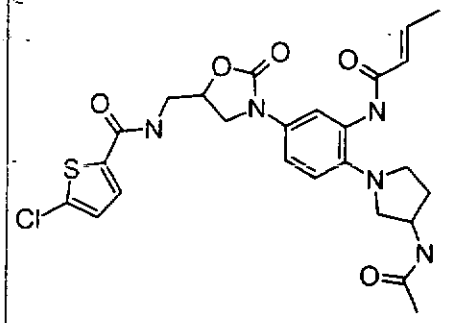
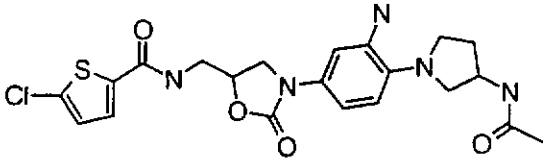
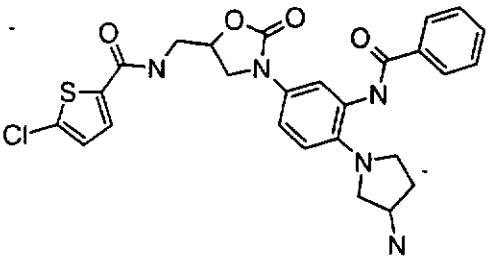
Example	Structure	Ret. time	HPLC [%]
219		4.57	51.5
220		2.68	100
221		4.53	63.5
222		2.66	89.2
223		4.76	69.3
224		3.45	77.4

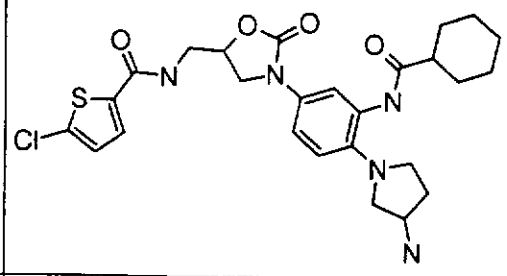
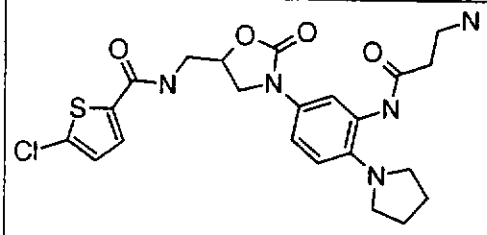
Example	Structure	Ret. time	HPLC [%]
225		3.97	63.2
226		3.94	61.4
227		4.15	66.3
228		4.41	55.1
229		2.83	41.1
230		2.7	83

Example	Structure	Ret. time	HPLC [%]
231		4.39	64.2
232		4.85	74.9
233		4.17	41
234		4.21	61.8
235		2.75	100
236		3.94	50

Example	Structure	Ret. time	HPLC [%]
237		4.65	75.8
238		4.4	75.3
239		4.24	62.2
240		4.76	75.1
241		4.17	72.5
242		4.6	74.8

Example	Structure	Ret. time	HPLC [%]
243		4.12	51.6
244		4.71	66.2
245		4.86	62
246		5.23	58.3
247		4.17	72.4

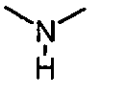
Example	Structure	Ret. time	HPLC [%]
248		3.35	59.6
249		2.41	60.3
250		3.31	65.2
251		2.86	36.5
252		2.69	89.8

Example	Structure	Ret. time	HPLC [%]
253		2.81	67.4
254		2.19	75.4

All products of the solid-phase-supported synthesis were characterized by LC-MS. As standard, the following separation system was used: HP 1100 with UV detector (208 – 400 nm), oven temperature 40°C, Waters-Symmetry C18 column (50 mm x 2.1 mm, 3.5 µm), mobile phase A: 99.9% acetonitrile/0.1% formic acid, mobile phase B: 99.9% water/ 0.1% formic acid; gradient:

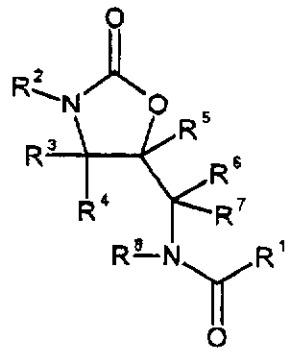
Time	A:%	B:%	flow rate
0. 00	10. 0	90. 0	0. 50
4. 00	90. 0	10. 0	0. 50
6. 00	90. 0	10. 0	0. 50
6. 10	10. 0	90. 0	1. 00
7. 50	10. 0	90. 0	0. 50

The substances were detected using a Micromass Quattro LCZ MS, ionization: ESI positive/negative.

In the structures listed above which comprise the radical(s)  or -O, what is meant is in each case a  or -OH function.

Patent Claims

1. Compounds of the general formula (I)



(I),

in which:

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

R^2 represents any organic radical;

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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

and exept for compounds of the general formula (I) in which

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

R^2 represents D-A-:

where:

the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle,
which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;

where
the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen.

and their pharmaceutically acceptable salts, hydrates, hydrates of salts and prodrugs.

2. Compounds of the general formula (I) according to Claim 1, characterized in that

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,

R^2 represents one of the groups below:
A-,
A-M-,
D-M-A-,
B-M-A-,

B-,
B-M-,
B-M-B-,
D-M-B-,

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

where
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})-heteroaryl-carbonyl; (C_1-C_6)-alkanoyloxymethyloxy; (C_1-C_4)-hydroxy-alkylcarbonyl; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (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 $-C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1 and

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

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

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, $-CH_2C(NR^{27}R^{28})=NR^{29}$ or $-COR^{33}$,

where

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,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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

and exept for compounds of the general formula (I) in which

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

R^2 represents D-A-:

where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle,
which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;

where
the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen.

and their pharmaceutically acceptable salts, hydrates, hydrates of salts and prodrugs.

3. Compounds of the general formula (I) according to Claim 1, characterized in that

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,

R^2 represents one of the groups below:
A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

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

where
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})-heteroaryl-carbonyl; (C_1-C_6)-alkanoyloxymethyloxy; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (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 $-C(NR^{27}R^{28})=NR^{29}$,

where:

v is either 0 or 1 and

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

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

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, (C_1-C_4)-alkanoyl, (C_6-C_{14})-arylcarbonyl, (C_5-C_{10})-heteroarylcarbonyl, (C_1-C_4)-alkylaminocarbonyl or $-CH_2C(NR^{27}R^{28})=NR^{29}$,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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

and exept for compounds of the general formula (I) in which

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

R^2 represents D-A-:

where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle,
which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;

where

the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen.

and their pharmaceutically acceptable salts, hydrates, hydrates of salts and prodrugs.

4. Compounds of the general formula (I) according to Claim 1, characterized in that

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,

R^2 represents one of the groups below:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:
the radical "A" represents phenyl or naphthyl, in particular phenyl;
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;

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;

the radical "M" represents –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or represents a covalent bond;

where

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,

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},

where:

v is either 0 or 1, preferably 0, and

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
and/or

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

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,

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

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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

and exept for compounds of the general formula (I) in which

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

R^2 represents D-A-:

where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle,
which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;

where
the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen.

and their pharmaceutically acceptable salts, hydrates, hydrates of salts and prodrugs.

5. Compounds of the general formula (I) according to Claim 1, characterized in that

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

R^2 represents one of the groups below:
A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

where:
the radical "A" represents phenyl or naphthyl, in particular phenyl;
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;

the radical "D" represents a saturated or partially unsaturated 5- or 6-membered heterocycle which contains a nitrogen atom and optionally a further heteroatom and/or hetero chain member from the group consisting of S, SO, SO_2 and O; or contains up to two heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2 and O;
the radical "M" represents –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- or represents a covalent bond;

where
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; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-alkyl; and cyclopropyl, cyclopentyl or cyclohexyl,

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},

where:

v is either 0 or 1, preferably 0, and

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

and/or

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

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,

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_4)-alkyl

and their pharmaceutically acceptable salts, hydrates and prodrugs,

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

and exept for compounds of the general formula (I) in which

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

R^2 represents D-A-:

where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle,
which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom from the group consisting of S, N and O;

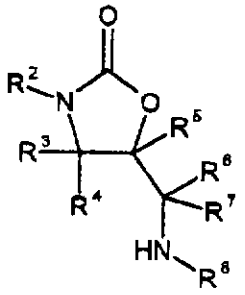
where
the group "A" defined above may optionally be mono- or disubstituted in the meta position with respect to the point of attachment to the oxazolidinone, by a radical from the group consisting of fluorine, chlorine, nitro, amino, trifluoromethyl, methyl and cyano,

R^3, R^4, R^5, R^6, R^7 and R^8 each represent hydrogen.

and their pharmaceutically acceptable salts, hydrates, hydrates of salts and prodrugs.

6. Process for preparing substituted oxazolidinones according to Claims 1 to 5, where
either according to a process alternative

[A] compounds of the general formula (II)

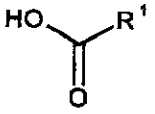


(II),

in which

the radicals R^2, R^3, R^4, R^5, R^6 and R^7 are each as defined in Claim 1

are reacted with carboxylic acids of the general formula (III)



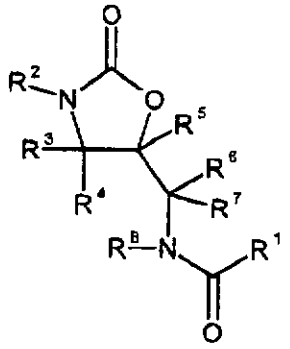
(III),

in which

the radical R^1 is as defined in Claim 1,

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

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



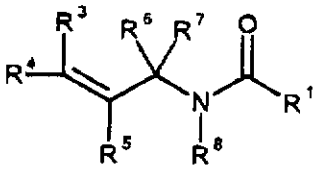
(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 1,

or else according to a process alternative

[B] compounds of the general formula (IV)

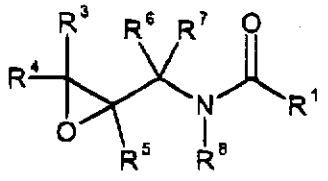


(IV),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 1,

are converted, using a suitable selective oxidizing agent in an inert solvent, into the corresponding epoxide of the general formula (V)



(V),

in which

the radicals R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 1,

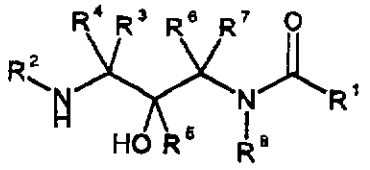
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the general formula (VI)

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

in which

the radical R^2 is as defined in Claim 1,

the compounds of the general formula (VII)



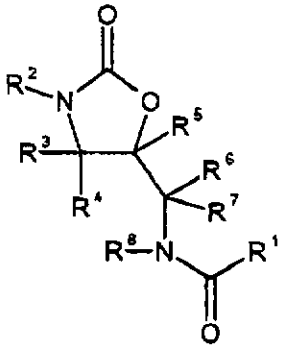
(VII),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 1,

are initially prepared and,

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



(I),

in which

the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are each as defined in Claim 1,

where - both for process alternative [A] and for process alternative [B] - in the case where R^2 contains a 3- to 7-membered saturated or partially unsaturated cyclic hydrocarbon radical having one or more identical or different heteroatoms from the group consisting of N and S, an oxidation with a selective oxidizing agent to afford the corresponding sulphone, sulphoxide or N-oxide may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a cyano group in the molecule, an amidination of this cyano group by customary methods may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a BOC amino

protective group in the molecule, removal of this BOC amino protective group by customary methods may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with various reagents such as carboxylic acids, carboxylic anhydrides, carbonyl chlorides, isocyanates, sulphonyl chlorides or alkyl halides to give the corresponding derivatives may follow

and/or

where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with amines to give the corresponding sulphonamides may follow.

7. Medicaments, comprising at least one compound of the general formula (I) according to Claims 1 to 5 and one or more pharmacologically acceptable auxiliaries or excipients.

8. Use of compounds of the general formula (I) according to Claims 1 to 5 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of thromboembolic disorders, in particular myocardial infarct, angina pectoris (including unstable angina), reocclusions and restenoses after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

9. Use of compounds of the general formula (I) according to Claims 1 to 5 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of disorders which are influenced positively by inhibition of factor Xa.

10. Use of compounds of the general formula (I) according to Claims 1 to 5 for preparing medicaments or pharmaceutical compositions for the treatment of disseminated intravascular coagulation (DIC).

11. Use of compounds of the general formula (I) according to Claims 1 to 5 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of disorders such as atherosclerosis; arthritis; Alzheimer's disease or cancer.

12. Use of compounds of the general formula (I) according to Claims 1 to 5 for preparing medicaments or pharmaceutical compositions for the inhibition of factor Xa.

13. Method for preventing the coagulation of blood in vitro, in particular in the case of banked blood or biological samples containing factor Xa, characterized in that compounds of the general formula (I) according to Claims 1 to 5 are added.