INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/01682

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/505; C07C 409/14
US CL :514/253; 544/293
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/253; 544/293

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,612,353 A (EWING et al.) 18 March 1997, whole document.	1-72

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
30 MARCH 1999

Date of mailing of the international search report
12MAY1999

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet)(July 1992)*

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/181,051	Alexander Straub	Le A 34122

INTERNATIONAL APPLICATION NO.	
PCT/EP00/12492	
I.A. FILING DATE	PRIORITY DATE
12/11/2000	12/24/1999

27941
JEFFREY M. GREENMAN
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CONFIRMATION NO. 5850
371 ACCEPTANCE LETTER

OC000000008806361

Date Mailed: 09/19/2002

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.494 OR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as an Elected Office (37 CFR 1.495) , has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

06/24/2002	06/24/2002
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- U.S. Basic National Fee
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Information Disclosure Statements
- Oath or Declaration
- Request for Immediate Examination

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

WINSTON M ALVARADO
Telephone: (703) 305-6421

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

PATENT APPLICATION SERIAL NO. 10/181051

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

07/18/2002 MKAYPAGH 00000051 133372 10181051

01 FC:970 890.00 CH
02 FC:964 168.00 CH

Adjustment date: 09/12/2002 MKAYPAGH
07718/2002 MKAYPAGH 00000051 133372 10181051
02 FC:964 168.00 CR

09/12/2002 MKAYPAGH 00000137 133372 10181051

01 FC:966 18.00 CH
02 FC:968 280.00 CH

PTO-1556
(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

10181051 .062402

ORIGINAL

533 Rec'd PCT/PTO 24 JUN 2002

FORM PTO-1390 (REV. 12-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY 'S DOCKET NUMBER: Le A 34 122

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 10/181051

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/12492	11 December 2000 (11.12.00)	24 December 1999 (24.12.99)

TITLE OF INVENTION: **Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation**

APPLICANT(S) FOR DO/EO/US: **Alexander STRAUB, et al.**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: **1) Certificate of Mailing under 37 C.F.R. 1.10;**
    2) Transmittal of Information Disclosure Statement under 37 C.F.R. 1.97(b);
    3) Information Disclosure Citation (Modified Form PTO-1449) and copies of references cited therein;
    4) Return Receipt Postcard.

Date of Deposit: JUN 24 2002
Express Mail Label No.: EU054495463US

U.S. APPLICATION NO. (if known, see 37 CFR 1.5) 10/181051	INTERNATIONAL APPLICATION NO. PCT/EP00/12492	ATTORNEY'S DOCKET NUMBER Le A 34 122

21. [X] The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	15 - 20 =	0	x $18.00	$ 00.00	
Independent claims	5 - 3 =	2	x $84.00	$ 168.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable) 0			+ $280.00	$ 00.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1,058.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +				$	
SUBTOTAL =				$ 1,058.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
TOTAL NATIONAL FEE =				$ 1,058.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 1,058.00	
				Amount to be refunded:	$
				charged:	$

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 13-3372 in the amount of $ 1,058.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3372 . A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: **Customer No. 27941**

Jeffrey M. Greenman
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William F. Gray
SIGNATURE

William F. Gray
NAME

Reg. No. 31,018
REGISTRATION NUMBER

Attorney's Docket No. Le A 34 122

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Alexander Straub, et al.

Serial No.: [to be assigend]
National Phase Filing of PCT/EP00/12492

Filed: herewith

For: Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation

BOX PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR 1.10

I hereby certify that the *attached* correspondence comprising:

- Transmittal Letter to the United States Designated/Elected Office (DO/EO/US) Concerning a Filing under 35 U.S.C. 371 [IN DUPLICATE];
- Original Combined Declaration and Power of Attorney (35 U.S.C. 371(c)(4));
- English Translation of the International Application as filed (35 U.S.C. 371(c)(2));
- Copy of the International Application as filed (35 U.S.C. 371(c)(2));
- Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98 consisting of Transmittal of Information Disclosure Statement under 37 C.F.R. 1.97(b), Information Disclosure Citation (Modified Form PTO-1449) and copies of references cited therein;
- Return Receipt Post Card.

is, on the date shown below, being deposited with the United States Postal Service, in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EU054495463US, addressed to:

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

June 24, 2002
Date

Signature of Person Certifying

Substituted oxazolidinones and their use

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").

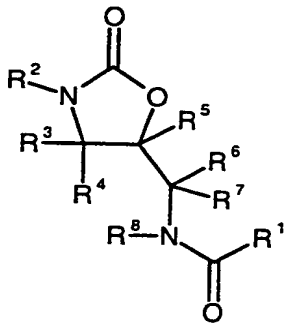
Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa (cf. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research **1999**, *93*, 203; F. Al-Obeidi, J.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

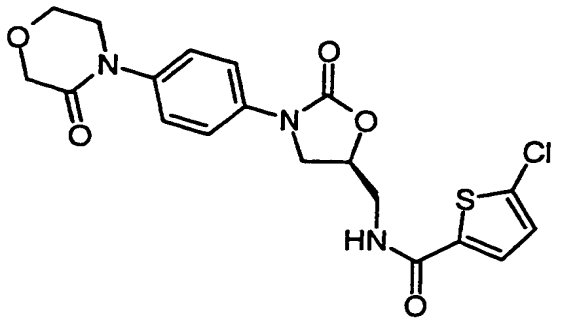
where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle, which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom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

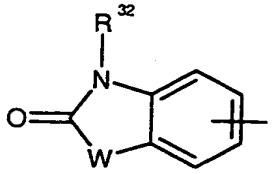
R^{27}, R^{28} and R^{29} are identical or different and independently of one another each represents hydrogen, (C_1-C_4)-alkyl or else cyclopropyl, cyclopentyl or cyclohexyl
and/or

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:



,

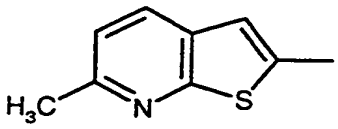
where

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

W represents S, NH or O, preferably S.

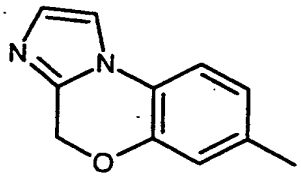
Moreover, in the compounds of the general formula (I), the radical

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, indolizinyl, 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.

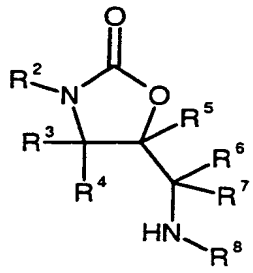
A 3- to 9-membered saturated or partially unsaturated, mono- or bicyclic, optionally benzo-fused heterocycle having up to 3 heteroatoms and/or hetero chain members from the group consisting of S, SO, SO_2, N, NO (N-oxide) and O represents a heterocycle which may contain one or more double bonds, which 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)

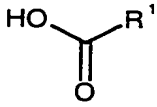


(II),

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)



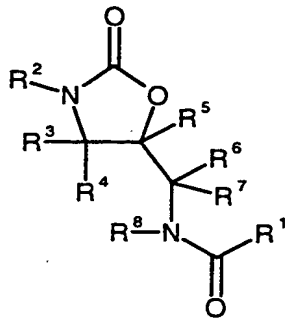
(III),

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)



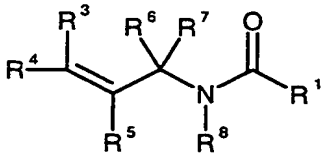
(I),

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)

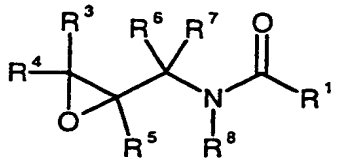


(IV),

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,

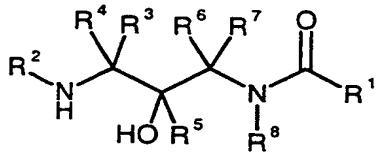
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the general formula (VI)

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

in which

the radical R^2 is as defined above,

the compounds of the general formula (VII)



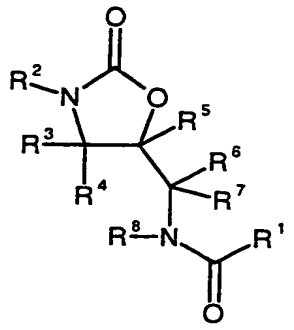
(VII),

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

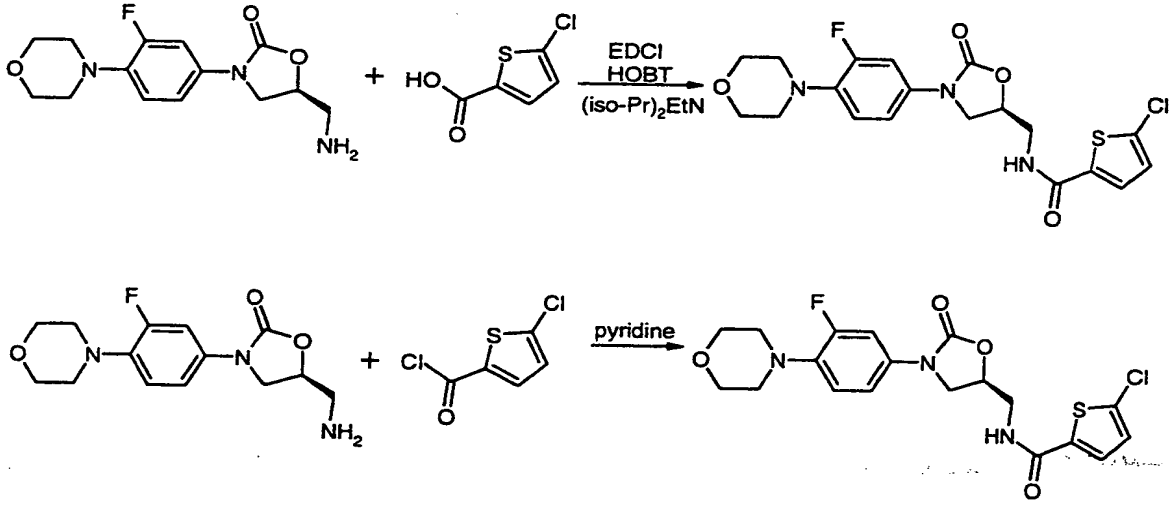
where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with various reagents such as carboxylic acids, carboxylic anhydrides, carbonyl chlorides,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

and/or

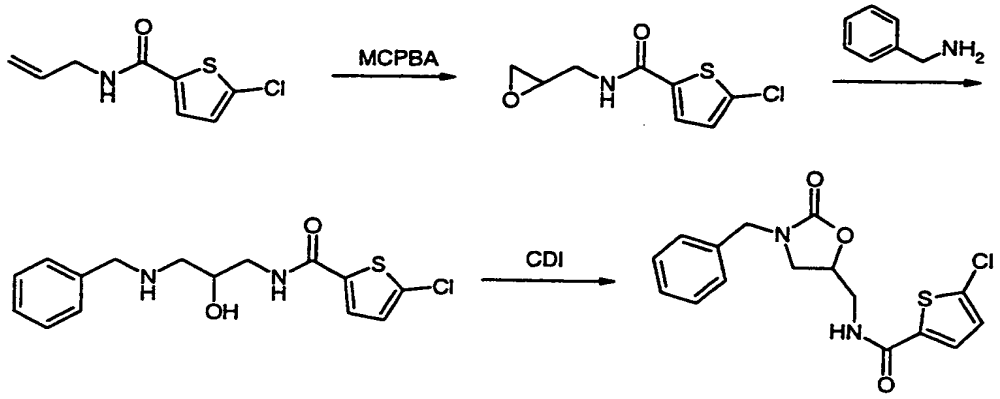
where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has a phenyl ring in the molecule, a reaction with chlorosulphonic acid and subsequent reaction with amines to give the corresponding sulphonamides may follow.

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

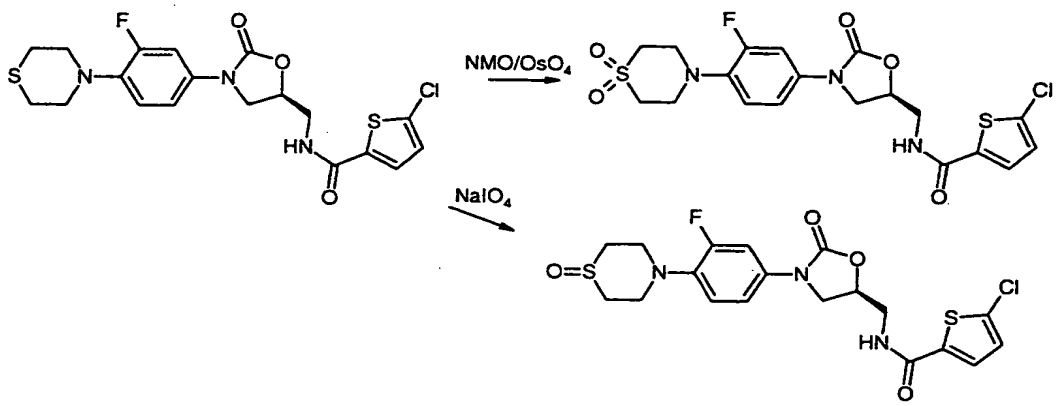
[A]



[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

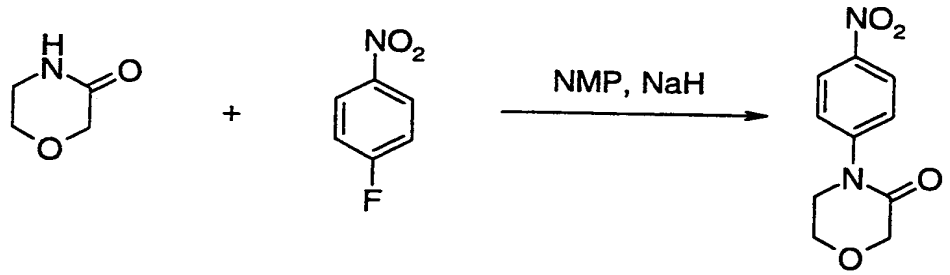
Starting materials

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

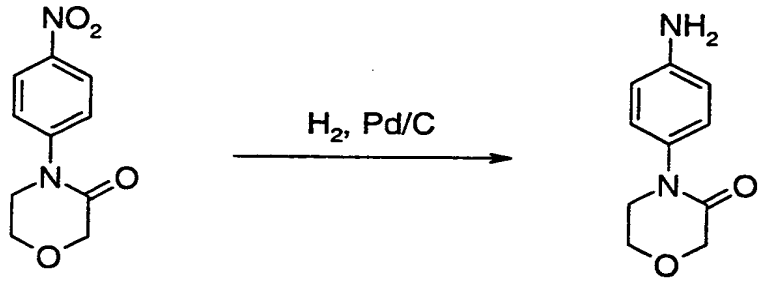
4-(N-piperidonyl)nitrobenzene

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.

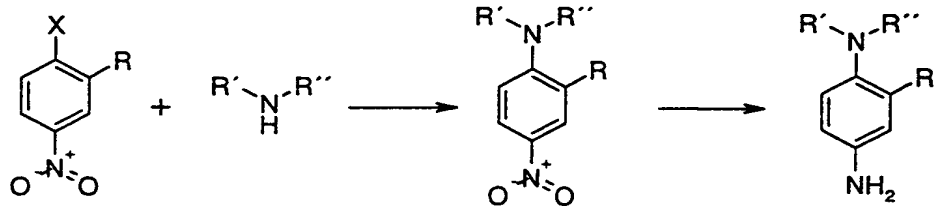
^{1}H-NMR (300 MHz, $CDCl_3$): 3.67 (m, 2 H, CH_2CH_2), 3.99 (m, 2 H, CH_2CH_2), 4.27 (s, 2 H, CH_2CO), 6.68 (d, 2 H, ^3J=8.71 Hz, CHCH), 7.03 (d, 2 H, ^3J=8.71 Hz, CHCH)

MS (r.I.%) = 192 (100, $M^{+\cdot}$), 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.

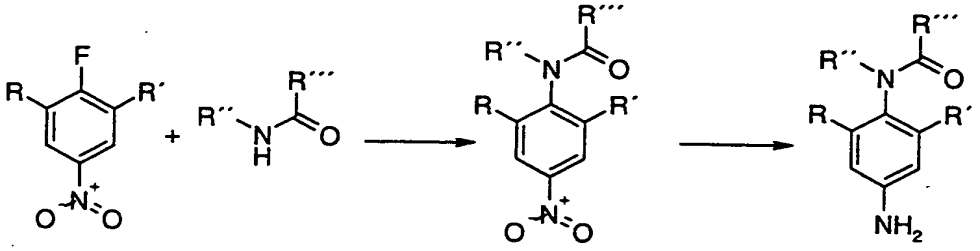
III.-13. 5-amino-2-(4-morpholinyl)benzamide
MS (ESI): m/z (%) = 222 (M+H, 100);
HPLC (method 4): rt = 0.77 min.

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);

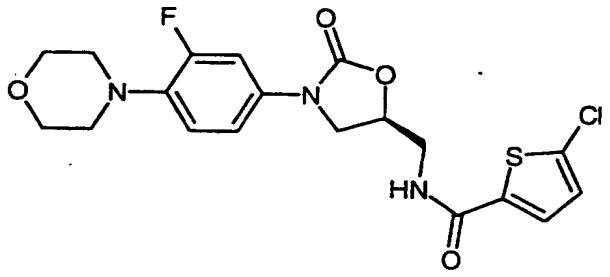
HPLC (method 4): rt = 2.43 min.

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.

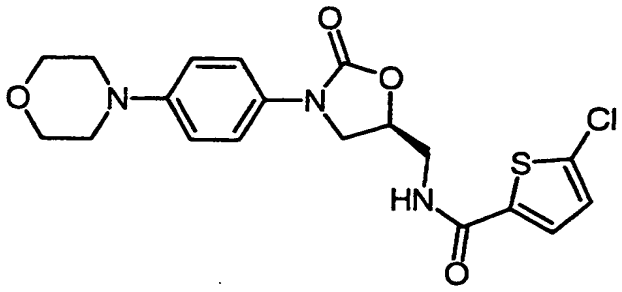
R_f (SiO_2, toluene/ethyl acetate 1:1) = 0.29 (starting material = 0.0);

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).

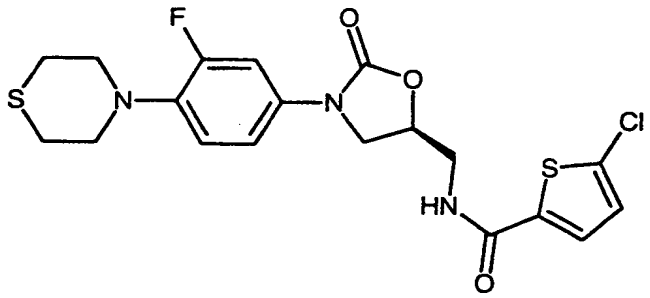
M.p.: 198°C;

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).

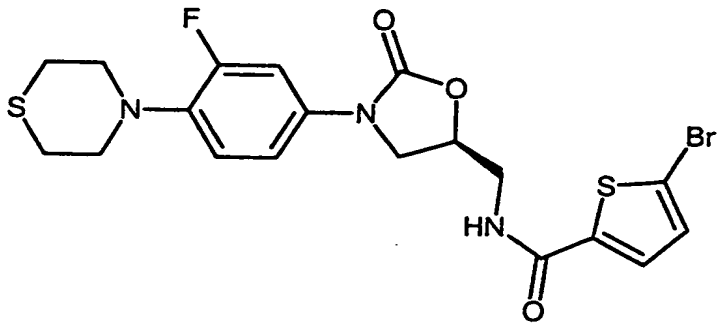
M.p.: 193°C;

Yield: 82%;

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

Example 4

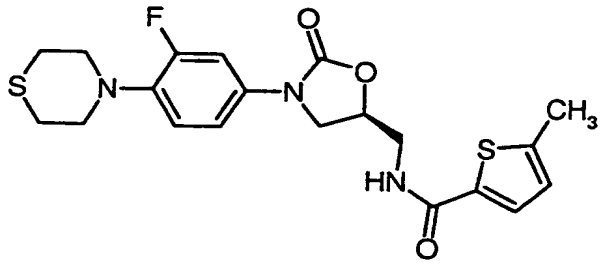
5-Bromo-N-({(5S)-3-[3-fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



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

Example 5

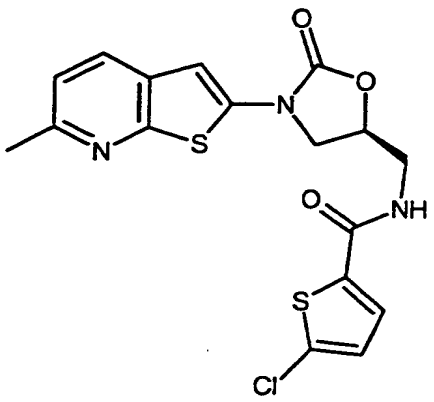
N-({(5S)-3-[3-Fluoro-4-(1,4-thiazinan-4-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-methyl-2-thiophenecarboxamide



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

Example 6

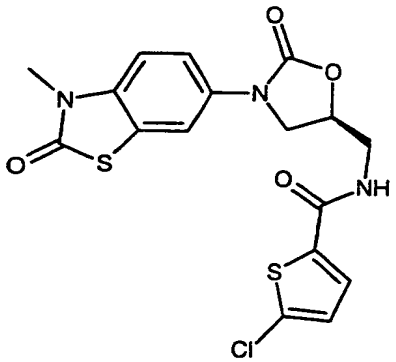
5-Chloro-N-{[(5S)-3-(6-methylthieno[2,3-b]pyridin-2-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



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

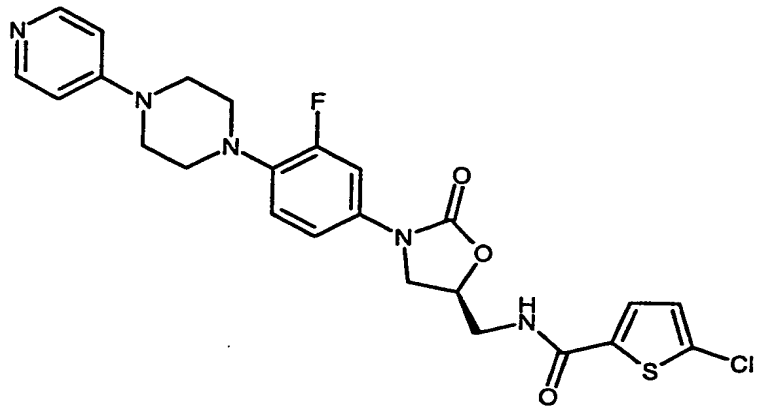
5-Chloro-N-{[(5S)-3-(3-methyl-2-oxo-2,3-dihydro-1,3-benzothiazol-6-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



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

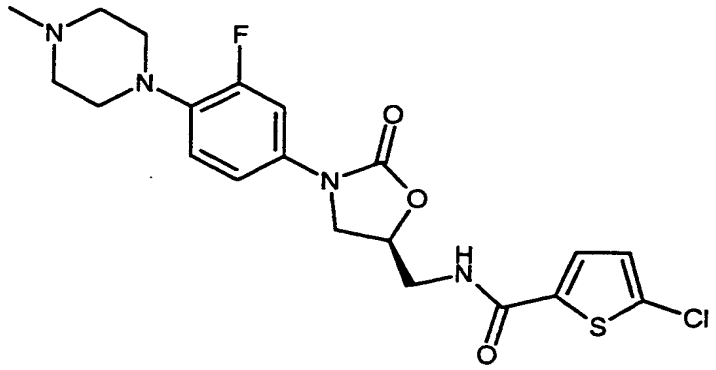


is obtained analogously from (5S)-5-(aminomethyl)-3-{3-fluoro-4-[4-(4-pyridinyl)piperazino]phenyl}-1,3-oxazolidin-2-one (preparation analogously to J. A. Tucker et al., J. Med. Chem. 1998, 41, 3727).

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

Example 9

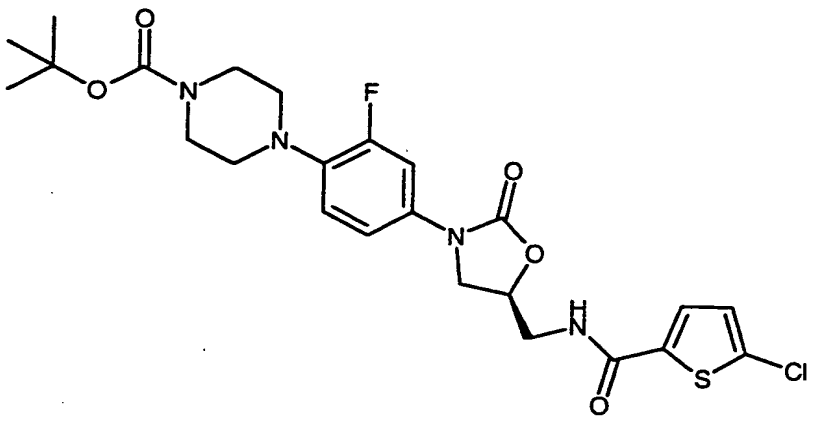
5-Chloro-N-({(5S)-3-[3-fluoro-4-(4-methylpiperazino)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide



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



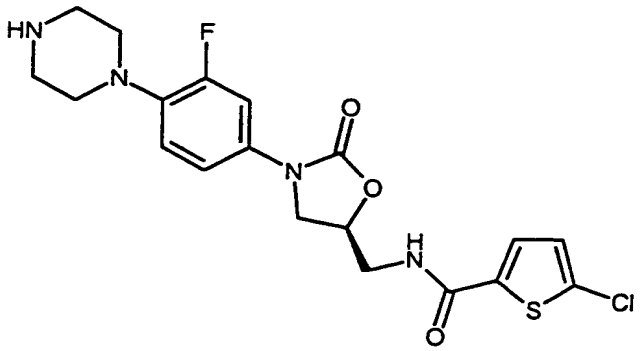
is obtained analogously from (5S)-5-(aminomethyl)-3-[3-fluoro-4-(4-tert-butoxy-carbonylpiperazin-1-yl)phenyl]-1,3-oxazolidin-2-one (preparation see WO-A-93/23384, which has already been cited).

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



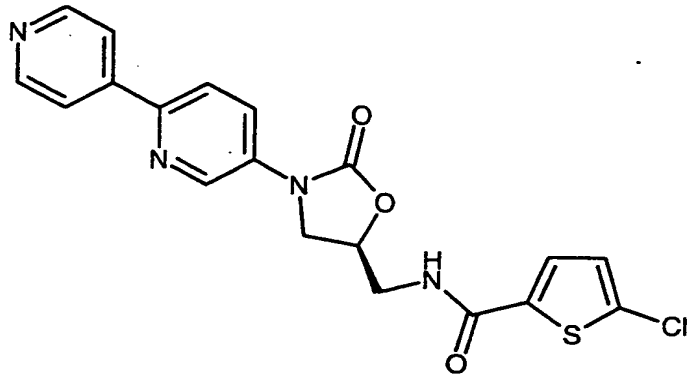
is obtained by reacting Example 12 with trifluoroacetic acid in methylene chloride.

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



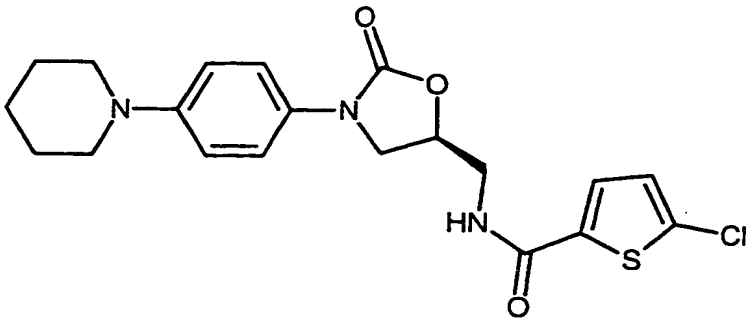
is obtained analogously from (5S)-5-aminomethyl-3-(2,4`-bipyridinyl-5-yl)-2-oxo-1,3-oxazolidin-2-one (preparation see EP-A-789 026).

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

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

Example 13

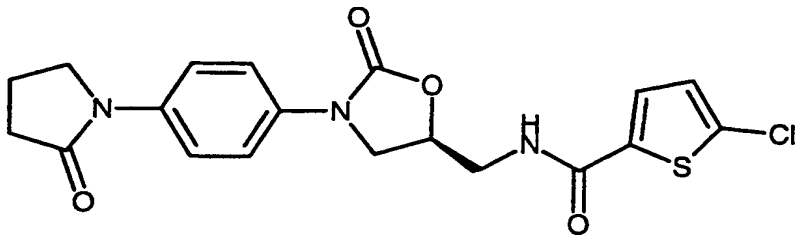
5-Chloro-N-{[(5S)-2-oxo-3-(4-piperidinophenyl)-1,3-oxazolidin-5-yl]methyl}-2-thiophenecarboxamide



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

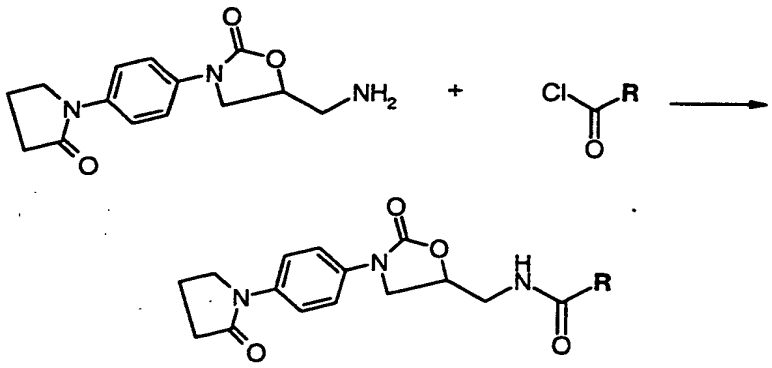
Example 40

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.

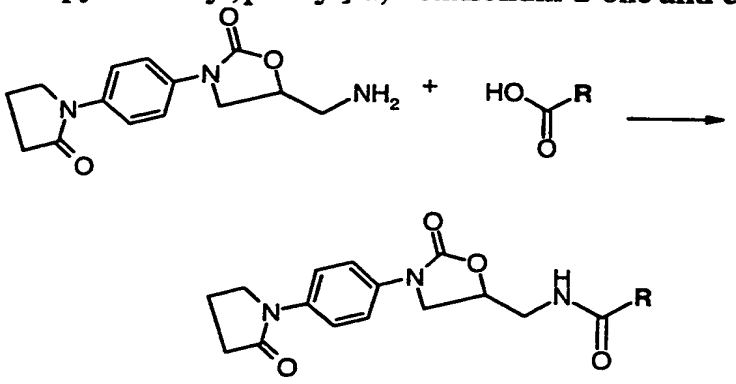
The following compounds were prepared in an analogous manner:

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

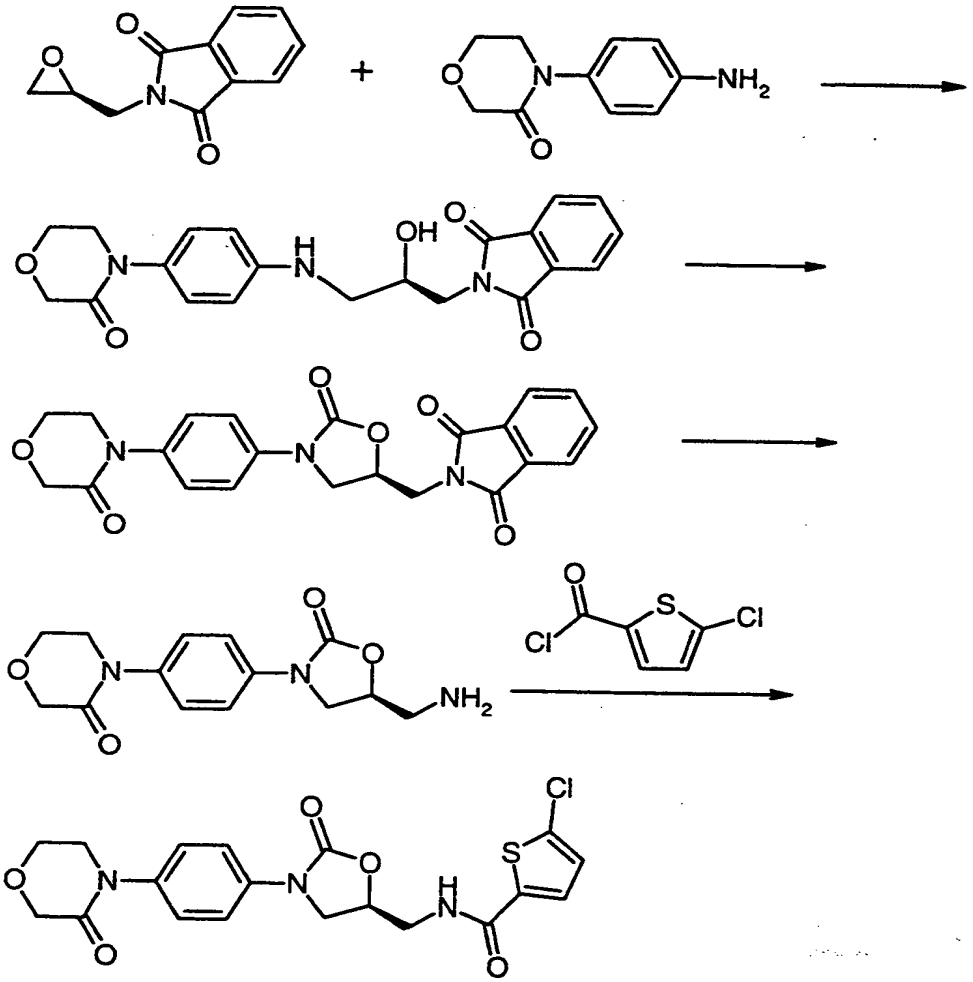
LC-MS : m/z (%) = 466 (M+H, 100);

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

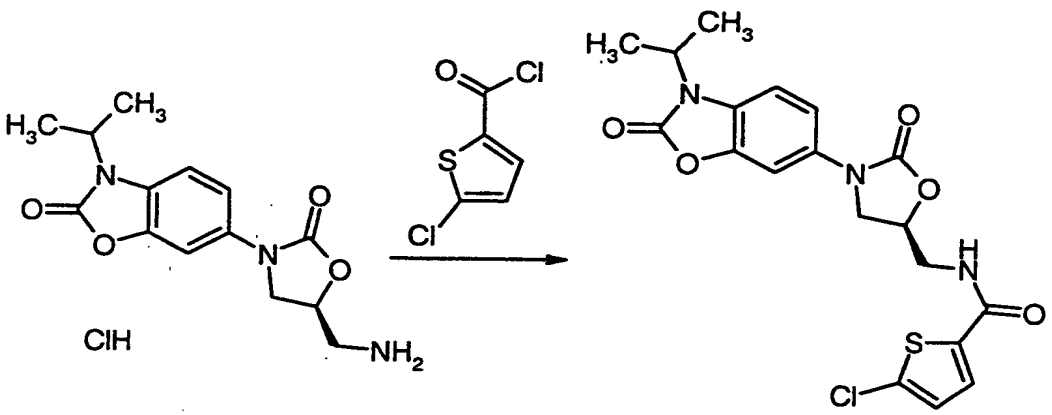
5-Methyl-*N*-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 831 ([2M+H]$^+$, 100), 416 ([M+H]$^+$, 66);
HPLC (method 3): rt (%) = 3.65 (100).
IC_{50}: 4.2 nM

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

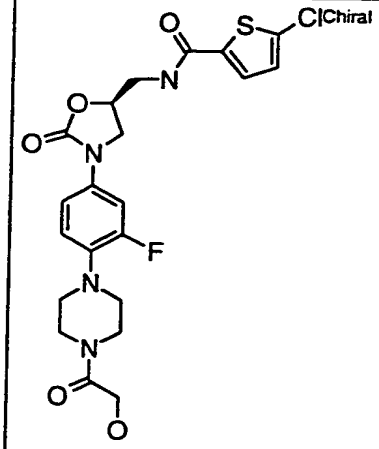
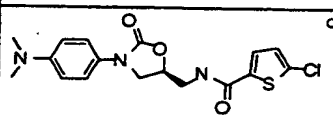
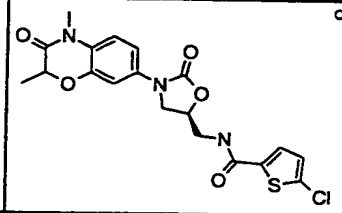
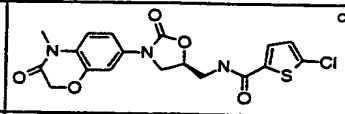
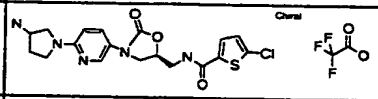
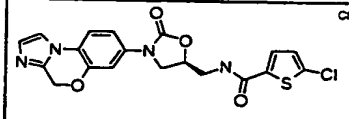


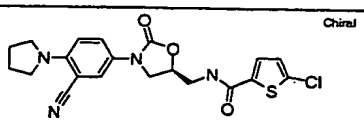
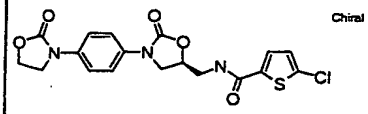
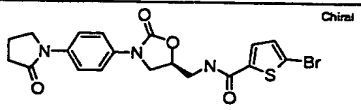
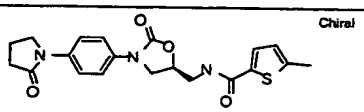
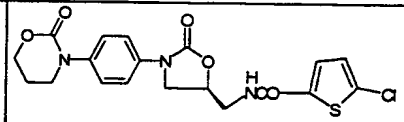
200 mg (0.61 mmol) of 6-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-3-isopropyl-1,3-benzoxazol-2(3H)-one hydrochloride (EP 738726) are suspended in 5 ml of tetrahydrofuran and admixed with 0.26 ml (1.83 mmol) of triethylamine and 132 mg (0.73 mmol) of 5-chlorothiophene-2-carbonyl chloride. The reaction 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:

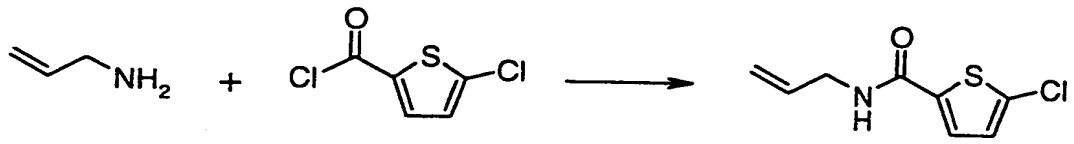
Example No.	Structure	M.p. [°C]	IC_{50} [μM]
48		210	0.12
49		234	0.074
50		195	1.15
51		212	1.19
52		160	0.19
53		MS (ESI): m/z (%) = 431 ([M+H]$^+$, 100), Cl pattern	0.74

Example No.	Structure	M.p. [°C]	IC_{50} [µM]
54	 from 5-amino-2-pyrrolidino-benzonitrile (Grell, W., Hurnaus, 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
255		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).

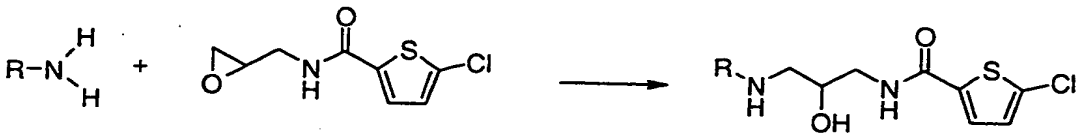
Example 21

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.

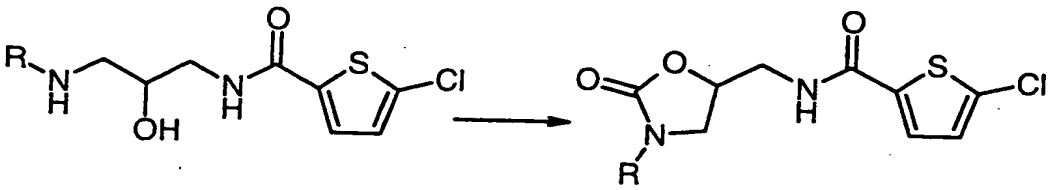
Example 91a

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**

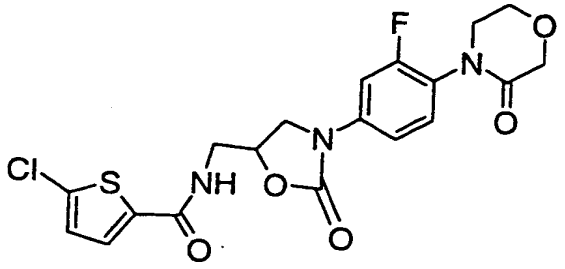
starting from Example 60:

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

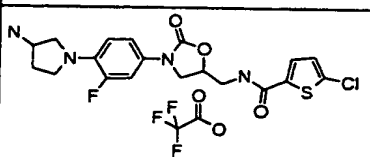
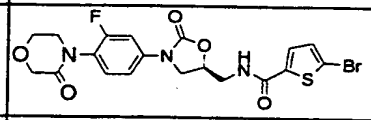
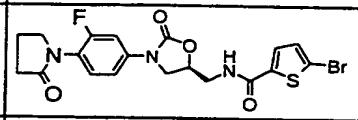
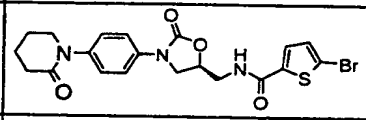
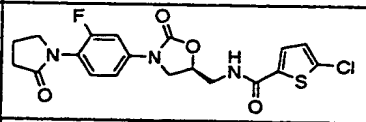
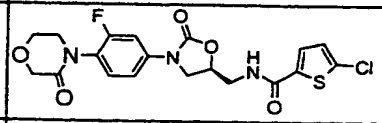
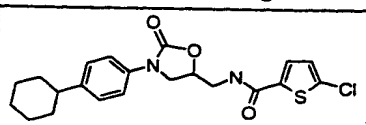
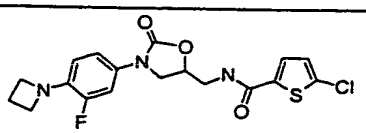
5-Chloro-N-({3-[3-chloro-4-(2-methyl-5-oxo-4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 484 (M+H, 100);
HPLC (method 4): rt = 3.63 min.

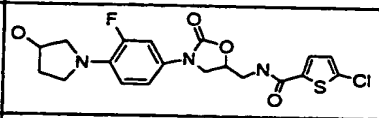
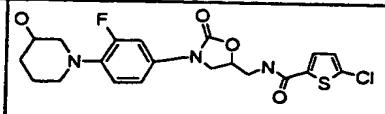
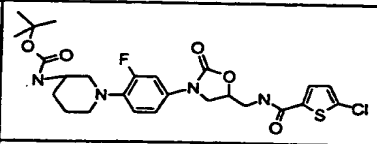
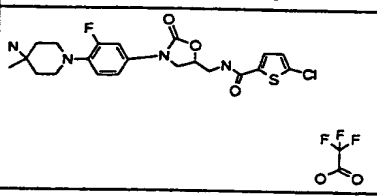
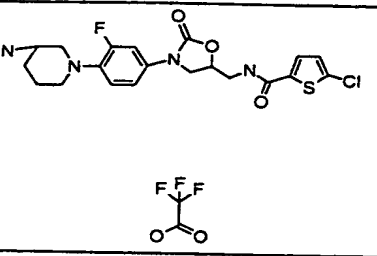
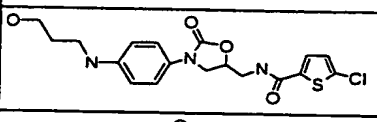
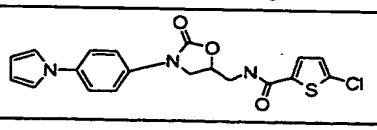
Example 125a

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:

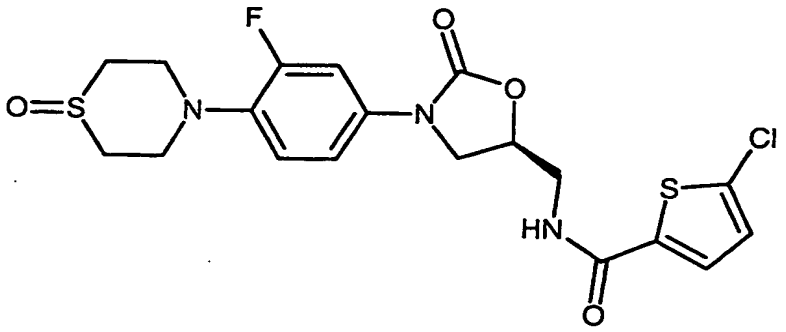
Example No.	Structure	M.p. [°C]	IC_{50} [μM]
126		229Z	0.013
127		159	0.0007
		198	0.002
129		196	0.001
130		206	0.0033
130a		194	
131		195	0.85
132		206	0.12

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;

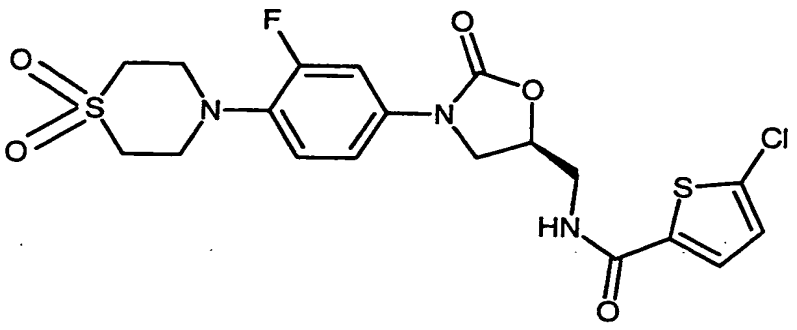
R_f (silica gel, toluene/ethyl acetate 1:1) = 0.54 (starting material = 0.46);

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

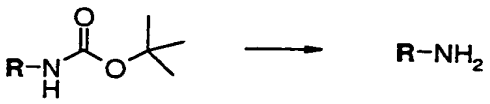
Example 147

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**

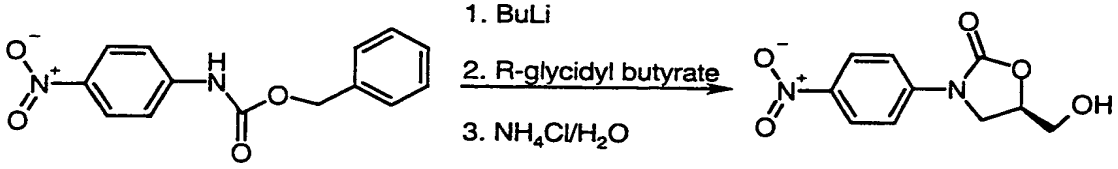
starting from Example 93:

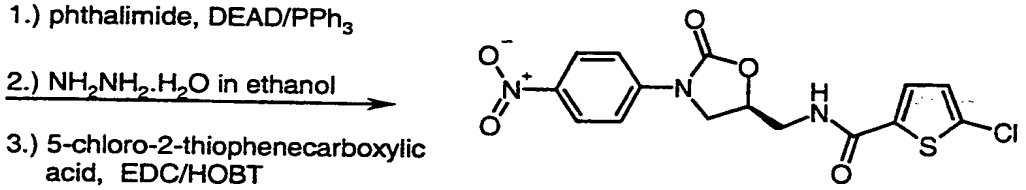
MS (ESI): m/z (%) = 352 (M+H, 25);

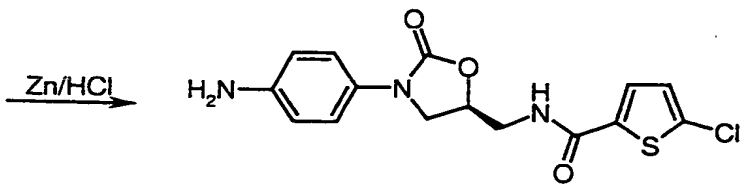
HPLC (method 1): rt (%) = 3.50 (100).

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);

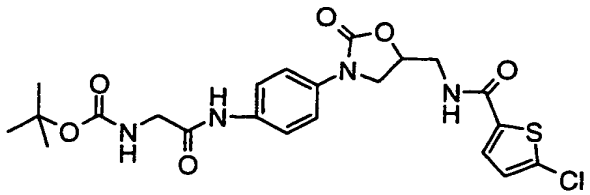
HPLC (method 3): rt (%) = 2.99 (100).

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

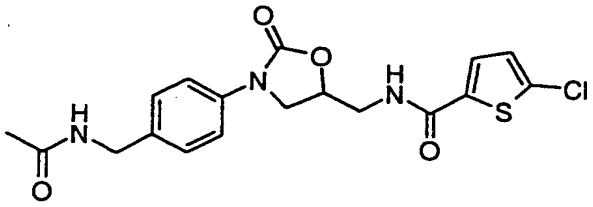


At 0°C, 754 mg (2.1 mmol) of *N*-{[3-(4-aminophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}-5-chloro-2-thiophenecarboxamide (from Example 149) are added to a solution of 751 mg (4.3 mmol) of Boc-glycine, 870 mg (6.4 mmol) of HOBT (1-hydroxy-1H-benzotriazole x H_2O), 1790 mg (4.7 mmol) of HBTU [O-(benzotriazol-1-yl)-N,N,N´,N´-tetramethyluronium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

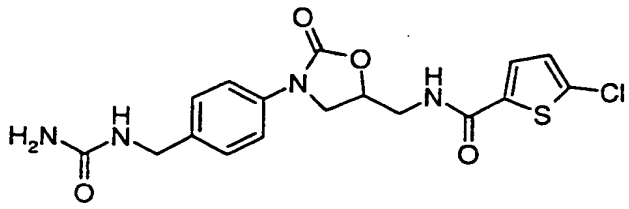
***N*-[(3-{4-[(Acetylamino)methyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-5-chloro-2-thiophenecarboxamide**



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**



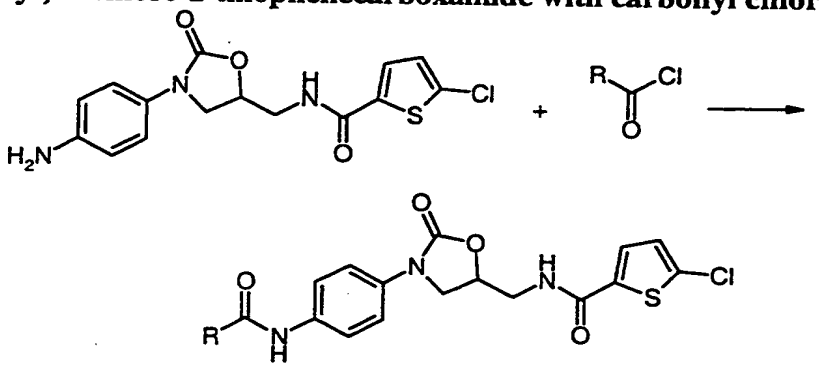
At room temperature, 0.19 ml (0.82 mmol) of trimethylsilylisocyanate are added dropwise to a mixture of 30 mg (0.082 mmol) of *N*-({3-[4-(aminomethyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)-5-chloro-2-thiophene-carboxamide (from Example 148) in 1.0 ml of dichloromethane. The mixture is stirred overnight 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

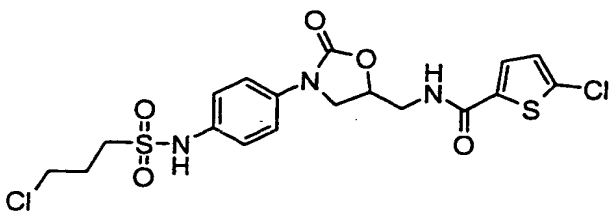
5-Chloro-*N*-[(3-{4-[(methoxyacetyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)-methyl]-2-thiophenecarboxamide
LC-MS: m/z (%) = 424 (M+H, 100);
LC-MS (method 6): rt (%) = 3.39 (100).
IC_{50}: 0.73 μM

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),

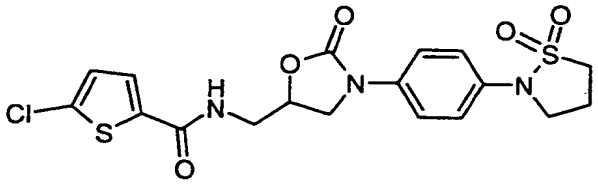
LC-MS: m/z (%) = 492 (M+H, 100);

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),

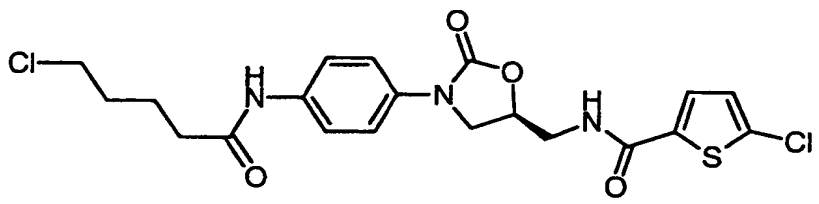
MS (ESI): m/z (%) = 456 (M+H, 15), 412 (100);

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

IC_{50}: 0.14 μM

Example 161

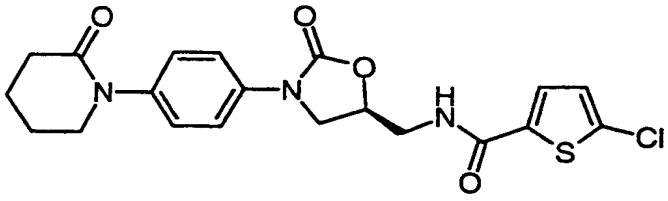
5-Chloro-N-[((5S)-3-{4-[(5-chloropentanoyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



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.

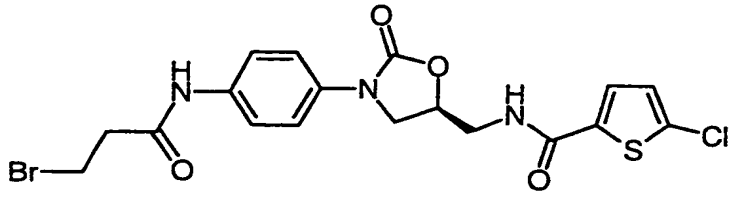
M.p.: 205°C;

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

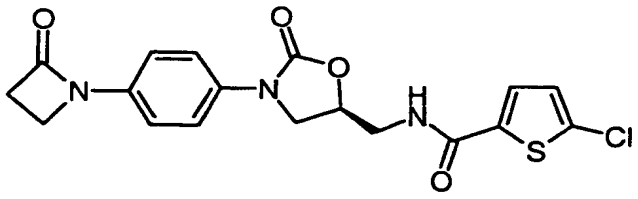
5-Chloro-N-[((5S)-3-{4-[(3-bromopropionyl)amino]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-2-thiophenecarboxamide



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



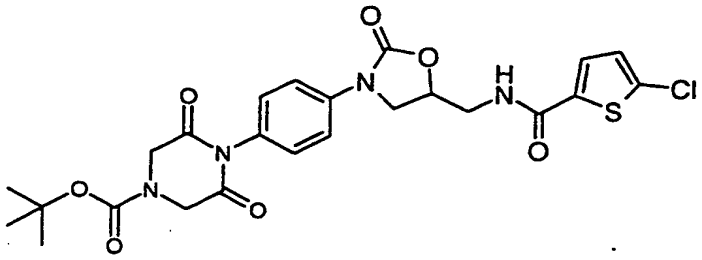
is obtained in an analogous manner by cyclization of the open-chain bromopropionyl compound from Example 163 using NaH/DMSO.

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);

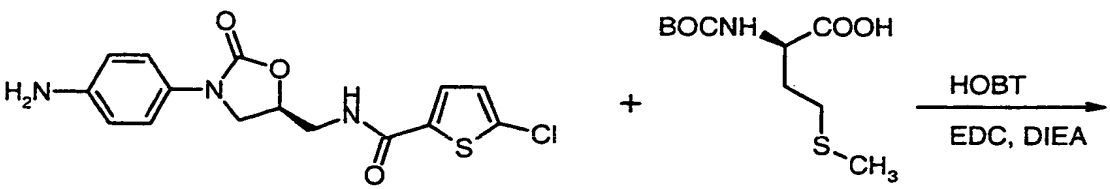
MS (ESI): m/z (%) = 571 (M+Na, 82), 493 (100);

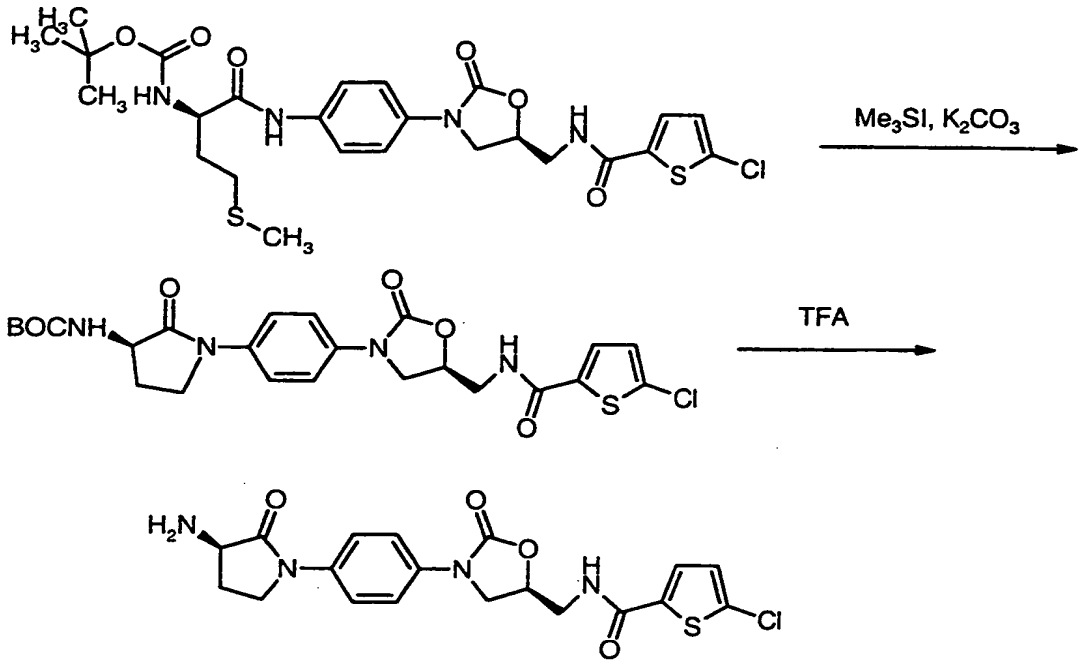
HPLC (method 3): rt (%) = 4.39 (90).

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

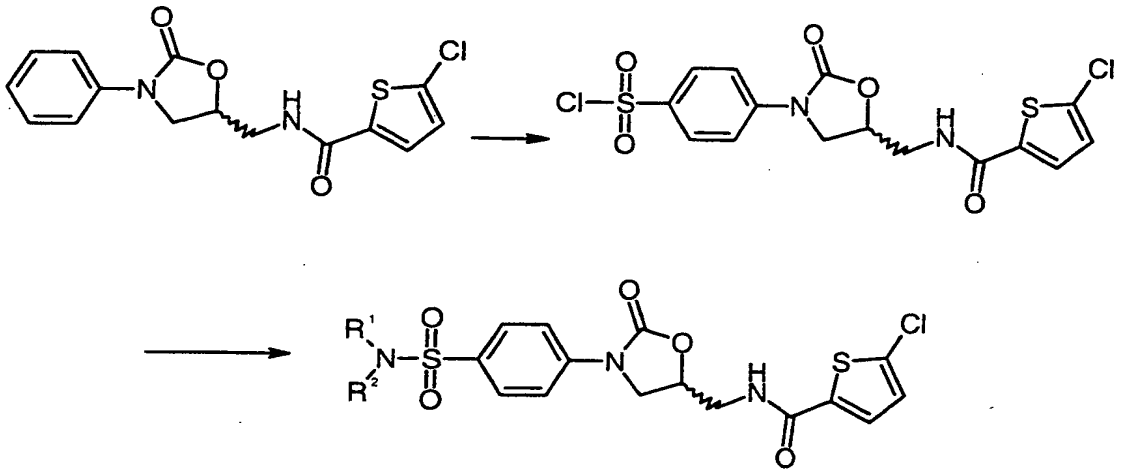
97 mg (0.181 mmol) of tert-butyl (3R)-1-{4-[(5S)-5-({[(5-chloro-2-thienyl)carbonyl]amino}methyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-2-oxo-3-pyrrolidinylcarbamate are suspended in 4 ml of methylene chloride, 1.5 ml of trifluoroacetic acid are added and the mixture is stirred at room temperature for 1 hour. 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

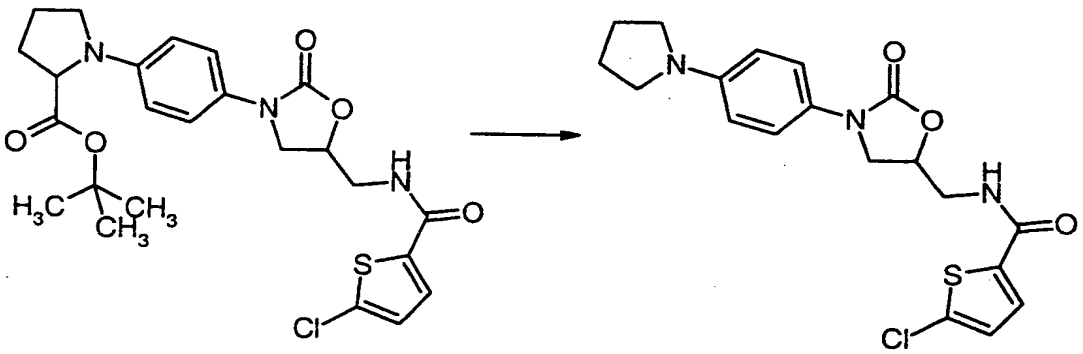
5-Chloro-*N*-({2-oxo-3-[4-(1-piperidinylsulphonyl)phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide
MS (ESI): m/z (%) = 484 ($[M+H]^+$, 100), Cl pattern;
HPLC (method 2): rt (%) = 4.4 (100).

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

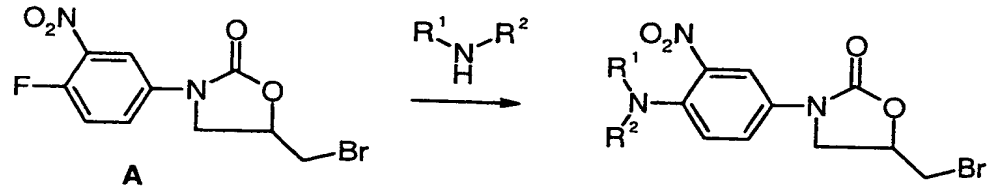
[7] MHZ-7Q, Instrument Micromass Quattro LCZ
Column Symmetry C18, 50 mm x 2.1 mm, 3.5 µm, temperature: 40°C, flow rate = 0.5 ml min^{-1}, eluent A = CH_3CN + 0.1% formic acid, eluent B = water + 0.1% formic acid, gradient: 0.0 min 5% A -> 1 min 5% A -> 5 min 90% A -> 6 min 90% A

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

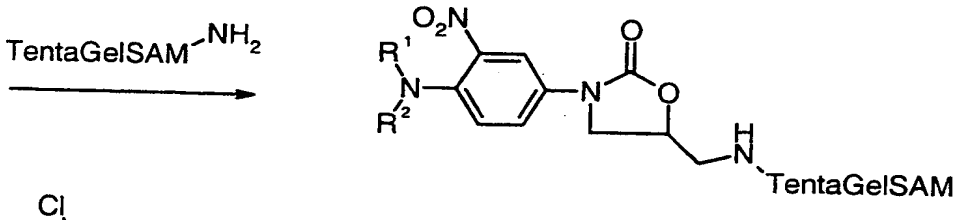
Reactions with different resin-bonded products were carried out in a set of separated reaction vessels.

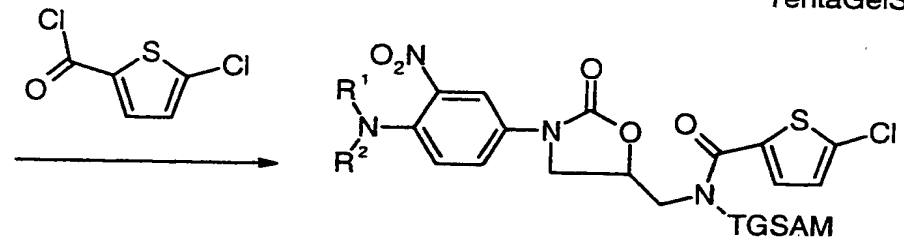
5-(Bromomethyl)-3-(4-fluoro-3-nitrophenyl)-1,3-oxazolidin-2-one **A** (prepared from epibromohydrin and 4-fluoro-3-nitrophenyl isocyanate using LiBr/Bu_3PO in xylene analogously to US 4128654, Ex.2) (1.20 g, 3.75 mmol) and ethyldiisopropylamine (DIEA, 1.91 ml, 4.13 mmol) were dissolved in DMSO (70 ml), 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

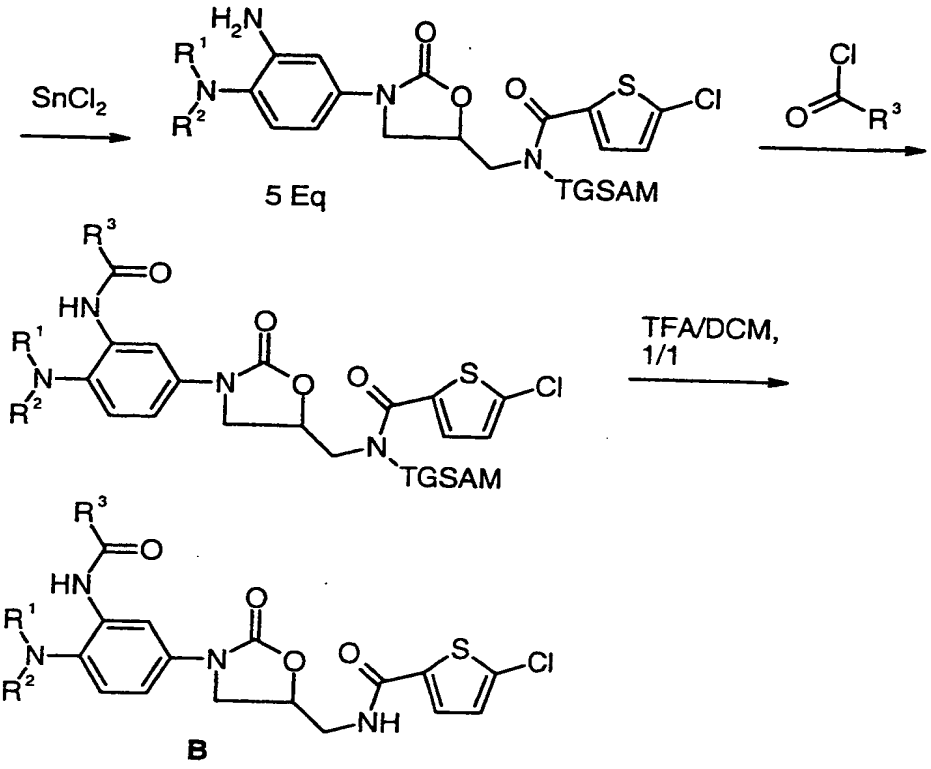
suspended in DMF/water (v/v 9:2, 80 ml), admixed with $SnCl_2*2H_2O$ (5 eq.) and reacted at room temperture for 18 h. The resin was washed repeatedly with MeOH, DMF, water, MeOH, DCM and diethyl ether and dried. This resin was suspended in DCM, admixed with DIEA (10 eq.) and, at 0°C, with an acid chloride (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**.



A



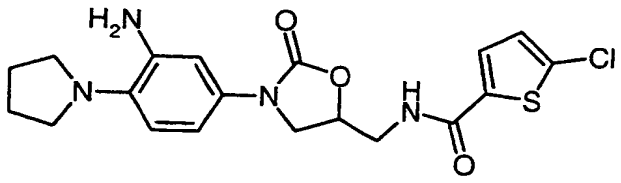




Compounds which were prepared by solid-phase-supported synthesis:

Example 172

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



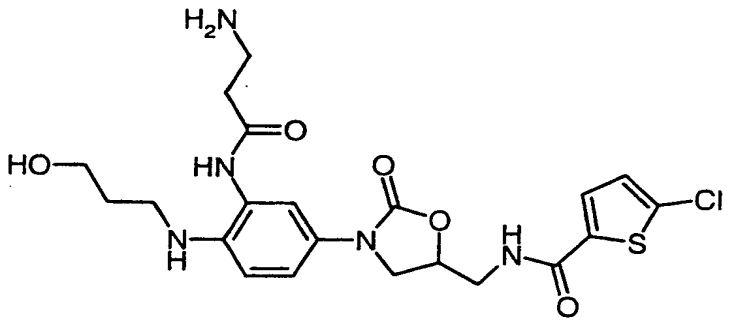
Analogously to the general procedure for preparing the derivatives **B**, 5 g (1.25 mmol) of TentaGel SAM resin were reacted with pyrrolidine as amine derivative 1. The aniline obtained after reduction with $SnCl_2*2H_2O$ was, without any further acylation step, removed from the solid phase and concentrated. 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

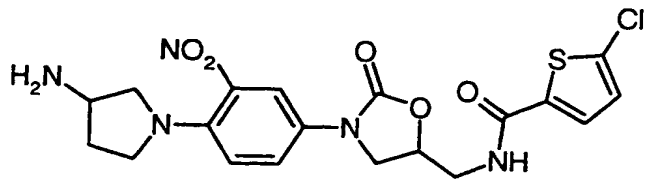


Analogously to the general procedure for preparing the derivatives **B**, 5 g (1.25 mmol) of TentaGel SAM resin were reacted with azetidine as amine derivative 1 and Fmoc-ß-alanine as acid derivative 1. The crude product obtained after the removal was stirred in methanol at room temperature for 48 h 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

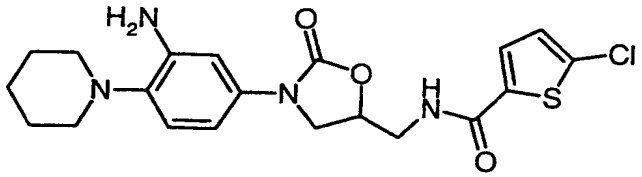


Analogously to the general procedure for preparing the derivatives **B**, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted with *tert*-butyl 3-pyrrolidinylcarbamate as amine derivative 1. The nitrobenzene derivative obtained after the acylation with 5-chlorothiophenecarboxylic acid was removed from 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

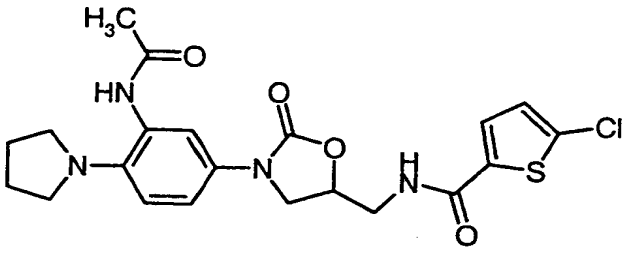


Analogously to the general procedure for preparing the derivatives **B**, 130 mg (32.5 μmol) of TentaGel SAM resin were reacted with piperidine as amine derivative 1. The aniline obtained after the reduction was, without any further acylation step, removed from the solid phase and concentrated. This 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

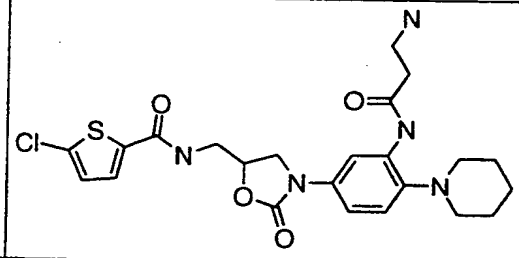
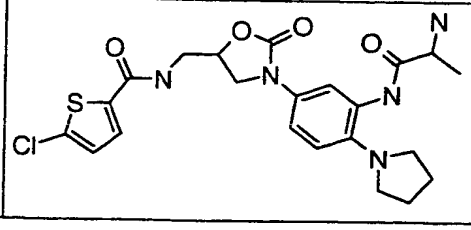
N-({3-[3-(Acetylamino)-4-(1-pyrrolidinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)-5-chloro-2-thiophenecarboxamide

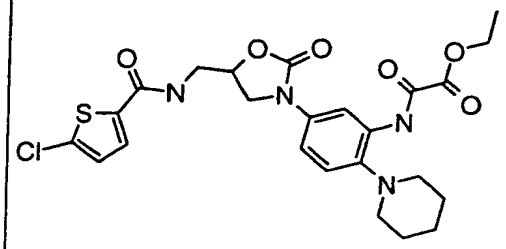
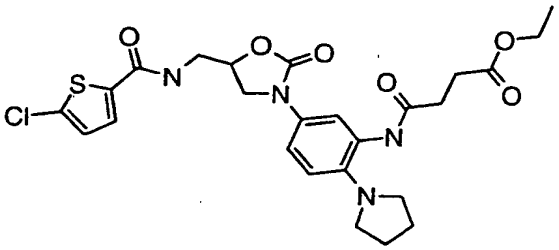
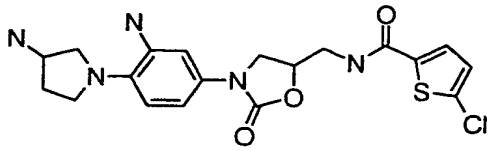
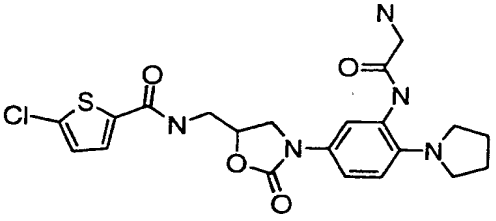
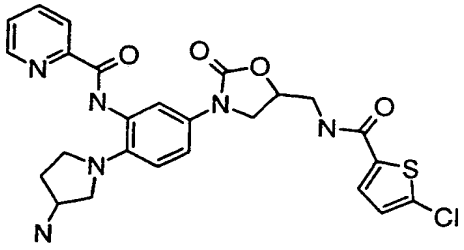
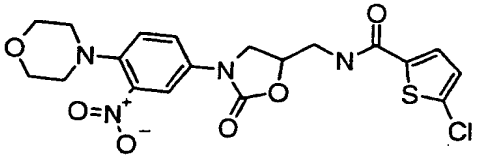


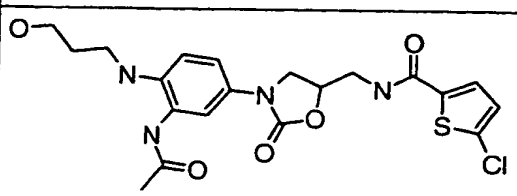
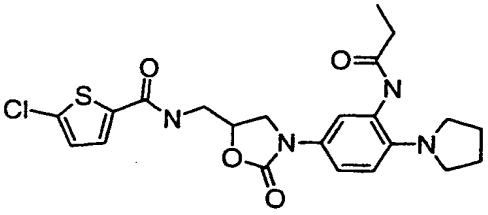
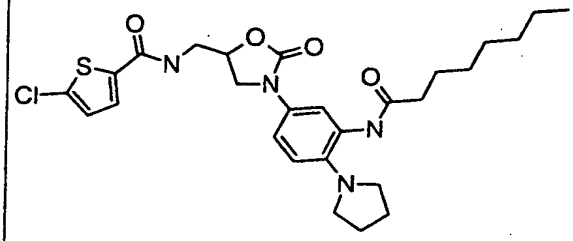
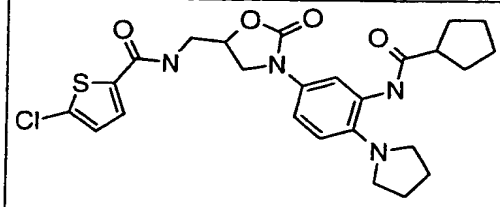
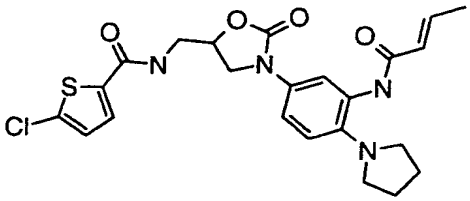
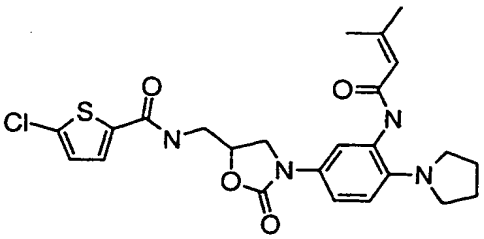
Analogously to the general procedure for preparing the derivatives **B**, 130 mg (32.5 µmol) of TentaGel SAM resin were reacted pyrrolidine as amine derivative 1 and acetyl chloride as acid derivative 1. The crude product was partitioned between ethyl acetate $NaHCO_3$ solution and the organic phase 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).

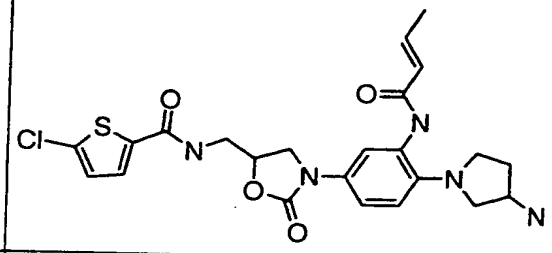
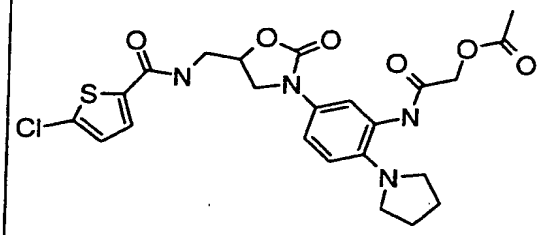
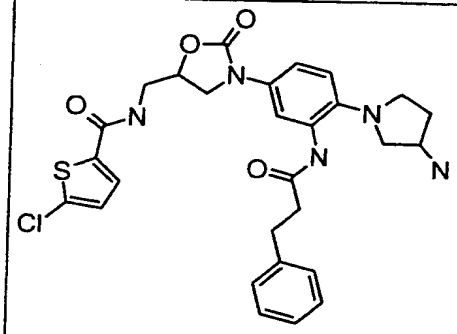
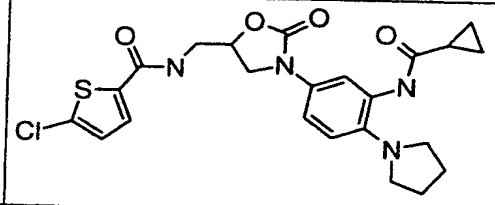
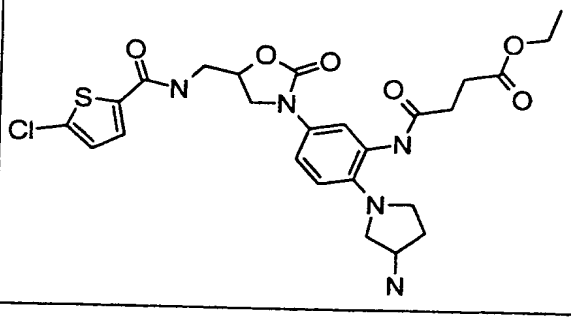
^{1}H-NMR (400 MHz, CD_3OH): 1.93 – 2.03, br, 4 H; 2.16, s, 3 H; 3.20-3.30, br, 4 H; 3.70, d, 2 H; 3.86, dd, 1H; 4.10, dd, 1 H; 4.14, dd, 1 H; 4.80-4.90, m, 1 H; 7.00, d, 1 H; 7.07, d, 1 H; 7.31, dd, 1 H; 7.51, d, 1 H; 7.60, d, 1 H.

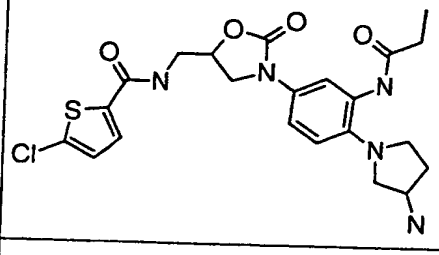
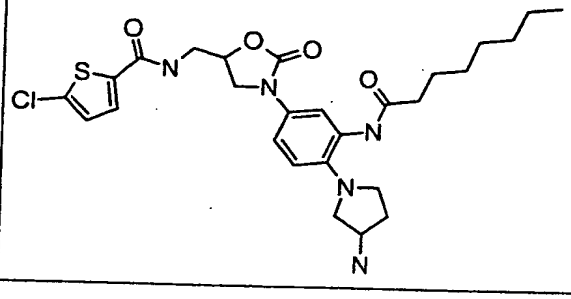
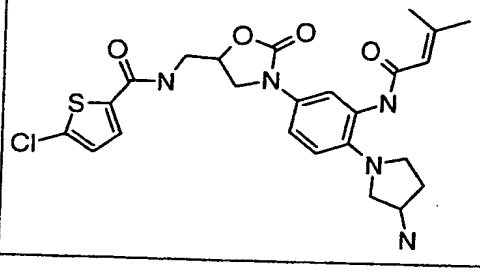
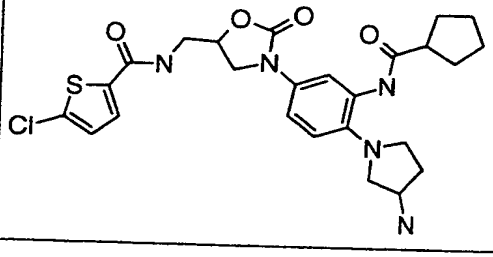
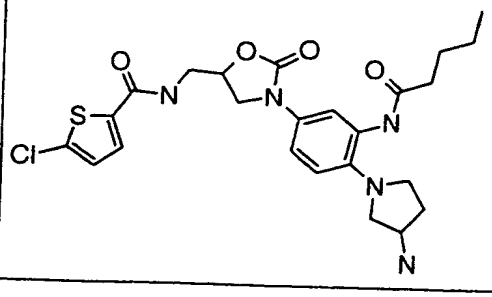
The following compounds were prepared analogously to the general procedure.

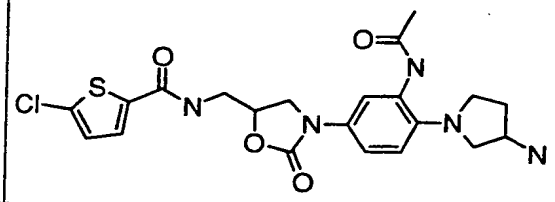
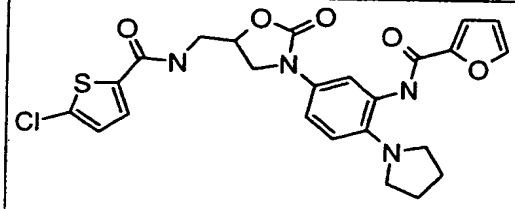
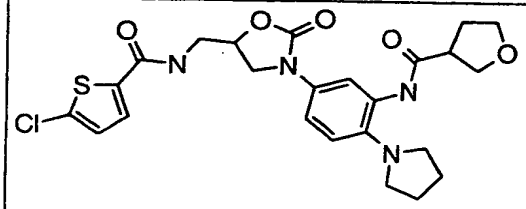
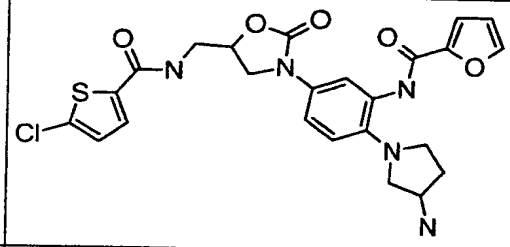
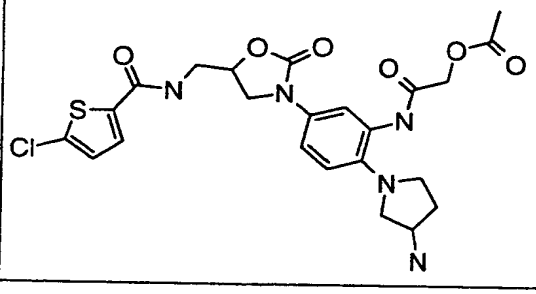
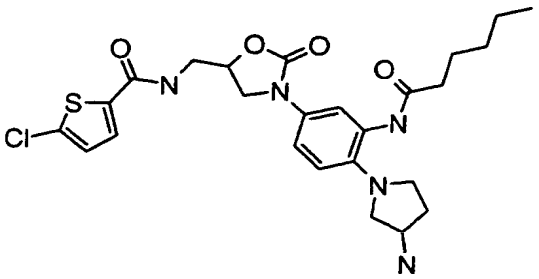
Example	Structure	Ret. time	HPLC [%]
177		2.62	79.7
178		2.49	33.7

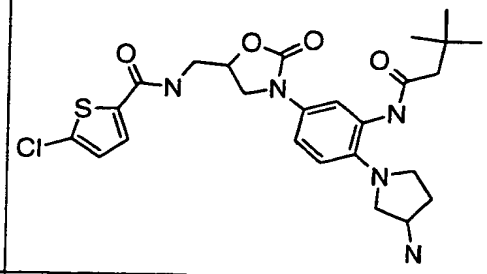
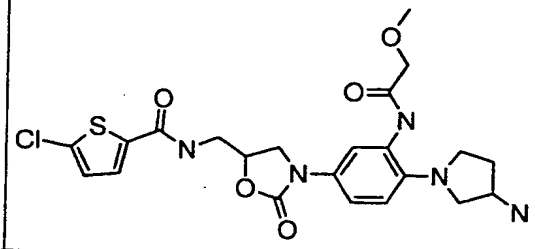
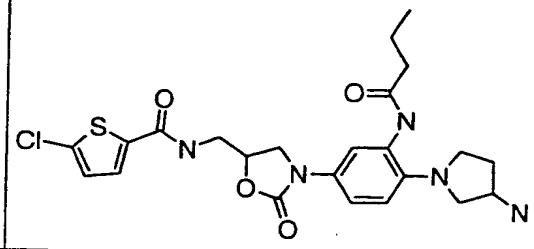
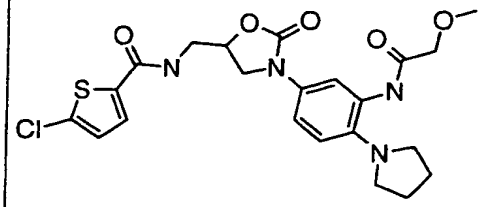
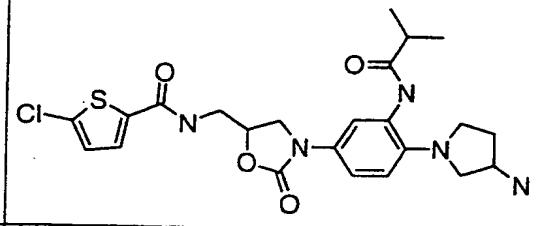
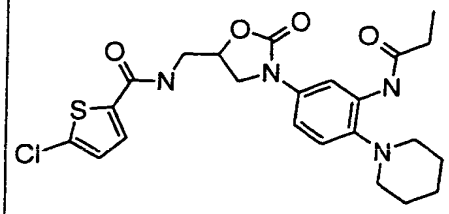
Example	Structure	Ret. time	HPLC [%]
179		4.63	46.7
180		3.37	44.8
181		2.16	83
182		2.31	93.3
183		2.7	100
184		3.91	51

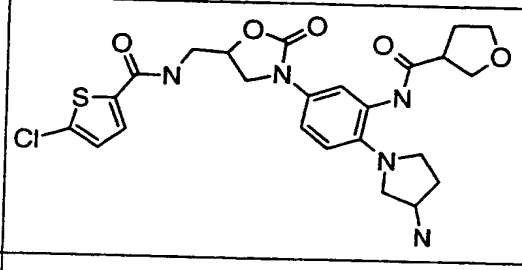
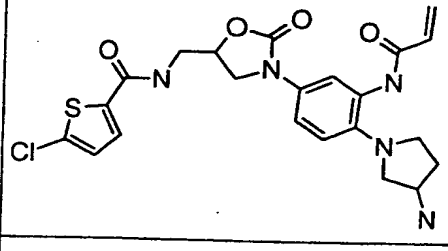
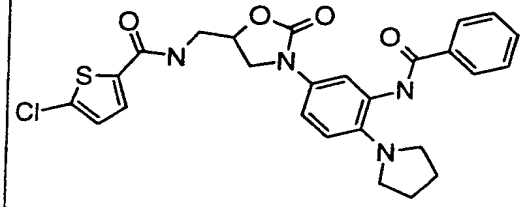
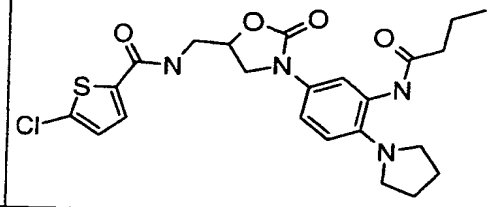
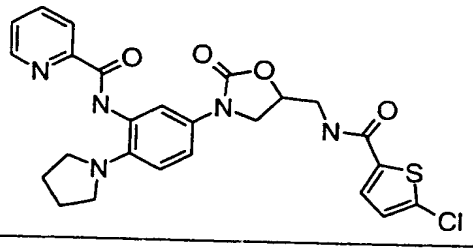
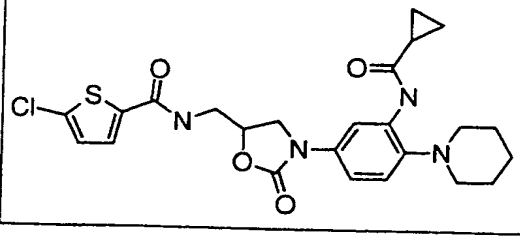
Example	Structure	Ret. time	HPLC [%]
185		2.72	75.2
186		3.17	46
187		4.61	50.2
188		3.89	56.6
189		3.37	52.9
190		3.6	63.9

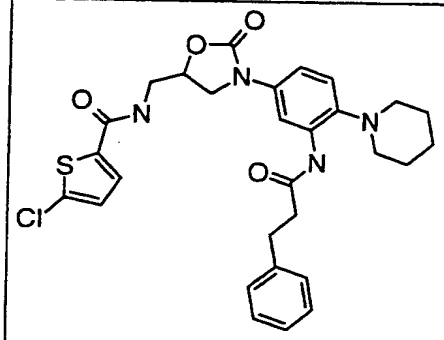
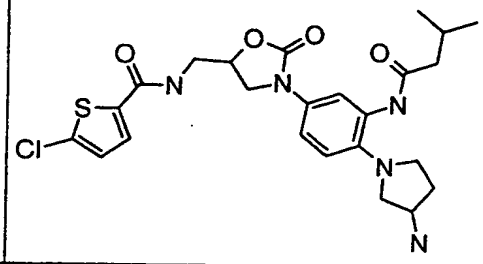
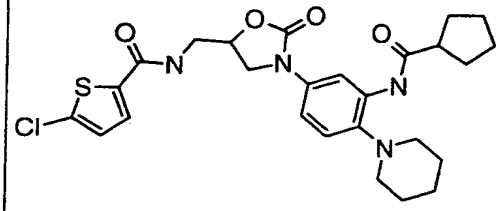
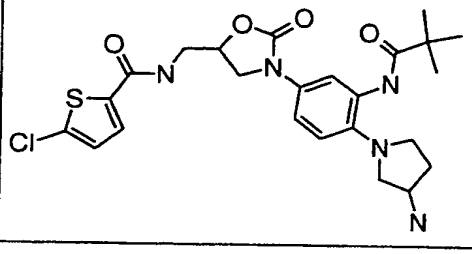
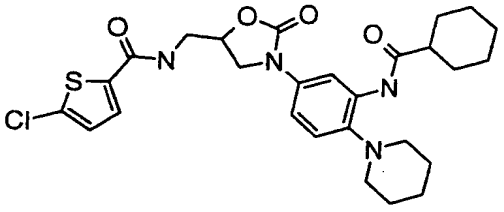
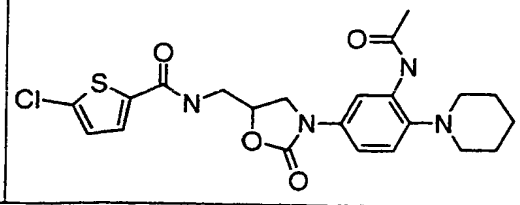
Example	Structure	Ret. time	HPLC [%]
191		2.52	70.1
192		3.52	46.6
193		2.87	50.1
194		3.25	71.1
195		2.66	67

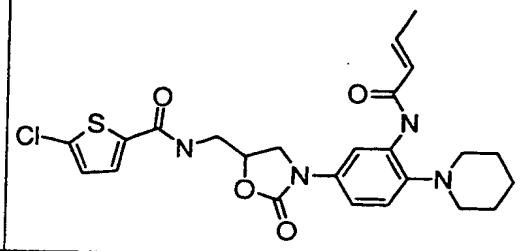
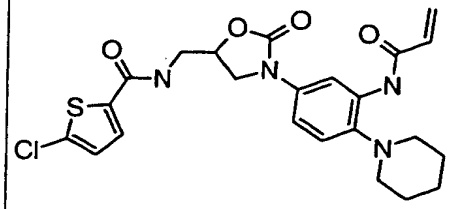
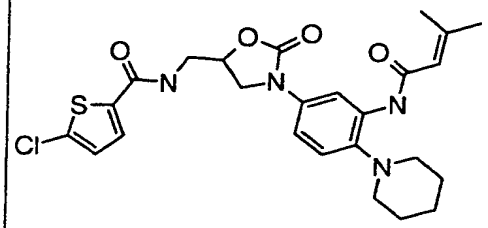
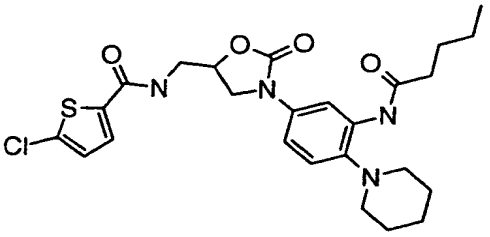
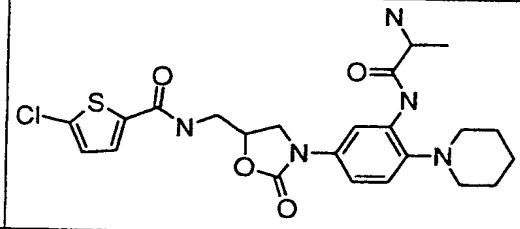
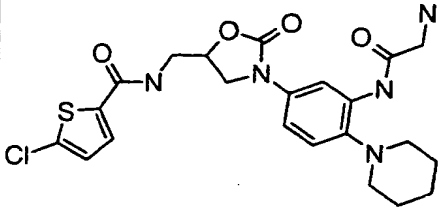
Example	Structure	Ret. time	HPLC [%]
196		2.4	52.1
197		3.13	48.9
198		2.67	75.5
199		2.72	65.7
200		2.71	57.3

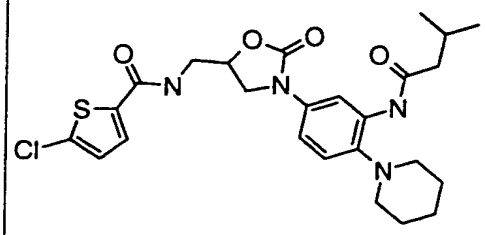
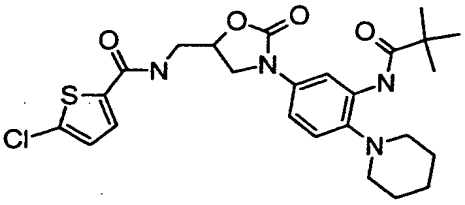
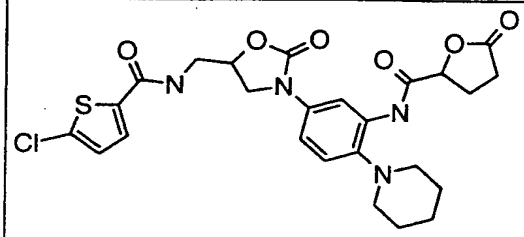
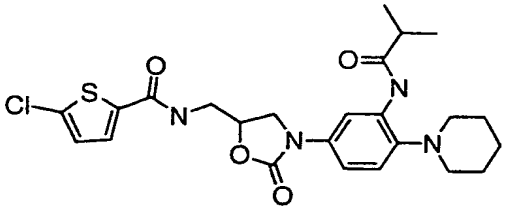
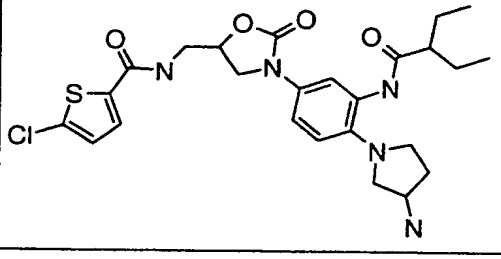
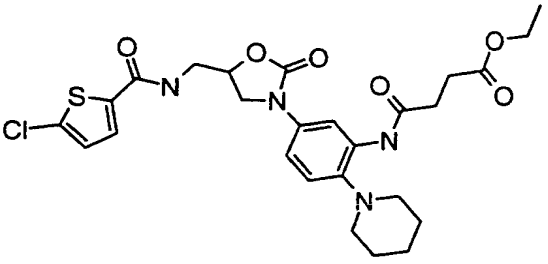
Example	Structure	Ret. time	HPLC [%]
201		2.22	100
202		3.89	75.7
203		3.19	49.6
204		2.55	88.2
205		2.44	68.6
206		2.86	71.8

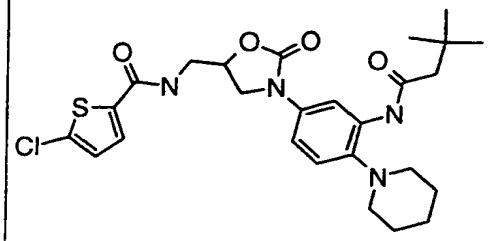
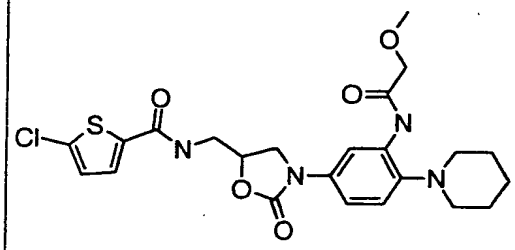
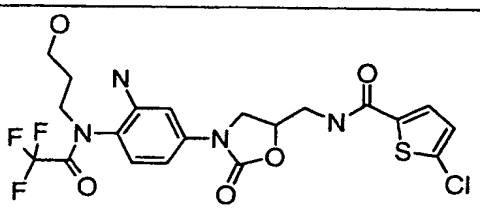
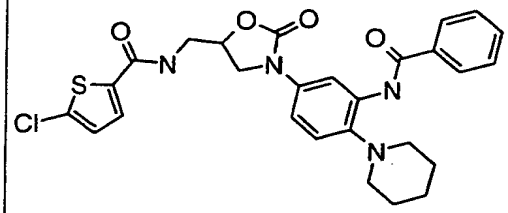
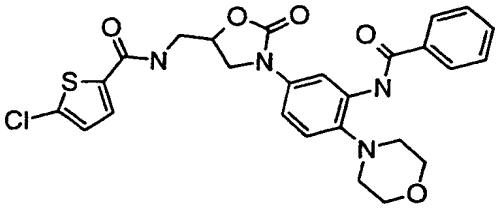
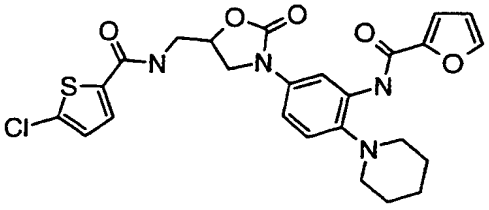
Example	Structure	Ret. time	HPLC [%]
207		2.8	63.6
208		2.41	77
209		2.56	67.9
210		3.67	78.4
211		2.54	69.8
212		3.84	59.2

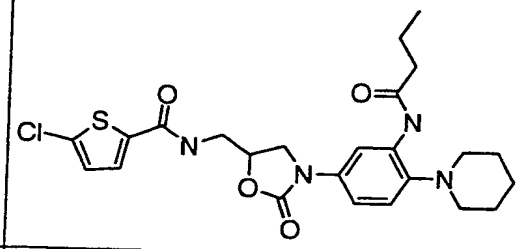
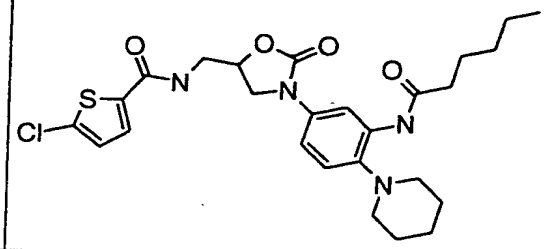
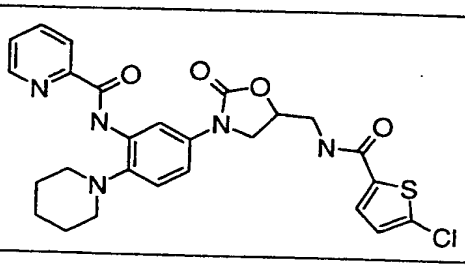
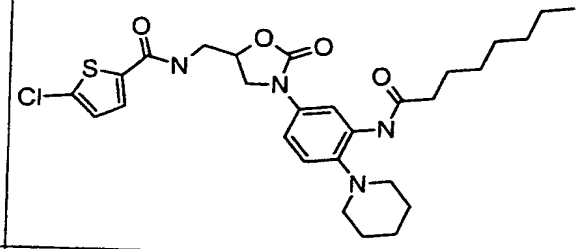
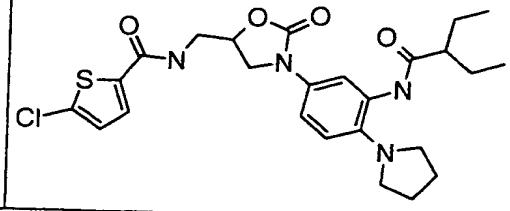
Example	Structure	Ret. time	HPLC [%]
213		2.41	67.8
214		2.41	75.4
215		4.01	81.3
216		3.46	49.5
217		4.4	60.2
218		3.79	70.9

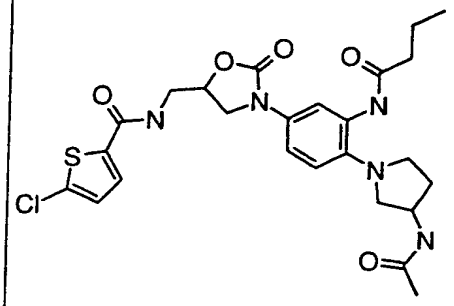
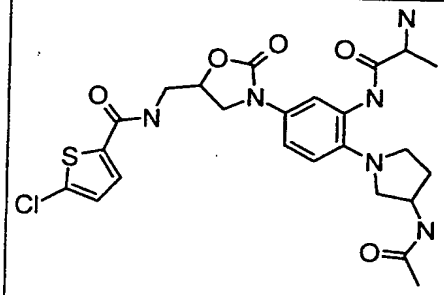
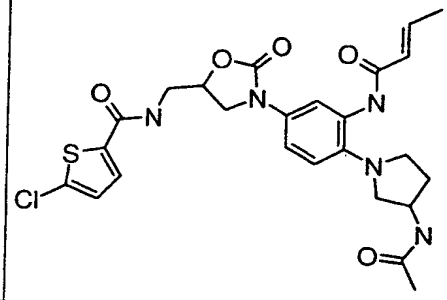
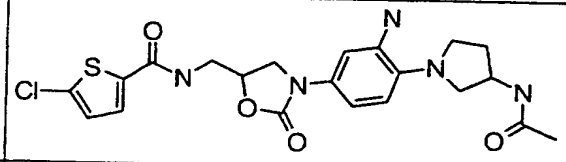
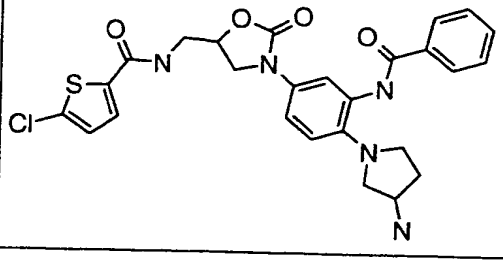
Example	Structure	Ret. time	HPLC [%]
219		4.57	51.5
220		2.68	100
221		4.53	63.5
222		2.66	89.2
223		4.76	69.3
224		3.45	77.4

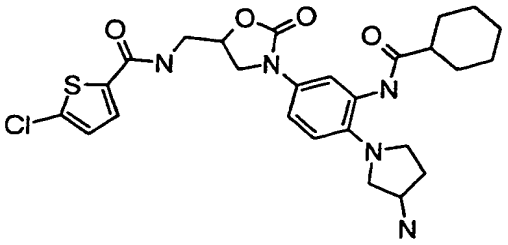
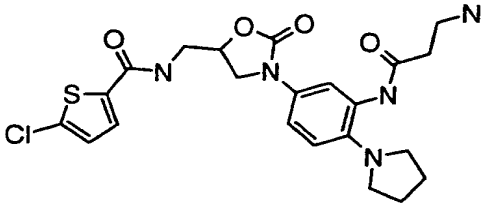
Example	Structure	Ret. time	HPLC [%]
225		3.97	63.2
226		3.94	61.4
227		4.15	66.3
228		4.41	55.1
229		2.83	41.1
230		2.7	83

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

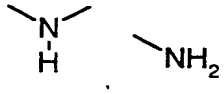
Example	Structure	Ret. time	HPLC [%]
248		3.35	59.6
249		2.41	60.3
250		3.31	65.2
251		2.86	36.5
252		2.69	89.8

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:

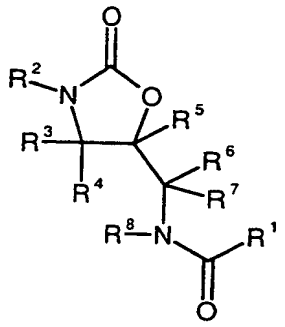
Time	A:%	B:%	flow rate
0. 00	10. 0	90. 0	0. 50
4. 00	90. 0	10. 0	0. 50
6. 00	90. 0	10. 0	0. 50
6. 10	10. 0	90. 0	1. 00
7. 50	10. 0	90. 0	0. 50

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.

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)-hydroxyalkylcarbonyl; $-COOR^{27}$; $-SO_2R^{27}$; $-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (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.

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.

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.

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.

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

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-:

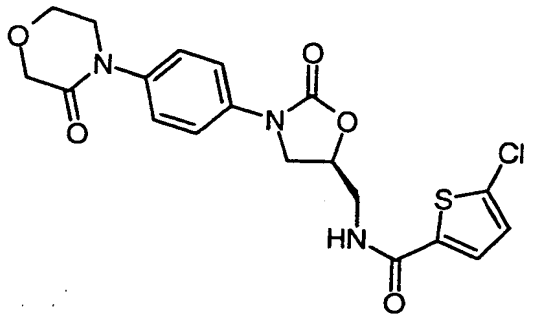
where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle,
which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom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

7. Compound according to Claim 1 having the following formula

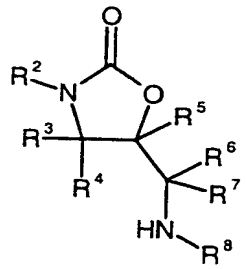


and its pharmaceutically acceptable salts, hydrates and prodrugs.

8. Process for preparing substituted oxazolidinones according to Claims 1 to 7, where

either according to a process alternative

[A] compounds of the general formula (II)

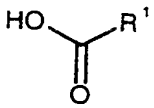


(II),

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)



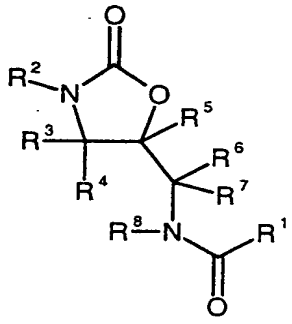
(III),

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)



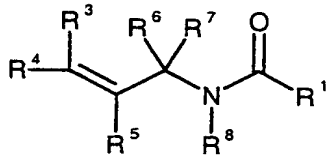
(I),

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)

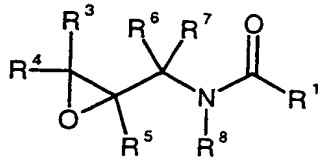


(IV),

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,

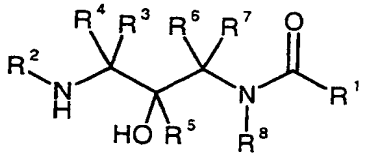
and, by reaction in an inert solvent, if appropriate in the presence of a catalyst, with an amine of the general formula (VI)

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

in which

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

the compounds of the general formula (VII)



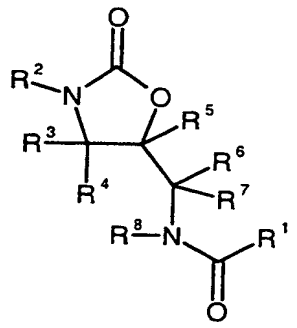
(VII),

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

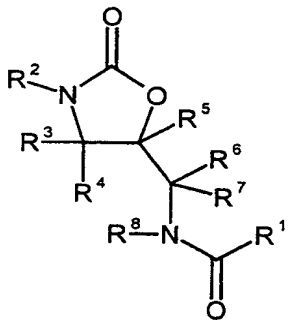
where - both for process alternative [A] and for process alternative [B] - in the case where the compound prepared in this manner has an aniline or benzylamine radical in the molecule, a reaction of this amino group with various reagents such as carboxylic acids, carboxylic anhydrides, carbonyl chlorides, 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.

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

10. Use of 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,

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.

11. Use of compounds of the general formula (I) according to Claim 10 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of disorders which are influenced positively by inhibition of factor Xa.

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

13. Use of compounds of the general formula (I) according to Claim 10 for preparing medicaments or pharmaceutical compositions for the prophylaxis and/or treatment of disorders such as atherosclerosis; arthritis; Alzheimer's disease or cancer.

14. Use of compounds of the general formula (I) according to Claim 10 for preparing medicaments or pharmaceutical compositions for the inhibition of factor Xa.

15. 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 Claim 10 are added.

COMBINED DECLARATION AND POWER OF ATTORNEY	ATTORNEY DOCKET NO Le A 34 122

As a below named inventor, I/we hereby declare that:

My/our residence, post office address and citizenship are as stated below next to my/our name. I/we believe I am/we are the original, first and sole/joint inventor/s of the subject matter which is claimed and for which a patent is sought on the invention entitled

SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

the specification of which is attached hereto,

or was filed on **December 11, 2000**

as a PCT Application Serial No. **PCT/EP00/12492**

I/we hereby state that I/we have reviewed and understand the contents of the above-identified specification, including the claims.

I/we acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I/we hereby claim priority benefits under Title 35, United States Code, §119 and § 119(e)(1) of any foreign and/or U.S. provisional application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

199 62 924.2	**Germany**	**December 24, 1999**
(Number)	(Country)	(Month/Day/Year Filed)

I/we hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I/we acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occured between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I/we hereby declare that all statements made herein of my/our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Le A 34 122-US

10181851.062402

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

6 - Jeffrey M. Greenman, Reg.No. 26,552
Barbara A. Shimei, Reg. No. 29,862
William F. Gray, Reg. No. 31,018
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27941
PATENT TRADEMARK OFFICE

all of Bayer Corporation, 400 Morgan Lane, West Haven, Connecticut 06516

Send Correspondence To:	Direct Telephone Calls To:
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1-00	Alexander Straub		10.6.02
	RESIDENCE	CITIZENSHIP	
	D 42113 Wuppertal, Germany DEX	German	
	POST OFFICE ADDRESS		
	c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany		
	FULL NAME OF SECOND INVENTOR	INVENTOR'S SIGNATURE	DATE
2-00	Thomas Lampe		29. Mai 2002
	RESIDENCE	~~CITIZENSHIP~~	
	D 42105 Wuppertal, Germany DEX	German	
	POST OFFICE ADDRESS		
	c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany		
	FULL NAME OF THIRD INVENTOR	INVENTOR'S SIGNATURE	DATE
3-00	Jens Pohlmann		28.05.02
	RESIDENCE	CITIZENSHIP	
	D 42285 Wuppertal, Germany DEX	German	
	POST OFFICE ADDRESS		
	c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany		
	FULL NAME OF FOURTH INVENTOR	INVENTOR'S SIGNATURE	DATE
4-00	Susanne Röhrig		3-6-2002
	RESIDENCE	CITIZENSHIP	
	D 45276 Essen, Germany DEX	German	
	POST OFFICE ADDRESS		
	c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany		
	FULL NAME OF FIFTH INVENTOR	INVENTOR'S SIGNATURE	DATE
5-00	Elisabeth Perzborn		23.05.02
	RESIDENCE	CITIZENSHIP	
	D 42327 Wuppertal, Germany DEX	German	
	POST OFFICE ADDRESS		
	c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany		
	FULL NAME OF SIXTH INVENTOR	INVENTOR'S SIGNATURE	DATE
6-00	Karl-Heinz Schlemmer		04.06.02
	RESIDENCE	CITIZENSHIP	
	D 42113 Wuppertal, Germany DEX	German	
	POST OFFICE ADDRESS		
	c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany		
	FULL NAME OF SEVENTH INVENTOR	INVENTOR'S SIGNATURE	DATE
7-00	Joseph Pernerstorfer		5/6/02
	RESIDENCE	CITIZENSHIP	
	D 42109 Wuppertal, Germany DEX	Austrian	
	POST OFFICE ADDRESS		
	c/o Bayer Aktiengesellschaft, D 51368 Leverkusen, Germany		

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

plication or Docket Number
10/181051

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	21 minus 20=	* 1
INDEPENDENT CLAIMS	2 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☑

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	890
X$ 9=		OR	X$18=	18
X42=		OR	X84=	
+140=		OR	+280=	280
TOTAL		OR	TOTAL	1188

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPEND. . CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO.	FILING DATE
APPLICANT(S) 10/181051	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
3		1				
4		1				
5		1				
6		1				
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8		0				
9		7				
10	1					
11		1				
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TOTAL IND.	2	⬇		⬇		⬇
TOTAL DEP.	19					
TOTAL CLAIMS	21					

	*		*		*	
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100						
TOTAL IND.		⬇		⬇		⬇
TOTAL DEP.						
TOTAL CLAIMS						

* *MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Alexander Straub, et al.

Serial No.: National Stage Filing of PCT/EP00/12492

Filed: Herewith

For: Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation

BOX PCT
ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT BEFORE MAILING OF FIRST OFFICE ACTION (37 C.F.R. 1.97(b))

Dear Sir:

Applicants wish to cite for the record in the above-identified application the references shown on the accompanying copy of PTO form 1449.

IDENTIFICATION OF TIME OF FILING THE ACCOMPANYING INFORMATION DISCLOSURE STATEMENT

The information disclosure statement transmitted herewith is being filed ***before*** the mailing date of the first Office action on the merits.

FEE PAYMENT

Applicants believe that no fees are due with this submission. However, the Commissioner is hereby authorized to charge any fees that may have been overlooked but that are required to Deposit Account 13-3372. Additionally, please credit any overpayment to the same account.

Respectfully submitted,

William F. Gray

Reg. No. 31,018

Telephone: (203) 812-2712

Date: 24 June '02

William F. Gray
Attorney for Applicant(s)
Bayer Corporation
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West Haven, CT 06516

10/181051
528 Rec'd PCT/PTC 24 JUN 2002

Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Serial No.	Group Art	Filing Date JUN 24 2002	Atty. Docket No. Le A 34 122
INFORMATION DISCLOSURE CITATION		Applicant(s)	**Alexander STRAUB, et al.**		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE MM/DD/YY	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	U_1	5 5 6 1 1 4 8	10/01/96	Gante et al.	514	376	09/22/94

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE DD/MM/YY	COUNTRY	PRIMARY CLASS	SUB-CLASS	TRANSLATION YES	TRANSLATION NO
	F_1	7 4 4 0 0 2	05/07/99	AU				
	F_2	0 6 4 5 3 7 6	29/03/95	EP				

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, etc.)

	R_1	Becker, M. R., Ewing, W. R., Davis, R. S., Pauls, H. W., Ly, C., Li, A., Mason, H. J., Choi-Sledeski, Y. M., Spada, A. P., Chu, V., Brown, K. D., Colussi, D. J., Leadley, R. J., Bentley, R., Bostwick, J., Kasiewski, C., and Morgan, S., "Synthesis, Sar and in Vivo Activity of Novel Thienopyridine Sulfonamide Pyrrolidinones as Factor Xa Inhibitors", Bioorganic & Medicinal Chemistry Letters, 9: 2753-2758 (1999)

EXAMINER	DATE CONSIDERED

* EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

submitted on JUN 24 2002

= WO 99/31092 (F1)

(12) **PATENT**
(19) **AUSTRALIAN PATENT OFFICE**

(11) Application No. **AU 199919647 B2**
(10) Patent No. **744002**

(54) Title
Benzamine derivatives

(51)[7] International Patent Classification(s)
C07D 413/14 **C07C 257/18**
A61K 031/155 **C07D 295/26**
A61K 031/41 **C07D 413/12**
A61K 031/495

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(22) Application Date: **1998.11.27**

(87) WIPO No: **WO99/31092**

(30) Priority Data

(31) Number	(32) Date	(33) Country
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(74) Agent/Attorney
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PCT

WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro

INTERNATIONALE A[illegible]LDUNG VERÖFFENTLICHT NACH DEM [illegible]TRAG ÜBER DIE INTERNATIONALE Z[illegible]MENARBEIT AUF DEM GEBIET DES P[illegible]TWESENS (PCT)

(51) Internationale Patentklassifikation 6 :
C07D 413/14, 413/12, 295/26, C07C 257/18, A61K 31/41, 31/495, 31/155

A1

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(22) Internationales Anmeldedatum: 27. November 1998 (27.11.98)

(30) Prioritätsdaten:
197 55 268.4 12. Dezember 1997 (12.12.97) DE

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(72) Erfinder; und

(75) Erfinder/Anmelder *(nur für US)*: DORSCH, Dieter [DE/DE]; Königsberger Strasse 17A, D-64372 Ober-Ramstadt (DE). JURASZYK, Horst [DE/DE]; Kleiner Ring 14, D-64342 Seeheim (DE). WURZIGER, Hanns [DE/DE]; Greinstrasse 7b, D-64291 Darmstadt (DE). GANTE, Joachim [DE/DE]; Stormstrasse 4, D-64291 Darmstadt (DE). MEDERSKI, Werner [DE/DE]; Am Ohlenberg 29, D-64390 Erzhausen (DE). BUCHSTALLER, Hans-Peter [DE/DE]; Heinrichstrasse 54, D-64331 Weiterstadt (DE). ANZALI, Soheila [DE/DE]; Am Alten Berg 13, D-64342 Seeheim (DE). BERNOTAT-DANIELOWSKI, Sabine [DE/DE]; Liebigstrasse 5, D-61231 Bad Neuheim (DE). MELZER, Guido [DE/DE]; Mörikestrasse 6, D-65719 Hofheim (DE).

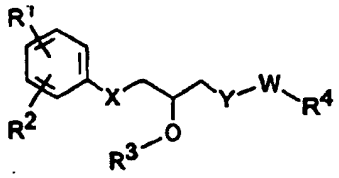
(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO Patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht

Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: BENZAMINE DERIVATIVES

(54) Bezeichnung: BENZAMIDINDERIVATE ALS KOAGULATIONSFAKTOR-XA-HEMMER



(1)

(57) Abstract

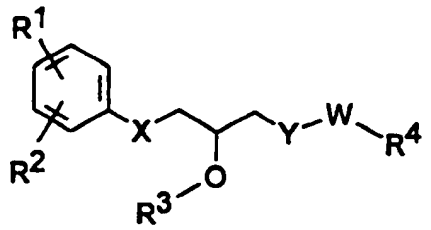
The invention relates to novel compounds of formula (1) wherein X, Y, W, R^1, R^2, R^3 and R^4 have the meaning cited in Claim 1. The inventive compounds are inhibitors of coagulation factor Xa and can be used in prophylaxis and/or therapy for thromboembolic diseases.

(57) Zusammenfassung

Neue Verbindungen der Formel (1), worin X, Y, W, R^1, R^2, R^3 und R^4 die in Patentanspruch 1 angegebene Bedeutung haben, sind Inhibitoren des Koagulationsfaktors Xa und können zur Prophylaxe und/oder Therapie von thromboembolischen Erkrankungen eingesetzt werden.

BENZAMIDINE DERIVATIVES AS COAGULATION FACTOR XA INHIBITOR

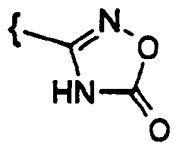
The invention relates to compounds of the formula I



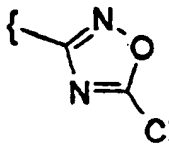
I

in which

R^1 is $-C(=NH)-NH_2$ which can also be monosubstituted by -COA, $-CO-[C(R^5)_2]_m-Ar$, -COOA, -OH or by a conventional amino-protective group,



or



R^2 is H, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NR^5COA, NHCOAr, $NHSO_2A$, $NHSO_2Ar$, $COOR^5$, $CON(R^5)_2$, CONHAr, COR^5, COAr, $S(O)_nA$ or $S(O)_nAr$,

R^3 is R^5 or $-[C(R^5)_2]_m-COOR^5$,

R^3 and X together are also -CO-N-, thus forming a 5-membered ring, where R^3 is -C=O and X is N,

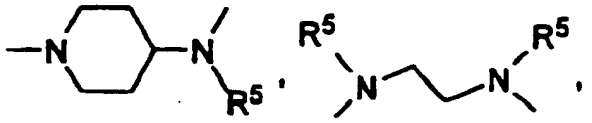
R^4 is A, cycloalkyl, $-[C(R^5)_2]_mAr$, $-[C(R^5)_2]_mHet$ or $-CR^5=CR^5-Ar$,

R^5 is H, A or benzyl,

X is O, NR^5 or CH_2,

Y is O, NR^5, N[C(R^5)$_2$]$_m$-Ar, N[C(R^5)$_2$]$_m$-Het,

N[C(R^5)$_2$]$_m$-COOR^5,



N[C(R^5)$_2$]$_m$-CON(R^5)$_2$, N[C(R^5)$_2$]$_m$-CONR^{5}Ar or N[C(R^5)$_2$]$_m$-CONAr$_2$,

W is a bond, -SO$_2$-, -CO-, or -CONR^5-,

A is alkyl having 1-20 C atoms in which one or two CH$_2$ groups can be replaced by O or S atoms or by -CR^5=CR^5- groups and/or 1-7 H atoms can be replaced by F,

Ar is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, Ar', OR^5, N(R^5)$_2$, NO$_2$, CN, Hal, NHCOA, NHCOAr', NHSO$_2$A, NHSO$_2$Ar', COOR^5, CON(R^5)$_2$, CONHAr', COR^5, COAr', S(O)$_n$A or S(O)$_n$Ar,

Ar' is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, OR^5, N(R^5)$_2$, NO$_2$, CN, Hal, NHCOA, COOR^5, CON(R^5)$_2$, COR^5 or S(O)$_n$A,

Het is a mono- or bicyclic saturated or unsaturated heterocyclic ring system which contains one, two, three or four identical or different hetero atoms such as nitrogen, oxygen and sulfur and which is unsubstituted or mono- or polysubstituted by Hal, A, Ar', OR^5, COOR^5, CN, N(R^5)$_2$, NO$_2$, NHCOA, NHCOAr' and/or carbonyl oxygen,

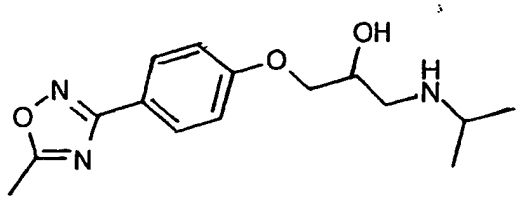
Hal is F, Cl, Br or I,

m is 0, 1, 2, 3 or 4,

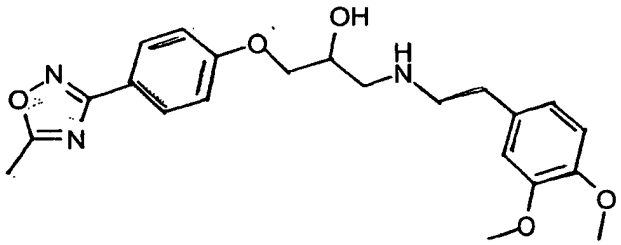
n is 0, 1 or 2,

and salts thereof,

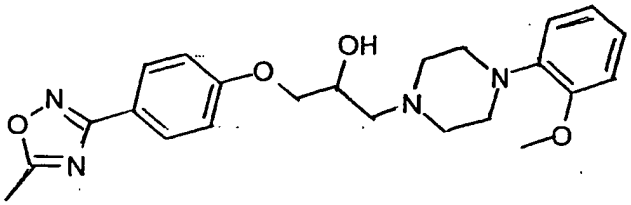
with the proviso that the following compounds are excluded:



1-isopropylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol;



1-[2-(3,4-dimethoxy-phenyl)-ethylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol; and



1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol.

The invention also provides the optically active forms, the racemates, the diastereomers and the hydrates and solvates of these compounds.

The invention was based on the object of discovering novel compounds having valuable properties, in particular those which can be used for preparing medicaments.

It has been found that the compounds of the formula I and their salts have very useful pharmacological properties, coupled with good tolerability. In particular, they have factor Xa-inhibiting properties and can therefore be employed for combating and preventing thromboembolic disorders such as thrombosis, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

Aromatic amidine derivatives having antithrombotic action are known, for example, from EP 0 540 051 B1. Cyclic guanidines for the treatment of thromboembolic disorders are described, for example, in WO 97/08165. Aromatic heterocycles having factor Xa-inhibiting activity are known, for example, from WO 96/10022.

The antithrombotic and anticoagulant effect of the compounds according to the invention is attributed to the inhibiting action on the activated coagulation protease, known under the name factor Xa, or to the inhibition of other activated serine proteases such as factor VIIa, factor IXa or thrombin.

inhibition of other activated serine proteases such as factor VIIa, factor IXa or thrombin.

Factor Xa is one of the proteases which is involved in the complex process of blood coagulation. Factor Xa catalyses the conversion of prothrombin into thrombin. Thrombin cleaves fibrinogen into fibrin monomers which, after crosslinking, contribute fundamentally to thrombus formation. An activation of thrombin can result in the occurrence of thromboembolic disorders. An inhibition of thrombin, however, can inhibit the fibrin formation involved in the formation of a thrombus.

The inhibition of thrombin can be measured, for example, by the method of G. F. Cousins et al. in *Circulation* **1996**, *94*, 1705-1712.

Inhibition of factor Xa can thus prevent thrombin formation.

The compounds of the formula I according to the invention and their salts intervene in the blood coagulation process by inhibiting factor Xa and thus inhibit the formation of thrombi.

The compounds of the formula I according to the invention can furthermore function as inhibitors of the blood clotting factors factor VIIa, factor IXa and thrombin of the blood clotting cascade.

The inhibition of factor Xa by the compounds according to the invention and the measurement of the anti-coagulating and antithrombotic activity can be determined by customary in vitro or in vivo methods. A suitable method is described, for example, by J. Hauptmann et al. in *Thrombosis and Haemostasis 63, 220-223 (1990)*.

The inhibition of factor Xa can also be measured, for example, by the method of T. Hara et al. in *Thromb. Haemostas. 71, 314-319 (1994)*.

The blood clotting factor VIIa initiates, after binding to tissue factor, the extrinsic part of the blood clotting cascade and contributes to the activation of factor X to factor Xa. An inhibition of factor VIIa thus prevents the formation of factor Xa and thus a subsequent formation of thrombin.

The inhibition of factor VIIa by the compounds according to the invention and the determination of the anticoagulant and antithrombotic activity can be determined using customary in vitro or in vivo methods. A customary process for measuring the inhibition of factor VIIa is described, for example, by H. F. Ronning et al. in *Thrombosis Research* **1996**, *84*, 73-81.

The compounds of the formula I can be employed as medicaments in human and veterinary medicine, in particular for combating and preventing thromboembolic disorders such as thrombosis, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

The invention provides the compounds of the formula I and their salts, and also a process for preparing compounds of the formula I according to Claim 1 and their salts, characterized in that

a) they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent, by

   i) liberating an amidino group from its oxadiazole derivative by hydrogenolysis,

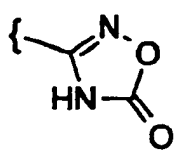
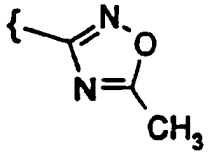
   ii) replacing a conventional amino-protective group by treatment with a solvolysing or hydrogenolysing agent with hydrogen or

liberating an amino group which is protected by a conventional protective group,

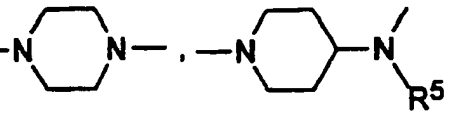
or

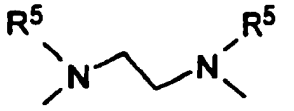
b) that for preparing compounds of the formula I

in which R^1 is


or

,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

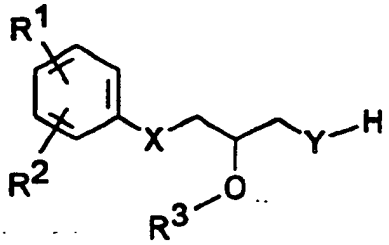
Y is NR^5,  or


,

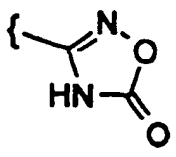
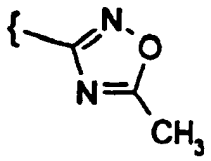
W is $-SO_2-$ or -CO-,

and R^2 and R^4 are as defined in Claim 1,

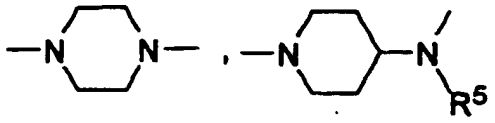
a compound of the formula II

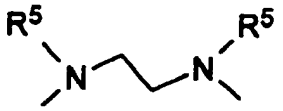

II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  or

 ,

and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula III

$$R^4\text{-}W\text{-}L \qquad \text{III}$$

in which

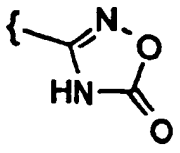
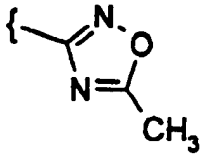
W is $-SO_2-$ or -CO-,

R^4 is as defined in Claim 1,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

or

c) that for preparing compounds of the formula I

in which R^1 is  or  ,

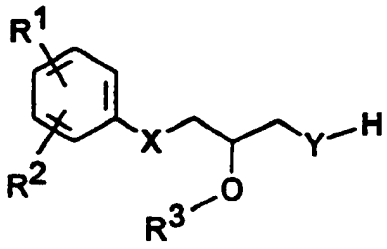
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is O,

W is a bond,

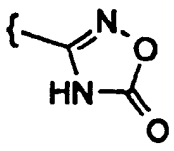
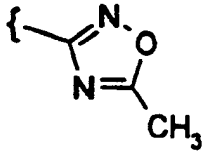
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II



II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is O,

and R^2 is as defined in Claim 1,

is reacted with a compound of the formula IV

$$R^4\text{-W-OH} \qquad \text{IV}$$

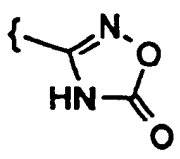
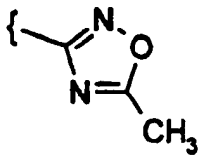
in which

W is a bond,

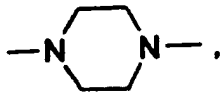
and R^4 is as defined in Claim 1,

or

d) that for preparing compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  ,

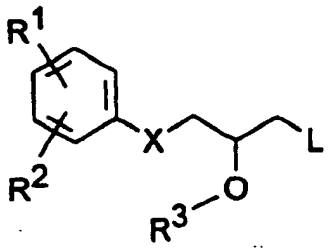
W is a bond,

R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$,

m is 0,

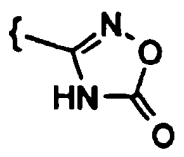
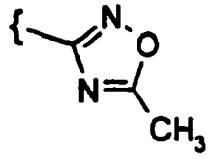
and R^2 is as defined in Claim 1,

a compound of the formula V



V

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

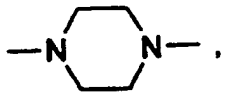
and R^2 is as defined in Claim 1,

is reacted with a compound of the formula VI

$$R^4\text{-}W\text{-}Y\text{-}H \qquad VI$$

in which

W is a bond,

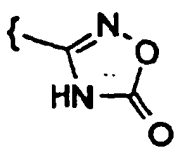
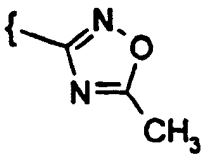
Y is  ,

R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$ and

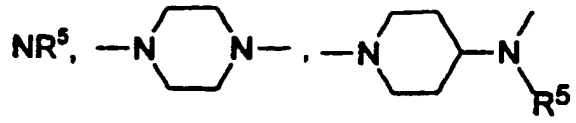
m is 0,

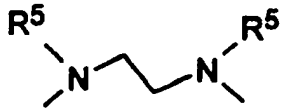
or

e) that for preparing compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

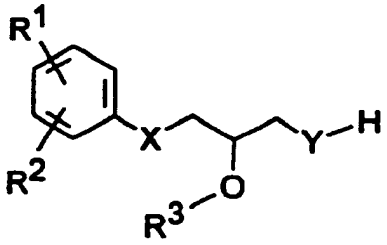
Y is NR^5,  or



W is -CONH-,

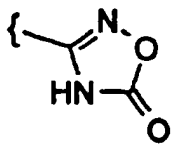
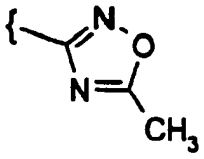
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II

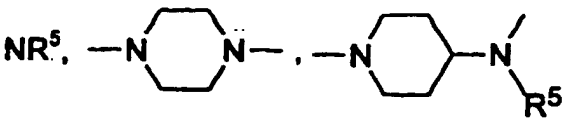


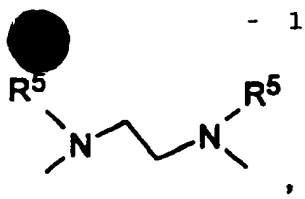
II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  or



and R^2 and R^5 are as as defined in Claim 1,

is reacted with a compound of the formula VII

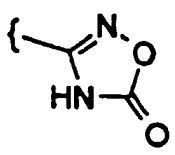
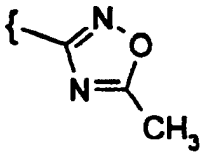
$$R^4\text{-}N{=}C{=}O \qquad \text{VII}$$

in which

R^4 is as defined in Claim 1,

or

f) that for preparing compounds of the formula I

in which R^1 is  or  ,

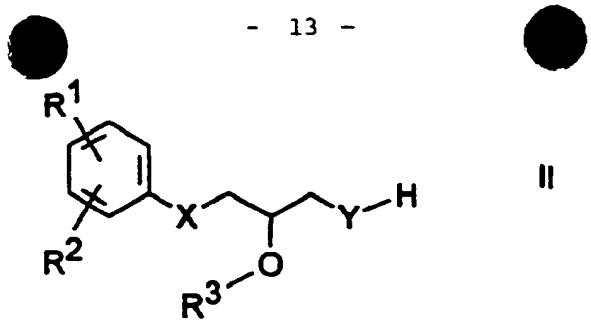
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m\text{-}COOR^5$,

W is SO_2,

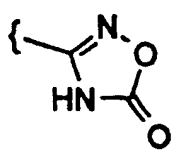
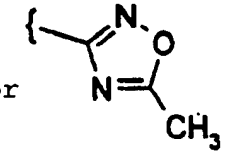
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II



II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$,

and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula VIII

$$R^4\text{-}SO_2\text{-}L \qquad \text{VIII}$$

in which

L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

and R^4 is as defined in Claim 1,

or

g) that for preparing compounds of the formula I

in which

X is NH and

R^3 is H

and R^1, R^2, R^4, Y and W are as defined in Claim 1,

these compounds are liberated from their oxazolidinone derivatives by treatment with a solvolysing or hydrogenolysing agent,

or

h) that for preparing compounds of the formula I

in which R^1 is $-C(=NH)-NH_2$,

a cyano group is converted into an amidino group,

or

i) in a compound of the formula I, one or more radicals Y, R^1, R^2, R^3 and/or R^4 are converted into one or more radicals R^1, R^2, R^3 and/or R^4,

by, for example,

i) hydrolysing an ester group to give a carboxyl group,

ii) reducing a nitro group,

iii) acylating an amino group,

and/or

k) converting a base or acid of the formula I into one of its salts.

For all the radicals which occur several times, such as, for example, R^5, the meanings thereof are independent of one another.

Hereinabove and hereinbelow, the radicals or parameters L, W, X, Y, R^1, R^2, R^3, R^4, R^5, m and n have the meanings given for the formulae I to VIII, unless expressly stated otherwise.

Solvates is [sic] addition compounds with, for example, organic inert solvents, such as, for example, with alcohols such as methanol, ethanol or propanol.

In the above formulae, A is alkyl, is linear or branched, and has 1 to 20, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 C atoms. A is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, heptyl, octyl, nonyl or decyl.
A is furthermore, for example, trifluoromethyl, pentafluoroethyl, allyl or crotyl.

OR^5 is OH, OA or benzyloxy, with OA preferably being methoxy, ethoxy, propoxy, butyloxy or hexyloxy.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Cycloalkyl is, for example, also the radical of a bicyclic terpene, such as, for example, 3-menthyl; particular preference is given to the camphor-10-yl radical.

COR^5 is acyl and is preferably formyl, acetyl, propionyl, furthermore also butyryl, pentanoyl or hexanoyl.

Hal is preferably F, Cl or Br, but also I.

R^2 is preferably H, fluorine, chlorine, bromine, iodine, hydroxyl, methoxy, ethoxy, propoxy, nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, acetamido, sulfonamido, methylsulfonamido, phenylsulfonamido, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, phenylsulfinyl, phenylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, furthermore also acyl or benzoyl.

R^2 is, in particular, H.

R^3 is preferably A, benzyl, CH_2COOH or CH_2COOA, but in particular H.

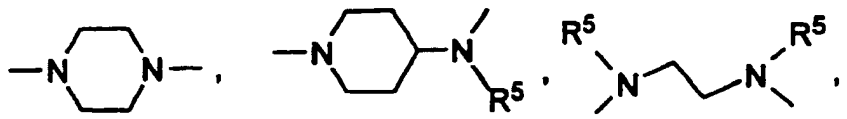
R^4 is preferably, for example, A, cycloalkyl, Ar, CH_2Ar, CH_2CH_2Ar, CH_2Het, CH_2CH_2Het or CH=CH-Ar.

R^5 is H, A or benzyl, but in particular H.

X is O, NH, NA or N-benzyl, furthermore also CH_2.

R^3 and X together are also -CO-N-, thus forming, together with the $-CH_2-CH-O-$ unit, a five-membered ring.

Y is preferably, for example, O, NH, N-methyl, N-ethyl, N-Ar, $N-CH_2-Ar$, N-Het, $N-CH_2-Het$, N-COOA, $N-CH_2-COOA$, $N-CH_2-COOH$, $N-CH_2-COObenzyl$,



NCH_2-CONH_2, $NCH_2-CONHA$, NCH_2-CONA_2, NCH_2-CONR^5Ar or $NCH_2-CONAr_2$.

W is preferably, for example, a bond, $-SO_2-$ or -CO-, furthermore also -COO- or -CONH-.

Ar is preferably unsubstituted phenyl or naphthyl, furthermore preferably naphthyl or phenyl which is mono-, di- or trisubstituted, for example by A, fluorine, chlorine, bromine, iodine, hydroxyl, methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy,

benzyloxy, phenethyloxy, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, phenylsulfinyl, phenylsulfonyl, nitro, amino, methylamino, ethylamino, dimethylamino, diethylamino, formamido, acetamido, propionylamino, butyrylamino, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, phenylsulfonamido, (4-methylphenyl)sulfonamido, carboxymethoxy, carboxyethoxy, methoxycarbonylmethoxy, methoxycarbonylethoxy, hydroxymethoxy, hydroxyethoxy, methoxyethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, phenylaminocarbonyl, acyl or benzoyl, furthermore also biphenyl.

Ar is therefore preferably, for example, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)-phenyl, o-, m- or p-acetylphenyl, o-, m- or p-formylphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-methylsulfonylphenyl, o-, m- or p-(phenylsulfonamido)phenyl, o-, m- or p-(methylsulfonamido)-phenyl, o-, m- or p-methylthiophenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro-, or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or

3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar is very particularly preferably phenyl which is unsubstituted or mono-, di- or trisubstituted by amino, OR^5, Hal, CN, alkyl having 1-10 carbon atoms, CF_3, CH_3SO_2, OCF_3, acetamido, -C(=NH)-NH_2, methoxycarbonyl or ethoxycarbonyl, furthermore naphthyl which is mono-substituted by Hal, dimethylamino or alkoxy having 1-6 carbon atoms and also unsubstituted biphenyl.

Ar' is in particular, for example, phenyl or naphthyl, furthermore preferably, for example, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-acetylphenyl, o-, m- or p-formylphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl or o-, m- or p-methylsulfonylphenyl.

Het is preferably, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-

triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo[1,4]oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Het may also be, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo[1,4]oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-

methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)-phenyl, 2,3-dihydrobenzofuran-5- or -6-yl, 2,3-(2-oxo-methylenedioxy)phenyl or else 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

Het is unsubstituted or mono- or polysubstituted by Hal, A, Ar', $COOR^5$, CN, $N(R^5)_2$, NO_2, Ar-CONH-CH_2.
"Poly" means di, tri, tetra or penta.
Het is very particularly preferably thiazole-2-, 4- or -5-yl, thiophen-2- or -5-yl, chroman-6-yl, pyridin-2-, -3- or -4-yl, pyrimidin-2- or -5-yl, benzothiophen-2-yl, 1,3-benzodioxol-4- or -5-yl, 1,4-benzodioxan-5- or -6-yl, 2,1,3-benzothiadiazol-4- or -5-yl which is unsubstituted or mono- or polysubstituted by Hal, A, phenyl, OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOphenyl and/or carbonyl oxygen.

The compounds of the formula I may have one or more chiral centres and may therefore be present in various stereoisomeric forms. The formula I embraces all of these forms.

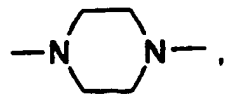
Consequently, the invention provides in particular those compounds of the formula I in which at least one of the abovementioned radicals has one of the preferred meanings given above. Some preferred groups of compounds can be expressed by the following moieties Ia to Ii which correspond to the formula I and where the radicals which are not defined more specifically have the meaning given for the formula I, but where

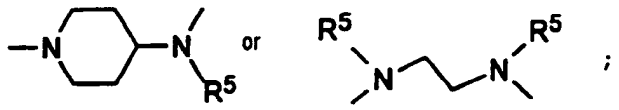
in Ia R^2 is H;

in Ib R^3 is R^5 or $-(CH_2)_m-COOR^5$;

in Ic R^4 is A, cycloalkyl, $-(CH_2)_nAr$ [sic], $-(CH_2)_mHet$ or $-CH=CH-Ar$;

in Id Y is O, NR^5, $N(CH_2)_m$-Ar, $N(CH_2)_m$-Het, $N(CH_2)_m$-$COOR^5$,





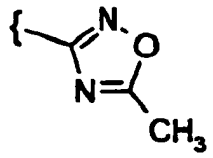
in Ie A is alkyl having 1-20 C atoms in which one or two CH_2 groups may be replaced by -CH=CH- groups and/or 1-7 H atoms may be replaced by F;

in If Ar is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, phenyl, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, NHCOphenyl, $NHSO_2A$, $NHSO_2$phenyl, $COOR^5$, $CON(R^5)_2$, CONHphenyl, COR^5, COphenyl, $S(O)_nA$ or $S(O)_nAr$;

in Ig Ar' is phenyl;

in Ih Het is thiazol-2-, -4- or -5-yl, thiophen-2- or -5-yl, chroman-6-yl, pyridin-2-, -3- or -4-yl, pyrimidin-2- or -5-yl, benzothiophen-2-yl, 1,3-benzodioxol-4- or -5-yl, 1,4-benzodioxan-5- or -6-yl or 2,1,3-benzothiadiazol-4- or -5-yl which is unsubstituted or mono- or polysubstituted by Hal, A, phenyl, OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOphenyl and/or carbonyl oxygen;

in Ii R^1 is $-C(=NH)-NH_2$, which can also be monosubstituted by -COA, $-CO-(CH_2)_m-Ar$, -COOA or OH,

or is  .

R^2 is H,

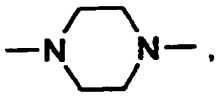
R^3 is R^5 or $-(CH_2)_m-COOR^5$,

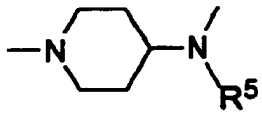
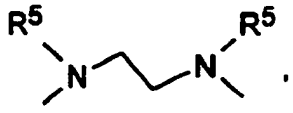
R^3 and X together are also -CO-N-, thus forming a 5-membered ring,

R^4 is A, cycloalkyl, $-(CH_2)_mAr$, $-(CH_2)_mHet$ or -CH=CH-Ar,

R^5 is H, A or benzyl,

X is O, NR^5 or CH_2,

Y is O, NR^5, $N(CH_2)_m-Ar$, $N(CH_2)_m-Het$, $N(CH_2)_m-COOR^5$,  ,

 or  .

NCH_2-CONH_2, $NCH_2-CONHA$, NCH_2-CONA_2, NCH_2-CONR^5Ar or $NCH_2-CONAr_2$,

W is a bond, $-SO_2-$, -CO-, -COO- or -CONH-,

A is alkyl having 1-20 C atoms in which one or two CH_2 groups may be replaced by -CH=CH- groups and/or 1-7 H atoms may be replaced by F,

Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by NH_2, OR^5, Hal, CN, alkyl having 1-10 carbon atoms, CF_3, CH_3SO_2, OCF_3, acetamido, $-C(=NH)-NH_2$, methoxycarbonyl or ethoxycarbonyl,

furthermore naphthyl which is mono-substituted by Hal, dimethylamino or methoxy and also unsubstituted biphenyl.

Het is thiazol-2-, -4- or -5-yl, thiophen-2- or -5-yl, chroman-6-yl, pyridin-2-, -3- or -4-yl, pyrimidin-2- or -5-yl, benzothiophen-2-yl, 1,3-benzodioxol-4- or -5-yl, 1,4-benzodioxan-5- or -6-yl, 2,1,3-benzothiadiazol-4- or -5-yl which is unsubstituted or mono- or polysubstituted by Hal, A, phenyl, OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOphenyl and/or carbonyl oxygen.

The compounds of the formula I and also the starting materials for their preparation are otherwise prepared by methods known per se, such as are described in the literature (for example in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), and in particular under the reaction conditions which are known and suitable for the reactions mentioned. In these reactions, variants which are known per se and are not mentioned here in more detail can also be utilized.

If desired, the starting materials can also be formed in situ, so that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of the formula I.

Compounds of the formula I can preferably be obtained by liberating the compounds of the formula I from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent.

Preferred starting materials for the solvolysis or hydrogenolysis are those which otherwise correspond to the formula I but, instead of one or more free amino

and/or hydroxyl groups, contain corresponding protected amino and/or hydroxyl groups, preferably those which, instead of an H atom which is bonded to an N atom, carry an amino-protective group, in particular those which, instead of an HN group, carry an R'-N group, in which R' is an amino-protective group, and/or those which, instead of the H atom of a hydroxyl group, carry a hydroxyl-protective group, for example those which correspond to the formula I but, instead of a -COOH group, carry a group -COOR", in which R" is a hydroxyl-protective group.

Preferred starting materials also include the oxadiazole derivatives which can be converted into the corresponding amidino compounds.

The introduction of the oxadiazole group is effected, for example, by reacting the cyano compounds with hydroxylamine and reaction with phosgene, dialkyl carbonate, chloroformic ester, N,N'-carbonyldiimidazole or acetic anhydride.

It is also possible for several - identical or different - protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If the protective groups present differ from one another, in many cases they can be cleaved off selectively.

The term "amino-protective group" is generally known and relates to groups which are suitable for protecting (blocking) an amino group from chemical reactions but which can easily be removed after the desired chemical reaction has been carried out at other sites of the molecule. Typical such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise not critical; however, those having 1-20, in particular 1-8

C atoms are preferred. The term "acyl group" is to be interpreted in the broadest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and in particular alkoxycarbonyl, aryloxycarbonyl and, above all, aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl or butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or toluyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert-butyloxycarbonyl), 2-iodoethoxycarbonyl; aralkyl-oxycarbonyl such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl, FMOC; arylsulfonyl such as Mtr. Preferred amino-protective groups are BOC and Mtr, and furthermore CBZ, Fmoc, benzyl and acetyl.

The term "hydroxyl-protective group" is also generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions but which can easily be removed after the desired chemical reaction has been carried out at other sites of the molecule. Typical such groups are the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, and furthermore also alkyl groups. The nature and the size of the hydroxyl-protective groups is not critical, since they are removed again after the desired chemical reaction or reaction sequence; groups having 1-20, in particular 1-10 C atoms are preferred. Examples of hydroxyl-protective groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, benzyl and tert-butyl being particularly preferred.

The liberation of the compounds of the formula I from their functional derivatives is effected - depending on the protective group used - for example with strong acids, expediently with TFA or perchloric acid, but

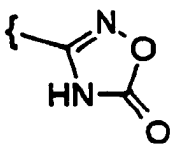
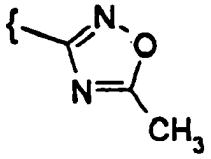
also with other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible but not always necessary. Suitable inert solvents are, preferably, organic solvents, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as DMF, halogenated hydrocarbons, such as dichloromethane, or furthermore also alcohols, such as methanol, ethanol or isopropanol, and water. Mixtures of the abovementioned solvents are furthermore possible. TFA is preferably used in excess without addition of a further solvent, and perchloric acid is used in the form of a mixture of acetic acid and 70% perchloric acid in a ratio of 9:1. The reaction temperatures for the cleavage are expediently between about 0 and about 50°, and the reaction is preferably carried out at between 15 and 30° (room temperature).

The groups BOC, OBut and Mtr can preferably be cleaved off, for example, with TFA in dichloromethane or with about 3 to 5N HCl in dioxane at 15-30°, and the FMOC group can be cleaved off with an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

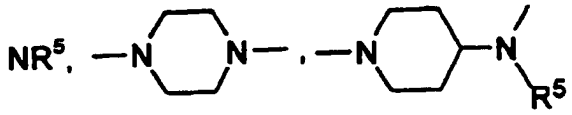
Protective groups which can be removed by hydrogenolysis (for example CBZ, benzyl or the liberation of the amidino group from its oxadiazole derivative) can be cleaved off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble metal catalyst, such as palladium, expediently on a support, such as carbon). Suitable solvents for this reaction are those mentioned above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis is generally carried out at temperatures between about

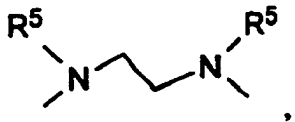
0 and 100° under pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group is effected readily, for example, on 5-10% Pd/C in methanol or with ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

Compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  or

 ,

W is $-SO_2-$ or -CO-,

and R^2 and R^4 are as defined in Claim 1,

can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

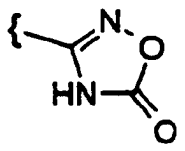
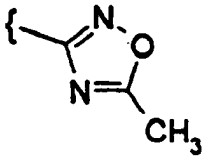
In the compounds of the formula III, L is preferably Cl, Br, I or a reactively modified OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy), or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy).

The reaction is generally carried out in an inert solvent, in the presence of an acid binder, preferably an alkali metal hydroxide, carbonate or bicarbonate or an alkaline earth metal hydroxide, carbonate or bicarbonate, or of another salt of a weak acid of the alkali metals or alkaline earth metals, preferably of potassium, sodium, calcium or caesium. The addition of an organic base such as triethylamine, dimethylaniline, pyridine or quinoline or of an excess of the amine component of the formula II or of the alkylation derivative of the formula III may also be favourable. Depending on the conditions used, the reaction time is between several minutes and 14 days, the reaction temperature is between approximately 0° and 150°, usually between 20° and 130°.

Suitable inert solvents are, for example, hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether (methylglycol or ethylglycol) or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the solvents mentioned.

The starting materials of the formulae II and III are generally known. Those which are novel, however, can be prepared by methods known per se.

Compounds of the formula I

in which R^1 is  or  .

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is O,

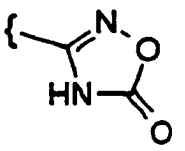
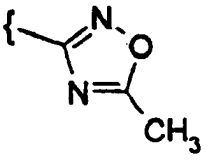
W is a bond,

and R^2 and R^4 are as defined in Claim 1,

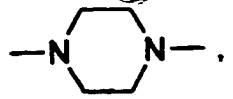
can preferably be obtained by reacting compounds of the formula II in which Y is O with compounds of the formula IV in a Mitsunobu reaction in the presence of, for example, triphenylphosphine and diethylazo dicarboxylate in an inert solvent.

The starting materials of the formula II in which Y is O, and those of the formula IV, are generally known. Those which are novel, however, can be prepared by methods known per se.

Compounds of the formula I

in which R^1 is  or  .

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  ,

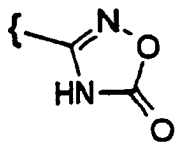
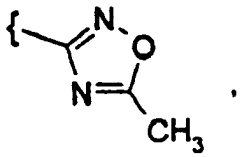
W is a bond,
R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$,
n [sic] is 0
and R^2 is as defined in Claim 1,
can preferably be obtained by reacting compounds of the formula V with compounds of the formula VI.

In the compounds of the formula V L is preferably Cl, Br, I or a reactively modified OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy), or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy).

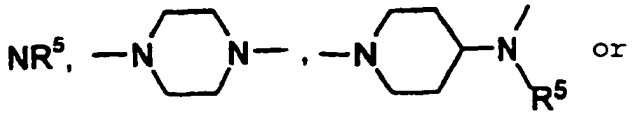
The reaction of the compounds of the formula V with compounds of the formula VI is preferably carried out in an inert solvent and at temperatures as indicated above.

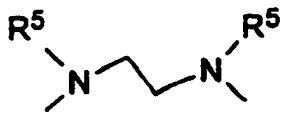
The starting materials of the formulae V and VI are generally known. Those which are novel, however, can be prepared by methods known per se.

Compounds of the formula I

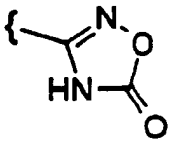
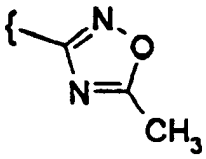
in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

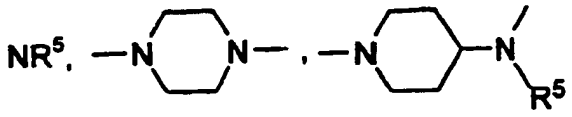
Y is  or

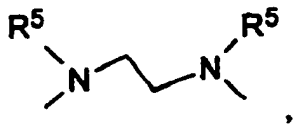


W is -CONH-,
and R^2 and R^4 are as defined in Claim 1,
can preferably be obtained by reacting compounds of the formula II

in which R^1 is  or 

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  or

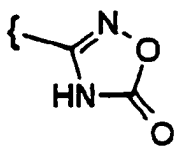
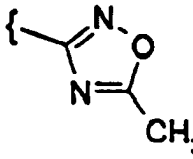


W is -CONH-,
and R^2 and R^5 are as defined in Claim 1,
with compounds of the formula VII.

The reaction of these compounds of the formula II in which W is -CONH- with compounds of the formula VII is preferably carried out in an inert solvent and at temperatures as indicated above.

The starting materials of the formula II in which W is -CONH- and of the formula VII are generally known. Those which are novel, however, can be prepared by methods known per se.

Compounds of the formula I

in which R^1 is  or  ,

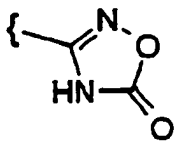
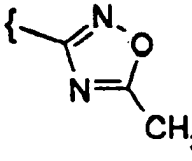
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$,

W is SO_2,

and R^2 and R^4 are as defined in Claim 1 can preferably be obtained by reacting compounds of the formula II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$

and R^2 and R^5 are as defined in Claim 1, with compounds of the formula VIII.

In the compounds of the formula VIII, L is preferably Cl, Br, I or a reactively derivatized OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl or p-tolylsulfonyloxy).

The reaction of the compounds of the formula II in which Y is $N[C(R^5)_2]_m$-$COOR^5$ with compounds of the

formula VIII is preferably carried out in an inert solvent and at the temperatures given above.

Compounds of the formula I in which
X is NH and
R^3 is H
and R^1, R^2, R^4, Y and W are as defined in Claim 1,
can be liberated from their oxazolidinone derivatives by treatment with a solvolysing or hydrogenolyzing agent. This is carried out under conditions like those described under "protective group removal".

Compounds of the formula I in which R^1 is $-C(=NH)-NH_2$ can furthermore be obtained from the corresponding cyano compound.
The conversion of a cyano group into an amidino group is carried out by reaction with, for example, hydroxylamine and subsequent reduction of the N-hydroxamidine with hydrogen in the presence of a catalyst, such as, for example, Pd/C.
To prepare an amidine of the formula I (R^1 = $-C(=NH)-NH_2$), ammonia can also be added onto a nitrile of the formula I (R^1 = CN). The addition is preferably carried out in several stages by a procedure in which, in a manner known per se, a) the nitrile is converted with H_2S into a thioamide, which is converted with an alkylating agent, for example CH_3I, into the corresponding S-alkyl-imidothioester, which in turn reacts with NH_3 to give the amidine, b) the nitrile is converted with an alcohol, for example ethanol, in the presence of HCl into the corresponding imidoester, and this is treated with ammonia, or c) the nitrile is reacted with lithium bis(trimethylsilyl)amide and the product is then hydrolysed.

Furthermore, it is possible to convert a compound of the formula I into another compound of the formula I by converting one or more radicals Y, R^1, R^2, R^3 and/or R^4 into one or more radicals Y, R^1, R^2, R^3 and/or R^4, for

example by acylating an amino group or reducing nitro groups (for example by hydrogenation over Raney nickel or Pd/carbon in an inert solvent, such as methanol or ethanol) to amino groups.

Esters can be hydrolysed, for example with acetic acid or with NaOH or KOH in water, water-THF or water-dioxane at temperatures between 0 and 100°.

It is furthermore possible to acylate free amino groups in a customary manner with an acyl chloride or acid anhydride or to alkylate with an unsubstituted or substituted alkyl halide, expediently in an inert solvent, such as dichloromethane or THF, and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60 and +30°.

A base of the formula I can be converted into the associated acid addition salt with an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, and subsequent evaporation. Acids which give physiologically acceptable salts are particularly suitable for this reaction. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, sulfaminic acid, or furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid,

naphthalene-mono- or -disulfonic acids and laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for isolation and/or purification of the compounds of the formula I.

On the other hand, compounds of the formula I can be converted with bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate) into the corresponding metal, in particular alkali metal or alkaline earth metal salts or into the corresponding ammonium salts.
It is also possible to use physiologically acceptable organic bases, such as, for example, ethanolamine.

Owing to their molecular structure, the compounds of the formula I according to the invention can be chiral and can consequently be present in various enantiomeric forms. They may therefore be present in racemic or in optically active form.

Since the pharmaceutical activity of the racemates and/or the stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the intermediates may be separated into enantiomeric compounds using chemical or physical means known to the person skilled in the art, or they may even be employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active separating agent. Suitable separating agents are, for example, optically active acids, such as the R- and S-forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitable N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline) or the various optically active camphorsulfonic acids. A chromatographic separation of the enantiomers can

also be advantageously carried out with the aid of an optically active separating agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other carbohydrate derivatives or chiral derivatized methacrylate polymers immobilized on silica gel). Solvents which are suitable for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/acetonitrile, for example in the ratio 82:15:3.

The invention furthermore provides the use of the compounds of the formula I and/or their physiologically acceptable salts for the preparation of pharmaceutical formulations, in particular by a non-chemical route. For this purpose, they can be brought into a suitable dosage form together with at least one solid, liquid and/or semi-liquid carrier or auxiliary, and if appropriate in combination with one or more further active compounds.

The invention furthermore provides pharmaceutical formulations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts.

These formulations can be used as medicaments in human or veterinary medicine. Possible carriers are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used, in particular, for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, and

furthermore suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilisates can be used, for example, for the preparation of injection formulations. The formulations mentioned can be sterilized and/or comprise auxiliaries, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, dyestuffs, flavourings and/or several further active compounds, for example one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be employed for combating and preventing thromboembolic disorders, such as thrombosis, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

For this purpose, the substances according to the invention are usually preferably administered in dosages of between about 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dosage is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on the most diverse factors, for example on the activity of the specific compound employed, on the age, body weight, general state of health, sex, diet, on the administration time and route, and on the rate of excretion, medicament combination and severity of the particular disease to which the therapy applies. Oral administration is preferred.

All temperatures hereinabove and hereinbelow are given in °C. In the following examples, "customary work-up" means: water is added, if necessary, the pH is brought to values of between 2 and 10, if necessary, depending

on the structure of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated and the residue is purified by chromatography over silica gel and/or crystallization. Rf values are for silica gel; mobile phase: ethyl acetate/methanol 9:1.

Mass spectrometry (MS):
EI (electron impact ionization) M^+
FAB (fast atom bombardment) $(M+H)^+$

Example 1

A solution of 100 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyl-oxazolidin-2-one ("A") [obtainable by reaction of 3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]-2-oxoxazolidin-5-ylmethyl methanesulphonate with 1-tert-butoxycarbonylpiperazine and sodium bicarbonate in acetonitrile; removal of the BOC group with HCl/dioxane and subsequent treatment with sodium hydroxide solution] and 110 mg of 2,4,6-trichlorobenzenesulphonyl chloride in 10 ml of dichloromethane is admixed with 400 mg of 4-dimethylaminopyridine on polystyrene and stirred at room temperature for 18 hours. The mixture is filtered and the solvent is removed, giving 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]5-[4-(24,6-trichlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one, FAB 586/588.

Similarly, reaction of "A"

with 4-biphenylylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-biphenylylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-phenylvinylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-phenylvinylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-nitrophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitrophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2,5-dimethoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,5-dimethoxyphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-naphthylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-chloro-4-fluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-chloro-4-fluorophenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with (2-acetamido-4-methylthiazol-5-yl)sulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((2-acetamido-4-methylthiazol-5-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-cyanophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-cyanophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 5-nitro-2-methylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(5-nitro-2-methylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with benzylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-benzylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with decylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-decylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 2-trifluoromethylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3-chloro-4-fluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-chloro-4-fluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-chloro-2,5-dimethylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-chloro-2,5-dimethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-fluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-fluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3,4-dibromophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-dibromophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3-chlorophenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-chlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2,6-dichlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,6-dichlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,4-dichlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-dichlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,5-dichlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,5-dichlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-naphthylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with methylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-methylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 2-methylsulfonylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-methylsulfonylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 2-nitrobenzylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitrobenzylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with (4-methoxycarbonyl-3-methoxythiophen-2-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((4-methoxycarbonyl-3-methoxythiophen-2-yl)sulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-trifluoromethoxyphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with (1S)-(camphor-10-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(((1S)camphor-10-yl)sulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with (1R)-(camphor-10-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(((1R)camphor-10-yl)sulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with (2,2,5,7,8-pentamethylchroman-6-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((2,2,5,7,8-pentamethylchroman-6-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-isopropylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-isopropylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-tert-butylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-tert-butylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-butylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-butylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,5-dinitro-4-methoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,5-dinitro-4-methoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with ethylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-ethylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 4-nitrophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-nitrophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-trifluoromethoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2,4-dinitrophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,4-dinitrophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with isopropylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-isopropylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 4-ethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-ethylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-bromo-2-trifluoromethoxyphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-bromo-2-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2,3,4-trifluorophenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,3,4-trifluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3,4-difluorophenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-difluorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2,2,2-trifluoroethylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,2,2-trifluoroethylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3-nitro-4-methylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-nitro-4-methylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 2-nitro-6-chlorophenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitro-6-chlorophenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 2,5-dimethoxyphenylacetyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,5-dimethoxyphenylacetyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,4-dichlorobenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-dichlorobenzoyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3-fluorobenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-fluorobenzoyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-trifluoromethoxybenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethoxybenzoyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3-pyridylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-pyridylcarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-benzothienylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-benzothienylcarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-chlorophenylacetyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-chlorophenylacetyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 1-naphthylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(1-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with (1,3-benzodioxol-5-yl)carbonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((1,3-benzodioxol-5-yl)carbonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 3-nitrobenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-nitrobenzoyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-biphenylylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-biphenylylcarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;
with cyclopentylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(cyclopentylcarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with [5-chloro-1-(4-methylphenyl)-1H-pyrazol-4-yl]-sulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[5-chloro-1-(4-methylphenyl)-1H-pyrazol-4-yl)sulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 4-chlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-chlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octyl-sulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octyl-sulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 2-butoxy-5-(1,1-dimethylpropyl)phenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-butoxy-5-(1,1-dimethylpropyl)phenylsulfonyl]-piperazin-1-ylmethyl}oxazolidin-2-one;

with 2-butoxy-5-(1,1,3,3-tetramethylbutyl)phenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-butoxy-5-(1,1,3,3-tetramethylbutyl)phenylsulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 2-nitro-4-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitro-4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-bromo-2-ethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-bromo-2-ethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3,4-difluorophenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-difluorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 1-naphthylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(1-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-methoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-methoxyphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-tolylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-tolylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-propylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-propylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 6-chloro-2-naphthylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-(naphth-1-yl)ethylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with isobutyl chloroformate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-isobutyloxycarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one.

Example 2

A solution of 100 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,4,6-trichlorophenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one in 15 ml of methanol is admixed with 100 mg of Raney nickel and a drop of acetic acid and hydrogenated at room temperature for 8 hours. The catalyst is filtered off and the solvent is removed. This gives 4-{2-oxo-5-[4-

(2,4,6-trichlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 546/548.

Similarly, the benzamidine derivatives below are obtained from the compounds obtained in Example 1 by hydrogenation

4-{2-oxo-5-[4-(4-biphenylylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 520;

4-{2-oxo-5-[4-(2-phenylethylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 472;

4-{2-oxo-5-[4-(2-aminophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 459;

4-{2-oxo-5-[4-(2,5-dimethoxyphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 504;

4-{2-oxo-5-[4-(2-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 494;

4-{2-oxo-5-[4-(2-chloro-4-fluorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 496;

4-{2-oxo-5-[4-((2-acetamido-4-methylthiazol-5-yl)-sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 522;

4-{2-oxo-5-[4-(2-cyanophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 469;

4-{2-oxo-5-[4-(5-amino-2-methylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 473;

4-{2-oxo-5-(4-benzylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 458;

4-{2-oxo-5-(4-decylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 508;

4-{2-oxo-5-[4-(2-trifluoromethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 512;

4-{2-oxo-5-[4-(3-chloro-4-fluorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 496;

4-{2-oxo-5-[4-(4-chloro-2,5-dimethylphenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 506;

4-{2-oxo-5-[4-(2-fluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 462;

4-{2-oxo-5-[4-(3,4-dibromophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 600/602/604;

4-{2-oxo-5-[4-(3-chlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 478;

4-{2-oxo-5-{4-(2,6-dichlorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 512;

4-{2-oxo-5-[4-(3,4-dichlorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 512;

4-{2-oxo-5-[4-(3,5-dichlorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512;

4-{2-oxo-5-[4-(2-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 458;

4-{2-oxo-5-(4-methylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 382;

4-{2-oxo-5-[4-(2-methylsulfonylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 522;

4-{2-oxo-5-[4-(2-aminobenzylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 473;

4-{2-oxo-5-[4-((4-methoxycarbonyl-3-methoxythiophen-2-yl)sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 538;

4-{2-oxo-5-[4-(3-trifluoromethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512;

4-{2-oxo-5-[4-(4-trifluoromethoxyphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 528;

4-{2-oxo-5-[4-(((1S)-camphor-10-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 518;

4-{2-oxo-5-[4-(((1R)-camphor-10-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 518;

4-{2-oxo-5-[4-((2,2,5,7,8-pentamethylchroman-6-yl)sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, acetate, FAB 570;

4-{2-oxo-5-[4-(4-isopropylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 486;

4-{2-oxo-5-[4-(4-tert-butylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate;

4-{2-oxo-5-[4-(4-butylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 500;

4-{2-oxo-5-[4-(3,5-diamino-4-methoxyphenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, acetate, FAB 504;

4-{2-oxo-5-(4-ethylsulfonylpiperazin-1-yl-methyl]oxazolidin-3-yl}benzamidine, acetate, FAB 396;

4-{2-oxo-5-[4-(4-nitrophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 459;

4-{2-oxo-5-[4-(2-trifluoromethoxyphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 528;

4-{2-oxo-5-[4-(2,4-diaminophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 474;

4-{2-oxo-5-(4-isopropylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 410;

4-{2-oxo-5-[4-(4-ethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 472;

4-{2-oxo-5-[4-(4-bromo-2-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 606/608;

4-{2-oxo-5-[4-(2,3,4-trifluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 498;

4-{2-oxo-5-[4-(3,4-difluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 480;

4-{2-oxo-5-[4-(2,2,2-trifluoroethylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 450;

4-{2-oxo-5-[4-(3-amino-4-methylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 473;

4-{2-oxo-5-[4-(2-amino-6-chlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 585;

4-{2-oxo-5-[4-(2,5-dimethoxyphenylacetyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 482;

4-{2-oxo-5-[4-(3,4-dichlorobenzoyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 476;

4-{2-oxo-5-[4-(3-fluorobenzoyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 426;

4-{2-oxo-5-[4-(4-trifluoromethoxybenzoyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 492;

4-{2-oxo-5-[4-(3-pyridylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 409;

4-{2-oxo-5-[4-(2-benzothienylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 463;

4-{2-oxo-5-[4-(4-chlorophenylacetyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 456;

4-{2-oxo-5-[4-(1-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 458;

4-{2-oxo-5-[4-((1,3-benzodioxol-5-yl)carbonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 452;

4-{2-oxo-5-[4-(3-aminobenzoyl)piperazin-1-yl-methyl]oxazolidin-3-yl}benzamidine, acetate, FAB 423;

4-{2-oxo-5-[4-(4-biphenylylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 484;

4-{2-oxo-5-[4-(cyclopentylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 400;

4-{2-oxo-5-{4-[5-chloro-1-(4-methylphenyl)-1H-pyrazol-4-yl)sulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, acetate, FAB 558;

4-{2-oxo-5-[4-(4-chlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 478;

4-{2-oxo-5-{4-[5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octylsulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 620;

4-{2-oxo-5-{4-[2-butoxy-5-(1,1-dimethylpropyl)-phenylsulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 586;

4-{2-oxo-5-{4-[2-butoxy-5-(1,1,3,3-tetramethylbutyl)phenylsulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 628;

4-{2-oxo-5-[4-(2-amino-4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate;

4-{2-oxo-5-[4-(4-bromo-2-ethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 550/552;

4-{2-oxo-5-[4-(4-trifluoromethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512;

4-{2-oxo-5-[4-(6-chloro-2-naphthylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 528;

4-{2-oxo-5-[4-(isobutyloxycarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 404.

Similarly, reaction of 3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyloxazolidin-2-one with 6-chloro-2-naphthylsulfonyl chloride and subsequent hydrogenation gives the compound

3-{2-oxo-5-[4-(6-chloro-2-naphthylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, m.p. 118°C.

Similarly, reaction of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyloxazolidin-2-one with 6-methoxy-2-naphthylsulfonyl chloride and subsequent hydrogenation gives the compound

4-{2-oxo-5-[4-(6-methoxy-2-naphthylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine.

Similarly, reaction of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyloxazolidin-2-one with 2-fluorobenzyl chloride and subsequent hydrogenation gives the compound

4-{2-oxo-5-[4-(2-fluorobenzyl)piperazin-1-yl-methyl]oxazolidin-3-yl}benzamidine.

Example 3

A solution of 100 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,4,6-trichlorophenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one in 8 ml of methanol is admixed with 3 ml of 1N aqueous sodium hydroxide solution and stirred at 60° for 48 hours. This gives, after customary work-up, 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(2,6-dichloro-4-methoxyphenylsulfonyl)piperazin-1-yl]propan-2-ol, FAB 556/558.

Similarly,

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-difluorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(3-fluoro-4-methoxyphenylsulfonyl)-piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(1-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl-amino]-1-[4-(1-naphthylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-biphenylylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-biphenylylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(3-trifluoromethylphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenylamino]-1-[4-(4-trifluoromethoxyphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-isopropylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-isopropylphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-butylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-butylphenylsulfonyl)piperazin-1-yl]propanol-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-methoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-methoxyphenylsulfonyl)piperazin-1-yl]-propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-tolylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-tolylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-propylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-propylphenylsulfonyl)piperazin-1-yl]-propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-phenylvinylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(2-phenylvinylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-ylmethyl}-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-yl}propan-2-ol.

Similarly, 4-{2-oxo-5-[4-(6-methoxy-2-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine gives the compound

4-{2-hydroxy-3-[4-(6-methoxynaphthalene-2-sulfonyl)piperazin-1-yl]propylamino}benzamidine, diacetate, FAB 498 and

4-{2-oxo-5-[4-(2-fluorobenzyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine gives the compound

4-{2-hydroxy-3-[4-(2-fluorobenzyl)piperazin-1-yl]propylamino}benzamidine, acetate, FAB 386.

Example 4

A solution of 60 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(2,6-dichloro-4-methoxyphenylsulfonyl)piperazin-1-yl]propan-2-ol in 5 ml of methanol is admixed with 50 mg of Raney nickel and a drop of acetic acid and hydrogenated at room

temperature for 8 hours. The catalyst is filtered off and the solvent is removed. This gives 4-{3-[4-(2,6-dichloro-4-methoxyphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 516/518.

Similarly, the compounds below are obtained from the propan-2-ol derivatives listed under Example 3 by hydrogenation

4-{3-[4-(3-fluoro-4-methoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 466;

4-{3-[4-(1-naphthylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 468;

4-{3-[4-(4-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 486;

4-{3-[4-(4-biphenylylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 494;

4-{3-[4-(3-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 486;

4-{3-[4-(4-trifluoromethoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 502;

4-{3-[4-(4-isopropylphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 460;

4-{3-[4-(4-butylphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 474;

4-{3-[4-(4-methoxyphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 448;

4-{3-[4-(4-tolylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 432;

4-{3-[4-(4-propylphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 460;

4-{3-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 502;

4-{3-[4-(2-phenylvinylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 446;

4-{3-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-yl}-2-hydroxypropylamino}benzamidine, acetate, FAB 496.

Example 5

A solution of 10.0 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate, 6.73 g of 4-BOC-aminopiperidine and 8.5 g of sodium bicarbonate in 200 ml of acetonitrile is heated under reflux for 40 hours. Customary work-up

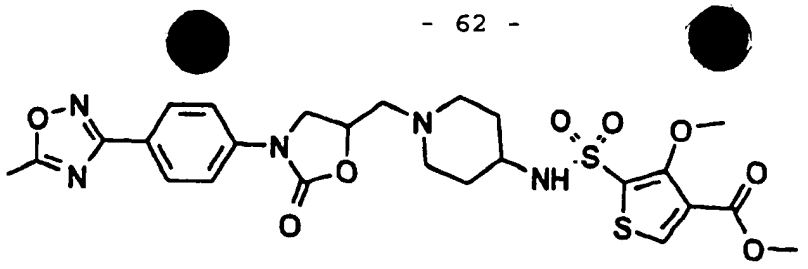
gives 5-(4-BOC-aminopiperidin-1-ylmethyl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one.

The BOC group is cleaved off using TFA in dichloromethane, giving 5-(4-aminopiperidin-1-ylmethyl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-oxazolidin-2-one ("B").

Similarly to Example 1, reaction of "B"

with (3-methoxy-4-methoxycarbonylthiophen-2-yl)sulfonyl chloride gives

N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-(3-methoxy-4-methoxycarbonylthiophen-2-yl)sulfonamide



;

with benzenesulfonyl chloride gives
N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-benzenesulfonamide;

with 3,4-dimethoxybenzenesulfonyl chloride gives
3,4-dimethoxy-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)benzenesulfonamide;

with butylsulfonyl chloride gives
N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-butylsulfonamide;

with 2,4,6-trimethylbenzenesulfonyl chloride gives
2,4,6-trimethyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)benzenesulfonamide;

with phenylvinylsulfonyl chloride gives
phenylvinyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)sulfonamide;

with 2-methylsulfonylbenzenesulfonyl chloride gives
2-methylsulfonyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)benzenesulfonamide;

with 4-biphenylylsulfonyl chloride gives

4-biphenylyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)sulfonamide;

with 5-dimethylamino-1-naphthylsulfonyl chloride gives
5-dimethylamino-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)-1-naphthylsulfonamide;

with 1-naphthylsulfonyl chloride gives
N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-1-naphthylsulfonamide.

By hydrogenation similarly to Example 2, these give the compounds below

4-{5-[4-((3-methoxy-4-methoxycarbonylthiophen-2-yl)sulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 552;

4-{5-[4-(benzenesulfonylamino)piperidin-1-yl-methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 458;

4-{5-[4-(3,4-dimethoxybenzenesulfonyl-amino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 518;

4-{5-[4-(butylsulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 438;

4-{5-[4-(2,4,6-trimethylbenzenesulfonylamino)-piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 500;

4-{5-[4-(phenylethylsulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 486;

4-{5-[4-(2-methylsulfonylbenzenesulfonylamino)-piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 536;

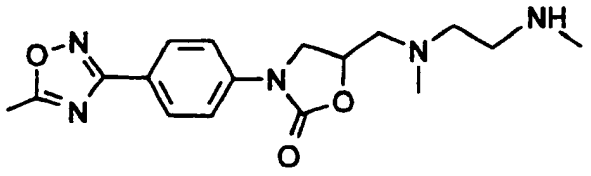
4-{5-[4-(4-biphenylylsulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 533;

4-{5-[4-(5-dimethylamino-1-naphthylsulfonyl-amino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 551;

4-{5-[4-(1-naphthylsulfonylamino)piperidin-1-yl-methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 458.

Example 6

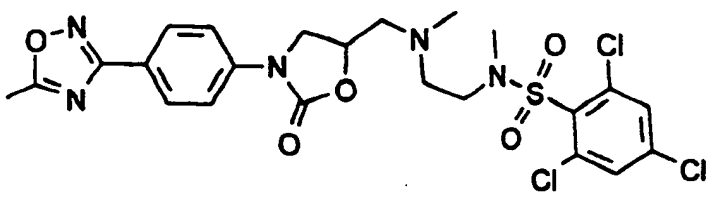
A solution of 10.0 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methane-sulfonate, 7.4 g of N,N'-dimethylethylenediamine and 8.5 g of sodium bicarbonate in 400 ml of acetonitrile is heated under reflux for 40 hours. Customary work-up gives 5-{[methyl-(2-methylaminoethyl)amino]methyl}-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one ("C").



"C"

Similarly to Example 1, reaction of "C"

with 2,4,6-trichlorophenylsulfonyl chloride gives 2,4,6-trichloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide



with 2-trifluoromethoxyphenylsulfonyl chloride gives
2-trifluoromethoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 2,4,6-trichlorophenylsulfonyl chloride gives
2,4,6-trichloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-trifluoromethylphenylsulfonyl chloride gives
4-trifluoromethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-isopropylphenylsulfonyl chloride gives
4-isopropyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-propylphenylsulfonyl chloride gives
4-propyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-acetamidophenylsulfonyl chloride gives
4-acetamido-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 2-naphthylsulfonyl chloride gives

N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-2-naphthylsulfonamide;

with 3-trifluoromethylphenylsulfonyl chloride gives
3-trifluoromethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-chloro-3-nitrophenylsulfonyl chloride gives
4-chloro-3-nitro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with phenylvinylsulfonyl chloride gives
N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]phenylvinylsulfonamide;

with benzylsulfonyl chloride gives
4-trifluoromethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzylsulfonamide;

with tolylsulfonyl chloride gives
4-methyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-methoxyphenylsulfonyl chloride gives
4-methoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 1-naphthylsulfonyl chloride gives
N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-1-naphthylsulfonamide;

with 4-biphenylylsulfonyl chloride gives
N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-4-biphenylylsulfonamide;

with 3,4-difluorophenylsulfonyl chloride gives
3,4-difluoro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-pentylphenylsulfonyl chloride gives
4-pentyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

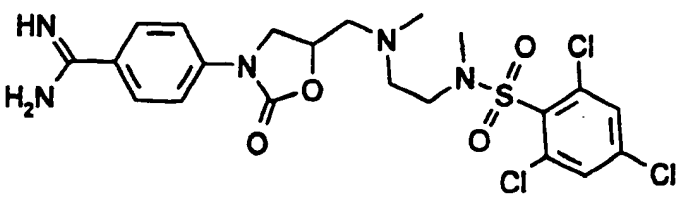
with 4-butylphenylsulfonyl chloride gives
4-butyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-methylsulfonylphenylsulfonyl chloride gives
4-methylsulfonyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 6-chloro-2-naphthylsulfonyl chloride gives
6-chloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-2-naphthylsulfonamide;

By hydrogenation similarly to Example 2, these give the compounds below

4-{5-[(methyl-{2-[methyl-(2,4,6-trichlorobenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 548/550



;

4-{5-[(methyl-{2-[methyl-(2-trifluoromethoxy-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxo-oxazolidin-3-yl}benzamidine, acetate, FAB 530;

4-{5-[(methyl-{2-[methyl-(4-trifluoromethyl-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 514;

4-{5-[(methyl-{2-[methyl-(4-isopropylbenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 488;

4-{5-[(methyl-{2-[methyl-(4-propylbenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 488;

4-{5-[(methyl-{2-[methyl-(4-acetamidobenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 503;

4-{5-[(methyl-{2-[methyl-(2-naphthylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, acetate, FAB 496;

4-{5-[(methyl-{2-[methyl-(3-trifluoromethyl-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 514;

4-{5-[(methyl-{2-[methyl-(3-amino-4-chlorobenzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 495;

4-{5-[(methyl-{2-[methyl(phenylethylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 474;

4-{5-[(methyl-{2-[methyl(benzylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 460;

4-{5-[(methyl-{2-[methyl-(4-tolylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 460;

4-{5-[(methyl-{2-[methyl-(4-methoxybenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 476;

4-{5-[(methyl-{2-[methyl-(1-naphthylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 496;

4-{5-[(methyl-{2-[methyl-(4-biphenylylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 522;

4-{5-[(methyl-{2-[methyl-(3,4-difluorobenzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 516;

4-{5-[(methyl-{2-[methyl-(4-pentylbenzene sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 516;

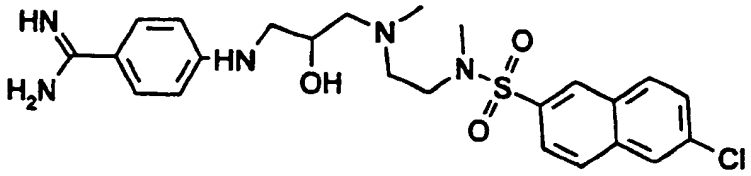
4-{5-[(methyl-{2-[methyl-(4-butylbenzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 502;

4-{5-[(methyl-{2-[methyl-(4-methylsulfonyl-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 502;

4-{5-[(methyl-{2-[methyl-(6-chloro-2-naphthyl sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 530.

Similarly to Examples 3 and 4, 6-chloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-amino)ethyl]-2-naphthylsulfonamide gives the compound

4-[3-({2-[(6-chloro-2-naphthylsulfonyl)methyl-amino]ethyl}methylamino)-2-hydroxypropylamino]-benzamidine, acetate, FAB 504



and 7-methoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl-methyl}amino)ethyl]-2-naphthylsulfonamide gives the compound

4-[3-({2-[(7-methoxy-2-naphthylsulfonyl)methyl-amino]ethyl}methylamino)-2-hydroxypropylamino]benz-amidine, acetate, FAB 500.

Similar to Example 3, cleavage of the oxazolidinone ring of

4-{5-[(methyl-{2-[methyl-(4-biphenylylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine,

4-{5-[(methyl-{2-[methyl-(4-isopropylbenzenesulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine,

4-{5-[(methyl-{2-[methyl-(1-naphthylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, give

the compounds below

4-[3-({2-[(4-biphenylylsulfonyl)methylamino]-ethyl}methylamino)-2-hydroxypropylamino]benzamidine, diacetate, EI 460 ($M^+ - NH_2$);

4-[3-({2-[(4-isopropylbenzenesulfonyl)methyl-amino]ethyl}methylamino)-2-hydroxypropylamino]-benzamidine, diacetate, EI 461;

4-[3-({2-[(1-naphthylsulfonyl)methylamino]ethyl}-methylamino)-2-hydroxypropylamino]benzamidine, diacetate, EI 469.

Example 7

A solution of 10.6 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methane-sulfonate and 3.17 g of sodium azide in 50 ml of acetonitrile is heated under reflux for 40 hours. Customary work-up gives 5-azidomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one.
7.7 g of azido compound are suspended in ethylene glycol dimethyl ether, 3.6 ml of trimethyl phosphite are then added and the mixture is stirred under reflux for 1.5 hours. 4.9 ml of half-concentrated HCl are added and the mixture is boiled for a further 3 hours. Customary work-up gives 5-aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one, hydrochloride.

The compound is suspended in dichloromethane, admixed with basic ion exchanger and stirred for 2 hours. Removal of the ion exchanger and the solvent gives 5-aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]oxazolidin-2-one ("D").

Similarly to Example 1, reaction of "D"

with 3,4-difluorobenzenesulfonyl chloride gives
3,4-difluoro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzene-sulfonamide;

with 4-methoxybenzenesulfonyl chloride gives
4-methoxy-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfon-amide;

with 4-chloro-3-nitrobenzenesulfonyl chloride gives
4-chloro-3-nitro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with butylsulfonyl chloride gives
N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]2-oxooxazolidin-5-ylmethyl}butylsulfonamide;

with 3-trifluoromethylbenzenesulfonyl chloride gives
3-trifluoromethyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 2-naphthylsulfonyl chloride gives
N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide.

Similarly to Example 2, the compounds below are obtained by hydrogenation of the sulfonamides

4-{5-[(3,4-difluorobenzenesulfonylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 411;

4-{5-[4-methoxybenzenesulfonylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 405;

4-{5-[(3-amino-4-chlorobenzenesulfonylamino)-methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 424;

4-{5-[(butylsulfonylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 355;

4-{5-[(3-trifluoromethylbenzenesulfonylamino)-methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 443;

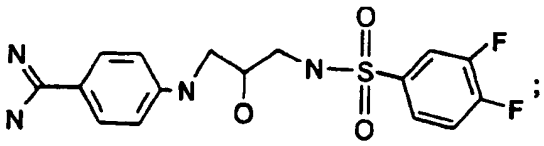
4-{5-[(2-naphthylsulfonylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 425.

Example 8

Similarly to Examples 3 and 4,

3,4-difluoro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazoloidin-5-ylmethyl}benzenesulfonamide gives

4-[3-(3,4-difluorobenzenesulfonylamino)-2-hydroxypropylamino]benzamidine, acetate, FAB 385



4-methoxy-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-[3-(4-methoxybenzenesulfonylamino)-2-hydroxypropylamino]benzamidine;

4-chloro-3-nitro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-[3-(3-amino-4-chlorobenzenesulfonylamino)-2-hydroxypropylamino]benzamidine;

N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}butylsulfonamide gives

4-[3-(butylsulfonylamino)-2-hydroxypropylamino]benzamidine, acetate, FAB 329;

3-trifluoromethyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-[3-(3-trifluoromethylbenzenesulfonylamino)-2-hydroxypropylamino]benzamidine, acetate, FAB 417;

N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-propylsulfonamide gives

4-[3-(propylsulfonylamino)-2-hydroxypropylamino]benzamidine, acetate, FAB 391.

Example 9

A solution of 30.0 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate and 300 ml of aqueous methylamine solution in 300 ml of THF is heated under pressure at 80°C for 18 hours. Customary work-up gives 5-methylaminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one ("E").

Similarly to Example 1, reaction of "E"

with butylsulfonyl chloride gives

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}butylsulfonamide;

with 4-isopropylbenzenesulfonyl chloride gives
4-isopropyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 3-trifluoromethylbenzenesulfonyl chloride gives
3-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with phenylvinylsulfonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}phenylvinylsulfonamide;

with 2-naphthylsulfonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide;

with 4-propylbenzenesulfonyl chloride gives
4-propyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 4-methoxybenzenesulfonyl chloride gives
4-methoxy-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 2,4,6-trimethylbenzenesulfonyl chloride gives
2,4,6-trimethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with benzoyl chloride gives

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzamide;

with 2-naphthylcarbonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthyl-carboxamide;

with cyclohexylcarbonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}cyclohexyl-carboxamide;

with 4-biphenylylcarbonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-4-biphenylyl-carboxamide;

with 4-chlorobenzoyl chloride gives
4-chloro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzamide;

with 4-(1,1-dimethylpropyl)benzenesulfonyl chloride gives
4-(1,1-dimethylpropyl)-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with 3,4-difluorobenzenesulfonyl chloride gives
3,4-difluoro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 4-tert-butylbenzenesulfonyl chloride gives
4-tert-butyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

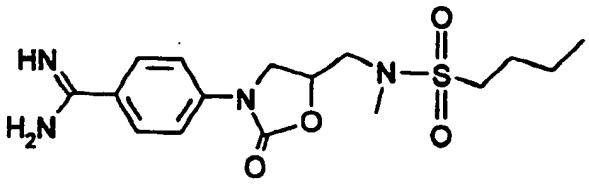
with 4-trifluoromethylbenzenesulfonyl chloride gives
4-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with 4-pentylbenzenesulfonyl chloride gives
4-pentyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 1-naphthylsulfonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-1-naphthylsulfonamide.

Similarly to Example 2, the compounds below are obtained

5-{5-[((butylsulfonyl)methylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 369



;

5-{5-[((4-isopropylbenzenesulfonyl)methylamino)-methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 431;

5-{5-[((3-trifluoromethylbenzenesulfonyl)methyl-amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 457;

5-{5-[((phenylethylsulfonyl)methylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 417;

5-{5-[((2-naphthylsulfonyl)methylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[((4-propylbenzenesulfonyl)methylamino)-methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[((4-methoxybenzenesulfonyl)methylamino)-methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[((2,4,6-trimethylbenzenesulfonyl)methylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(benzoylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(2-naphthylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(cyclohexylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(4-biphenylylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(4-chlorobenzoylmethylamino)methyl]-2-oxo-oxazolidin-3-yl}benzamidine.

Similarly, methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate and butylamine give the compound 5-butylaminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one ("E-1")

Reaction of "E-1"

with 6-chloro-2-naphthylsulfonyl chloride gives

6-chloro-N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide;

with 4-biphenylylsulfonyl chloride gives

N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-4-biphenylyl-sulfonamide;

with 2-naphthylsulfonyl chloride gives

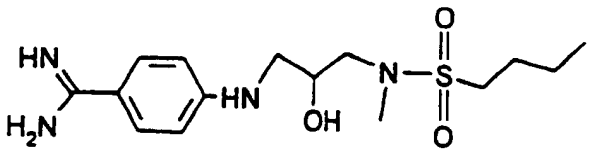
N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide.

Example 10

Similarly to Examples 3 and 4,

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}butylsulfonamide gives

4-{3-[(butane-1-sulfonyl)methylamino]-2-hydroxy-propylamino}benzamidine



;

4-isopropyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-{3-[(4-isopropylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 405;

3-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide gives

4-{3-[(3-trifluoromethylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 431;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}phenylvinylsulfonamide gives

4-{3-[(phenylethylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 413;

6-chloro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(6-chloro-2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 447;

4-propyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-{3-[(4-propylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 405;

4-methoxy-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-{3-[(4-methoxybenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 393;

2,4,6-trimethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide gives

4-{3-[(2,4,6-trimethylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 405;

5-{5-[(benzoylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives

4-{3-[(benzoylmethylamino]-2-hydroxypropylamino}-benzamidine;

5-{5-[(2-naphthylcarbonylmethylamino)methyl]-2-oxo-oxazolidin-3-yl}benzamidine gives

4-{3-[(2-naphthylcarbonylmethylamino]-2-hydroxypropylamino}benzamidine;

5-{5-[(cyclohexylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives
4-{3-[(cyclohexylcarbonylmethylamino]-2-hydroxypropylamino}benzamidine;

5-{5-[(4-biphenylylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives
4-{3-[(4-biphenylylcarbonylmethylamino]-2-hydroxypropylamino}benzamidine;

5-{5-[(4-chlorobenzoylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives
4-{3-[(4-chlorobenzoylmethylamino]-2-hydroxypropylamino}benzamidine;

4-(1,1-dimethylpropyl)-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-{3-[(4-(1,1-dimethylpropyl)benzenesulfonyl)-methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 433;

3,4-difluoro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-{3-[(3-fluoro-4-methoxybenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 411;

4-tert-butyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-{3-[(4-tert-butylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 419;

4-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide gives

4-{3-[(4-trifluoromethylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 431;

4-pentyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-{3-[(4-pentylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 433;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-1-naphthylsulfonamide gives

4-{3-[(1-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 413;

6-chloro-N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(6-chloro-2-naphthylsulfonyl)butylamino]-2-hydroxypropylamino}benzamidine;

N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-4-biphenylylsulfonamide gives

4-{3-[(4-biphenylylsulfonyl)butylamino]-2-hydroxypropylamino}benzamidine;

N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(2-naphthylsulfonyl)butylamino]-2-hydroxypropylamino}benzamidine.

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-(7-methoxy-2-naphthyl)sulfonamide gives

4-{3-[(6-methoxy-2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 443;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-(6-methoxy-2-naphthyl)sulfonamide gives

4-{3-[(6-methoxy-2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 443.

Example 11

A solution of 10.9 g of 3-(4-cyanophenyl)-5-hydroxymethyloxazolidin-2-one ("F"), 5.9 g of 3-cyanophenol, 26.2 g of triphenylphosphine and 13.1 g of diethyl azodicarboxylate in 250 ml of THF is stirred under an atmosphere of protective gas for 4 hours. Customary work-up gives 3-(4-cyanophenyl)-5-[(3-cyanophenoxy)-methyl]oxazolidin-2-one.

A solution of 8.5 g of the dicyano compound, 5.5 g of hydroxylammonium chloride and 11.2 g of sodium carbonate in 130 ml of DMF is stirred at 60°C for 3 hours. Customary work-up gives 3-(4-N-hydroxyamidinophenyl)-5-[(3-N-hydroxyamidinophenoxy)methyl]-oxazolidin-2-one.

Similarly to Example 2, by hydrogenation, this gives the compound 3-(4-amidinophenyl)-5-[(3-amidinophenoxy)methyl]oxazolidin-2-one, diacetate, m.p. 159-160°C, FAB 354.

Similarly, reaction of "F"

with 4'-hydroxybiphenyl-4-carbonitrile, reaction with hydroxylammonium chloride and reduction gives the compound

3-(4-amidinophenyl)-5-[(4'-amidino-4-biphenylyl-oxy)methyl]oxazolidin-2-one, diacetate, m.p. 214-224°C;

with 4-cyanophenol, reaction with hydroxylammonium chloride and reduction gives the compound

3-(4-amidinophenyl)-5-[(4-amidinophenoxy)methyl]-oxazolidin-2-one, diacetate, m.p. 164°C (decomposition);

with 4-cyano-N-(ethoxycarbonyl)benzenesulfonamide gives the compound

N-[3-(4-cyanophenyl)-2-oxooxazolidin-5-ylmethyl]-N-ethoxycarbonyl-4-cyanobenzenesulfonamide, diacetate, FAB 489.

Example 12

A solution of 400 mg of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate, 240 mg of phenylpiperazine and 120 mg of sodium bicarbonate in 10 ml of acetonitrile is heated at 80°C for 18 hours. Customary work-up gives 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-phenylpiperazin-1-ylmethyl)oxazolidin-2-one.

By hydrogenation similarly to Example 2, this gives

4-[2-oxo-5-(4-phenylpiperazin-1-ylmethyl)oxazolidin-3-yl]benzamidine, acetate, FAB 380.

Similarly, the reaction of "A" with 5-bromomethylbenzo-[2,1,3]-thiadiazole gives the compound

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(benzo-[2,1,3]-thiadiazol-5-ylmethyl)piperazin-1-ylmethyl]oxazolidin-2-one.

By hydrogenation similarly to Example 2, this gives

4-{2-oxo-5-[4-(benzo-[2,1,3]-thiadiazol-5-ylmethyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512.

Similarly, reaction of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate

with 2-piperazin-1-ylpyrimidine gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(pyrimidin-2-yl)piperazin-1-ylmethyl]oxazolidin-2-one,

with benzylpiperazine gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-benzylpiperazin-1-ylmethyl]oxazolidin-2-one,

with (benzo-[2,1,3]-thiadiazol-5-yl)piperazine gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(benzo-[2,1,3]-thiadiazol-5-yl)piperazin-1-ylmethyl]oxazolidin-2-one.

Similarly to Examples 3 and 4, the cleavage of the oxazolidinone ring and the oxadiazole ring

of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(pyrimidin-2-yl)piperazin-1-ylmethyl]oxazolidin-2-one gives
4-[2-hydroxy-3-(4-pyrimidin-2-ylpiperazin-1-yl)-propylamino]benzamidine, acetate, FAB 356;

of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-benzylpiperazin-1-ylmethyl]oxazolidin-2-one gives
4-[2-hydroxy-3-(4-benzylpiperazin-1-yl)propylamino]benzamidine, acetate, FAB 368;

of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(benzo-[2,1,3]-thiadiazol-5-yl)piperazin-1-ylmethyl]-oxazolidin-2-one gives
4-[2-hydroxy-3-(4-(benzo-[2,1,3]-thiadiazol-5-yl)-piperazin-1-yl)propylamino]benzamidine, trifluoroacetate, FAB 412.

4-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,5-dimethoxybenzyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

4-{2-hydroxy-3-[4-(3,5-dimethoxybenzyl)piperazin-1-yl]propylamino}benzamidine, FAB 428.

Similarly, reaction of methyl {3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate with 4-piperazin-1-ylpyridine gives

3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(pyridin-4-yl)piperazin-1-ylmethyl]oxazolidin-2-one which is converted by hydrogenation into

3-{2-oxo-5-[4-(pyridin-4-yl)piperazin-1-ylmethyl]-oxazolidin-3-yl}benzamidine, acetate, FAB 381, m.p. 152-165 (decomp.).

Example 13

A solution of 200 mg of "A" and 66 mg of butyl isocyanate in 10 ml of dichloromethane is stirred for 4 hours. 400 mg of aminomethylpolystyrene are added, and the mixture is stirred for a further 12 hours. The polystyrene and solvent are removed, giving, after customary work-up, 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-butylaminocarbonylpiperazin-1-ylmethyl)oxazolidin-2-one.

Similarly, reaction of "A"

with cyclohexyl isocyanate gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(cyclohexylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-methoxyphenyl isocyanate gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-methoxyphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 4-trifluoromethylphenyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-trifluoromethylphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

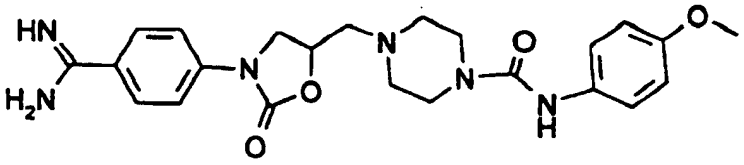
with 4-chlorophenyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-chlorophenyl)aminocarbonyl]piperazin-1-yl-methyl}oxazolidin-2-one;

with 3-ethoxycarbonylphenyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(3-ethoxycarbonylphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 1-naphthyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(naphth-1-ylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one.

By hydrogenation similarly to Example 2,

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-methoxyphenyl)aminocarbonyl]piperazin-1-ylmethyl}-oxazolidin-2-one gives
4-{2-oxo-5-{4-[N-(4-methoxyphenyl)aminocarbonyl]-piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, acetate, FAB 453



3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-trifluoromethylphenyl)aminocarbonyl]piperazin-1-yl-methyl}oxazolidin-2-one gives

4-{2-oxo-5-{4-[N-(4-trifluoromethylphenyl)amino-carbonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benz-amidine, acetate, FAB 473;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-chlorophenyl)aminocarbonyl]piperazin-1-ylmethyl}-oxazolidin-2-one gives

4-{2-oxo-5-{4-[N-(4-chlorophenyl)aminocarbonyl]-piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, acetate, FAB 457;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-butylaminocarbonylpiperazin-1-ylmethyl)oxazolidin-2-one gives

4-[2-oxo-5-(4-butylaminocarbonylpiperazin-1-yl-methyl)oxazolidin-3-yl]benzamidine, acetate, FAB 403;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(3-ethoxycarbonylphenyl)aminocarbonyl]piperazin-1-yl-methyl}oxazolidin-2-one gives

4-{2-oxo-5-{4-[N-(3-ethoxycarbonylphenyl)amino-carbonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benz-amidine, acetate, FAB 495;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(naphth-1-ylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

4-{2-oxo-5-[4-(naphth-1-ylaminocarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 403.

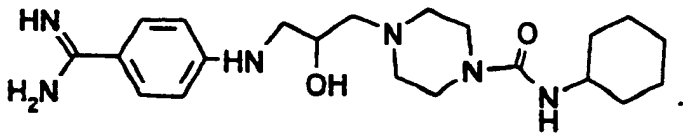
Similarly to Examples 3 and 4,

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-butylaminocarbonylpiperazin-1-ylmethyl)oxazolidin-2-one gives

4-[3-(4-butylaminocarbonylpiperazin-1-yl)-2-hydroxypropylamino]benzamidine, acetate, FAB 377;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(cyclohexylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

4-[3-(4-cyclohexylaminocarbonylpiperazin-1-yl)-2-hydroxypropylamino]benzamidine, acetate, FAB 403



Example 14

A solution of 1 equivalent of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}-methanesulfonate, 3 equivalents of glycine benzyl ester, methanesulfonate, and 3 equivalents of sodium bicarbonate in acetonitrile is heated under reflux for 18 hours. Customary work-up gives benzyl{{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino}acetate ("G").

Similarly to Example 1, reaction of "G" with 6-chloronaphth-2-ylsulfonyl chloride gives

benzyl {N-[6-chloronaphth-2-ylsulfonyl]-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxo-oxazolidin-5-ylmethyl}amino}acetate.

By hydrogenation similarly to Example 2, this gives

{N-[6-chloronaphth-2-ylsulfonyl]-N-[3-(4-amidino-phenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 517,

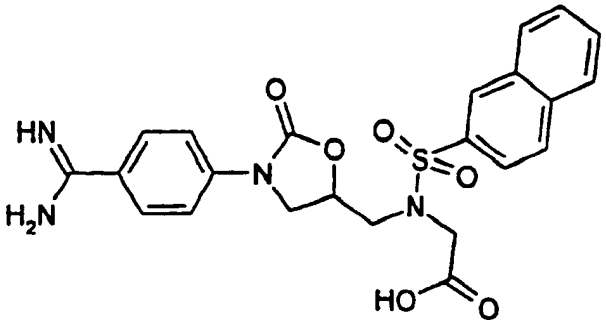
and

benzyl {N-[6-chloronaphth-2-ylsulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}-acetate.

Similarly, reaction of "G"

with naphth-2-ylsulfonyl chloride and subsequent hydrogenation gives

{N-[naphth-2-ylsulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 483



;

with 4-methoxybenzenesulfonyl chloride and subsequent hydrogenation gives

{N-[4-methoxybenzenesulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 453;

with phenylvinylsulfonyl chloride and subsequent hydrogenation gives

benzyl {N-[phenylvinylsulfonyl]-N-[3-(4-aminophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetate, acetate, FAB 549;

with 4-biphenylylsulfonyl chloride and subsequent hydrogenation gives

{N-[4-biphenylylsulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 509;

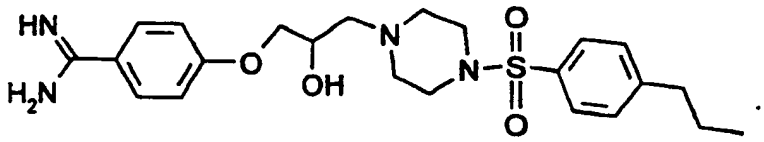
with 4-propylbenzenesulfonyl chloride and subsequent hydrogenation gives

benzyl {N-[4-propylbenzenesulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetate, acetate, FAB 565.

Example 15

A solution of 4-oxiranylmethoxybenzonitrile and BOC-piperazine in methanol is stirred under reflux for 4 hours. Customary work-up gives 4-[2-hydroxy-3-(4-BOC-piperazin-1-yl)propoxy]benzonitrile. The subsequent reaction with hydroxylamine hydrochloride affords N-hydroxy-4-[2-hydroxy-3-(4-BOC-piperazin-1-yl)propoxy]-benzamidine. Subsequent acylation with acetic anhydride gives 2-acetoxy-1-(4-BOC-piperazin-1-yl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propane. After removal of the BOC group with HCl in dioxane, reaction with 4-propylphenylsulfonyl chloride gives the compound 2-acetoxy-1-[4-(4-propylphenylsulfonyl)piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propane. Reaction similarly to Examples 3 and 4 gives the compound

4-{2-hydroxy-3-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine



The compounds below are obtained similarly

3-{2-hydroxy-3-[4-(4-biphenylylcarbonyl)piperazin-1-yl]propoxy}benzamidine, acetate, FAB 459;

3-{2-hydroxy-3-[4-(6-chloro-2-naphthylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 503;

3-{2-hydroxy-3-[4-(2-naphthylsulfonyl)piperazin-1-yl]propoxy}benzamidine, acetate, FAB 469;

3-{2-hydroxy-3-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 461;

3-{2-hydroxy-3-[4-(4-isopropylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 461;

3-{2-hydroxy-3-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 449;

3-{2-hydroxy-3-[4-(4-butylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 399;

3-{2-hydroxy-3-[4-benzoylpiperazin-1-yl]propoxy}-benzamidine, acetate, FAB 383;

3-{2-hydroxy-3-[4-(7-methoxy-2-naphthylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 499;

3-{2-hydroxy-3-[4-(3,5-dimethoxybenzyl)piperazin-1-yl]propoxy}benzamidine, acetate, FAB 429;

3-{2-hydroxy-3-[4-(4-biphenylylsulfonyl)piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 495;

3-{2-hydroxy-3-[4-(naphth-2-ylmethyl)piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 419;

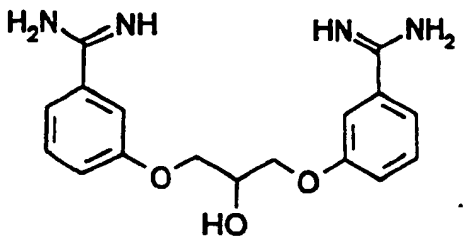
3-{2-hydroxy-3-[4-(2-naphthylcarbonyl)piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 433;

3-{2-hydroxy-3-[4-(4-biphenyl-4-ylmethyl)-piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 445.

Example 16

10.0 g of 3-oxiranylmethoxybenzonitrile ("H") and 7.1 g of 3-cyanophenol together with 173 mg of caesium fluoride are molten at 130°C. Customary work-up gives 11.8 g of 1,3-bis-(3-cyanophenoxy)-2-hydroxypropane. Subsequent reaction with hydroxylammonium chloride gives 1,3-bis-[3-(N-hydroxyamidino)phenoxy]-2-hydroxy-

propane. Hydrogenation similarly to Example 2 gives 1,3-bis-(3-amidinophenoxy)-2-hydroxypropane, diacetate, FAB 329



Similarly, the compounds

1,3-bis-(4-amidinophenoxy)-2-hydroxypropane, diacetate, FAB 329

and

1-(3-amidinophenoxy)-3-(4-amidinophenoxy)-2-hydroxypropane, are obtained.

Similarly, reaction of "H" with the phenols below

4-chlorophenol,
4-methylphenol,
phenol,
4-methoxyphenol,
4-cyclohexylphenol

and subsequent reaction with hydroxylammonium chloride and hydrogenation

gives the compounds below

1-(3-amidinophenoxy)-2-hydroxy-3-(4-chlorophenoxy)propane,

1-(3-amidinophenoxy)-2-hydroxy-3-(4-methylphenoxy)propane,

1-(3-amidinophenoxy)-2-hydroxy-3-phenoxypropane,

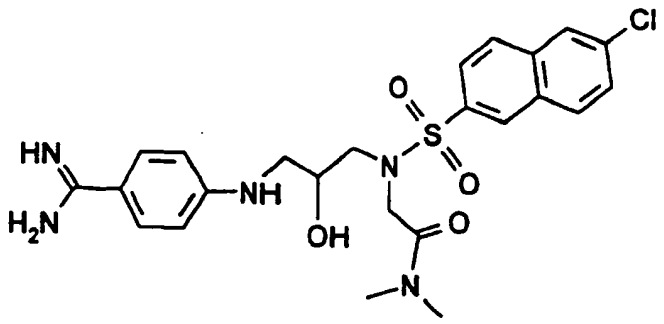
1-(3-amidinophenoxy)-2-hydroxy-3-(4-methoxyphenoxy)propane,

1-(3-amidinophenoxy)-2-hydroxy-3-(4-cyclohexyl-phenoxy)propane.

Example 17

A solution of 1 equivalent of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl-methyl}-(6-chloro-2-naphthyl)sulfonamide ("I") [obtainable by reaction of 5-aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl[oxazolidin-2-one with 6-chloro-2-naphthylsulfonyl chloride], 1.1 equivalents each of N,N'-dimethylchloroacetamide and caesium carbonate in DMF is stirred at room temperature for 12 hours. Customary work-up gives 2-((6-chloro-2-naphthylsulfonyl)-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidine-5-ylmethyl}amino)-N,N'-dimethylacetamide.

Similarly to Examples 3 and 4, this gives the compound 2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-dimethylacetamide



Similarly, reaction of "I" with

N,N'-diethylchloroacetamide,
N,N'-dipropylchloroacetamide,
N-phenylchloroacetamide,
N,N'-diphenylchloroacetamide and
ethyl chloroacetate

and subsequent cleavage of the oxazolidinone ring and the oxadiazole ring similarly to Examples 3 and 4 gives the compounds

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-diethylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-dipropylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N-phenylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-dipenylacetamide and

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]acetic acid, acetate FAB 491.

Similarly, by reaction of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl)-(4-isopropylphenyl)sulfonamide with

N,N'-dimethylchloroacetamide,
N,N'-diethylchloroacetamide,
N,N'-dipropylchloroacetamide,
N-phenylchloroacetamide,
N,N'-diphenylchloroacetamide,
benzyl bromide,
iodobutane,
4-chloromethyl-2-methylthiazole,
4-methoxybenzyl bromide,
ethyl chloroacetate,
ethyl 4-chlorobutyrate,
ethyl 3-chloromethylbenzoate,

ethyl 4-chloromethylbenzoate,
3,5-dimethoxybenzyl bromide,
4-(5-methyl-[1,2,4]-oxadiazol-3-yl)benzyl bromide,
3-(5-methyl-[1,2,4]-oxadiazol-3-yl)benzyl bromide and
2-fluorobenzyl bromide

and subsequent cleavage of the oxazolidinone ring and the oxadiazole ring similarly to Examples 3 and 4 gives the compounds

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'[-dimethylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'-diethylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'-dipropylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N-phenylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'-diphenylacetamide,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-benzylamino]propylamino}benzamidine, acetate, FAB 481,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-butylamino]propylamino}benzamidine, acetate, FAB 447,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(2-methylthiazol-4-ylmethyl)amino]propylamino}-benzamidine, acetate, FAB 502,

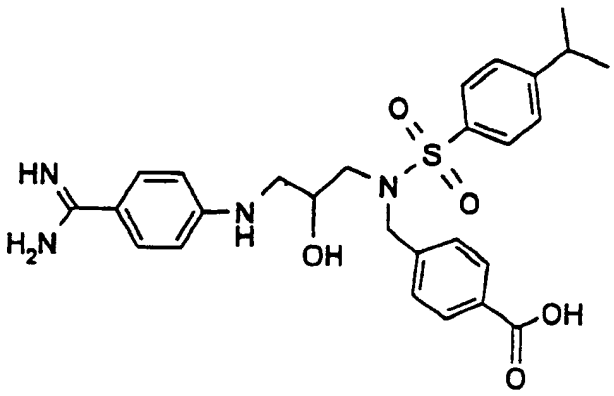
4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(4-methoxybenzyl)amino]propylamino}benzamidine, acetate, FAB 511,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]acetic acid, acetate, FAB 449,

4-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]butyric acid, diacetate, FAB 477,

3-{[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]methyl}benzoic acid, diacetate, FAB 525,

4-{[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]methyl}benzoic acid, diacetate, FAB 525



4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(3,5-dimethoxybenzyl)amino]propylamino}benzamidine, diacetate, FAB 541,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(4-amidinobenzyl)amino]propylamino}benzamidine, triacetate, FAB 523,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(3-amidinobenzyl)amino]propylamino}benzamidine, triacetate, FAB 523 and

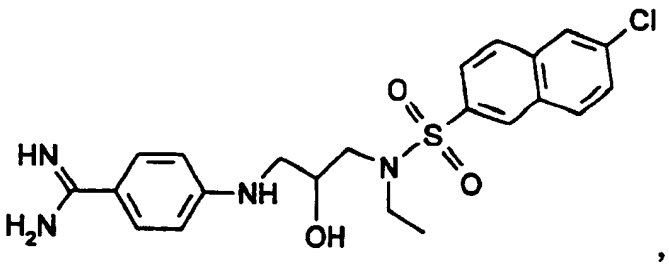
4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(2-fluorobenzyl)amino]propylamino}benzamidine, diacetate, FAB 499.

Similarly, reaction of "I" with

iodoethane,
benzyl bromide,
4-methoxybenzyl bromide,
2-bromomethylnaphthalene,
4-chloromethyl-2-methylthiazole and
4-methoxybenzyl chloride

and subsequent cleavage of the oxazolidinone ring and the oxadiazole ring similarly to Examples 3 and 4 gives the compounds

4-{3-[(6-chloro-2-naphthylsulfonyl)ethylamino]-2-hydroxypropylamino}benzamidine



,

4-{3-[(6-chloro-2-naphthylsulfonyl)benzylamino]-2-hydroxypropylamino}benzamidine,

4-{3-[(6-chloro-2-naphthylsulfonyl)-(4-methoxybenzyl)amino]-2-hydroxypropylamino}benzamidine,

4-{3-[(6-chloro-2-naphthylsulfonyl)-(naphth-2-ylmethyl)amino]-2-hydroxypropylamino}benzamidine,

4-{3-[(6-chloro-2-naphthylsulfonyl)-(2-methylthiazol-4-ylmethyl)amino]-2-hydroxypropylamino}-benzamidine, diacetate, FAB 544 and

4-{3-[(6-chloro-2-naphthylsulfonyl)-(4-methoxybenzyl)amino]-2-hydroxypropylamino}benzamidine, diacetate, FAB 553.

Similarly, reaction of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl)-(4-methoxyphenyl)sulfonamide with iodobutane and subsequent cleavage of the oxazolidinone and the oxadiazole ring similar to Example 3 and 4 gives the compound

4-{3-[(4-methoxyphenylsulfonyl)butylamino]-2-hydroxy-propylamino}benzamidine, acetate, FAB 435.

Similarly, reaction of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl)-(2-naphthyl)sulfonamide with

iodobutane and
iodoethane

and subsequent cleavage of the oxazolidinone and the oxadiazole ring similar to Example 3 and 4 gives the compounds

4-{3-[(2-naphthylsulfonyl)butylamino]-2-hydroxy-propylamino}benzamidine, acetate, FAB 455 and

4-{3-[(2-naphthylsulfonyl)ethylamino]-2-hydroxy-propylamino}benzamidine, acetate, FAB 427.

Example 18

Similarly to Example 11, the appropriate cyano derivatives give, by reaction with hydroxylammonium chloride, the compounds below

3-(3-N-hydroxyamidinophenyl)-5-[(4-N-hydroxy-amidinophenoxy)methyl]oxazolidin-2-one, m.p. 201-205°,

3-(3-N-hydroxyamidinophenyl)-5-[(3-N-hydroxy-amidinophenoxy)methyl]oxazolidin-2-one,

3-(4-N-hydroxyamidinophenyl)-5-[(3-N-hydroxyamidinobenzyloxy)methyl]oxazolidin-2-one,

3-(3-N-hydroxyamidinophenyl)-5-[(3-N-hydroxyamidinobenzyloxy)methyl]oxazolidin-2-one.

Similarly to Example 2, these give, by hydrogenation, the compounds

3-(3-amidinophenyl)-5-[(4-amidinophenoxy)methyl]-oxazolidin-2-one, diacetate, m.p. 150-166° (decomposition), FAB 354;

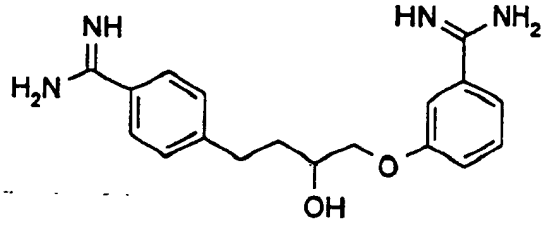
3-(3-amidinophenyl)-5-[(3-amidinophenoxy)methyl]-oxazolidin-2-one, diacetate, m.p. 312-318°;

3-(4-amidinophenyl)-5-[(3-amidinobenzyloxy)-methyl]oxazolidin-2-one, triacetate, m.p. 189-205° (decomp.), FAB 368;

3-(3-amidinophenyl)-5-[(3-amidinobenzyloxy)-methyl]oxazolidin-2-one, triacetate, m.p. 204-222° (decomp.), FAB 368.

Example 19

Similarly to Example 16, reaction of 4-oxiranylethylbenzonitrile and 3-cyanophenol, subsequent reaction with hydroxylammonium chloride and hydrogenation gives the compound 4-[3-hydroxy-4-(3-amidinophenoxy)butyl]benzamidine, diacetate, FAB 327



Example 20

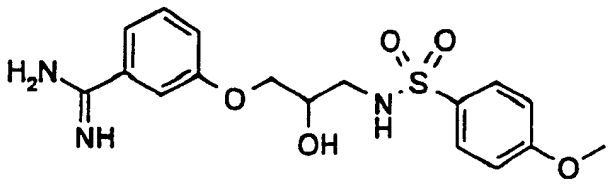
Under nitrogen, 10.0 g of 3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenol is added to 50 ml of DMF and 2.6 g of sodium hydride are subsequently added at 0°. 5.1 ml of epibromohydrin are added, and the mixture is stirred at room temperature for 24 hours. Customary work-up gives 5-methyl-3-(3-oxiranylmethoxyphenyl)-[1,2,4]-oxadiazol.

8.0 g of the oxiranyl compound are dissolved in 400 ml of methanol and NH_3 gas is introduced for 6 hours. The mixture is stirred for another 16 hours, yielding, after removal of the solvent, 1-amino-3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propan-2-ole ("AB").

500 mg of "AB" and 434 mg of 4-methoxyphenylsulfonyl chloride together with 2.0 g of polymeric DMAP (1.6 mmol of dimethylaminopyridine/g of resin) in 5 ml of pyridine are stirred at room temperature for 24 hours. The resin is filtered off and the filtrate is worked up as usual, giving N-{2-hydroxy-3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propyl}-4-methoxybenzenesulfonamide.

This gives, by hydrogenation similarly to Example 2, the compound

3-[2-hydroxy-3-(4-methoxybenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 380



Similarly, reaction of "AB" with

4-isopropylphenylsulfonyl chloride,
2-naphthylsulfonyl chloride,
6-chloro-2-naphthylsulfonyl chloride,
7-methoxy-2-naphthylsulfonyl chloride

and subsequent hydrogenation

gives the compounds below

3-[2-hydroxy-3-(4-isopropylbenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 392;

3-[2-hydroxy-3-(2-naphthylsulfonylamino)propoxy]-benzamidine, acetate, FAB 400;

3-[2-hydroxy-3-(6-chloro-2-naphthylsulfonylamino)-propoxy]benzamidine, acetate, FAB 434;

3-[2-hydroxy-3-(7-methoxy-2-naphthylsulfonyl-amino)propoxy]benzamidine, acetate, FAB 430;

Similarly, reaction of 1-amino-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propan-2-ole

with 4-methoxyphenylsulfonyl chloride,
4-isopropylphenylsulfonyl chloride,
2-naphthylsulfonyl chloride,
6-chloro-2-naphthylsulfonyl chloride,
7-methoxy-2-naphthylsulfonyl chloride

and subsequent hydrogenation

gives the following compounds

4-[2-hydroxy-3-(4-methoxybenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 380;

4-[2-hydroxy-3-(4-isopropylbenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 392;

4-[2-hydroxy-3-(2-naphthylsulfonylamino)propoxy]-benzamidine, acetate, FAB 400;

4-[2-hydroxy-3-(6-chloro-2-naphthylsulfonylamino)-propoxy]benzamidine, acetate, FAB 434;

4-[2-hydroxy-3-(7-methoxy-2-naphthylsulfonyl-amino)propoxy]benzamidine, acetate, FAB 430.

Example 21

10.7 ml of sodium methoxide (30% strength in methanol) are added to 30 ml of methanol, 4-(5-methyl-[1,2,4]-oxadiazol-3-yl)aniline is added under nitrogen and the mixture is stirred at 45° for 10 minutes. The mixture is subsequently added to a suspension of 480 mg of paraformaldehyde and 20 ml of methanol, and the mixture is stirred at 60°C for 2 hours. The mixture is then admixed with 440 mg of sodium borohydride and stirred at 60° for 1 hour. The mixture is subsequently admixed two more times with 1.44 g of paraformaldehyde, 3.1 g of sodium methoxide and 220 mg of sodium borohydride each time.

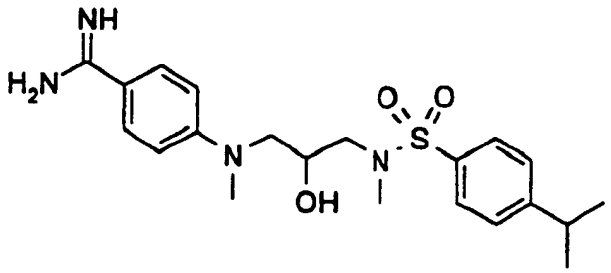
After [lacuna] hours, the mixture is hydrolyzed using 1N NaOH and worked up as usual. This gives, as a crude product, 1.93 g of N-methyl-4-(5-methyl-[1,2,4]-oxadiazol-3-yl)aniline.

A solution of 1.35 g of 4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-N-methylaniline and 1.0 ml of epichlorohydrin in 5 ml of ethanol and 3.5 ml of water is boiled under reflux for 12 hours. Customary work-up gives 0.4 g of N-methyl-N-oxiranylmethyl-4-(5-methyl-[1,2,4]-oxadiazol-3-yl)aniline. A solution of 0.39 g of N-methyl-N-oxiranylmethyl-4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-aniline and 30 ml of methylamine (33% strength in ethanol) in 10 ml of ethanol is stirred at 65° for 15 hours. Customary work-up gives 0.44 g of 1-methylamino-3-{methyl-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]amino}propan-2-ole ("BC").

100 mg of "BC" and 87 mg of 4-isopropylphenylsulfonyl chloride together with 300 mg of polymeric DMAP (1.6 mmol of dimethylaminopyridine/g of resin) in 5 ml of dichloromethane are stirred at room temperature for 16 hours. The resin is filtered off and the filtrate is worked up as usual. This gives 109 mg of N-(2-hydroxy-3-{methyl-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-amino}propyl)-4-isopropyl-N-methylbenzenesulfonamide.

By hydrogenation similarly to Example 2, this gives the compound

4-({2-hydroxy-3-[(4-isopropylbenzenesulfonyl)-N-methylamino]propyl}-N-methylamino)benzamidine, acetate, FAB 419



Similarly, reaction of "BC" with 2-naphthylsulfonyl chloride and subsequent hydrogenation gives the compound

4-({2-hydroxy-3-[(naphth-2-ylsulfonyl)-N-methyl-amino]propyl}-N-methylamino)benzamidine, diacetate, FAB 427.

The following examples relate to pharmaceutical formulations:

Example A: injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogen phosphate in 3 l of doubly distilled water is brought to pH 6.5 with 2 N hydrochloric acid and subjected to sterile filtration, and injection vials are filled with the solution, lyophilized under sterile conditions and closed under sterile conditions. Each injection vial contains 5 mg of active compound.

Example B: suppositories

A mixture of 20 g of an active compound of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed

to cool. Each suppository contains 20 mg of active compound.

Example C: solution

A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of doubly distilled water. It is brought to pH 6.8, topped up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D: ointment

500 g of an active compound of the formula I are mixed with 99.5 g of vaseline under aseptic conditions.

Example E: tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed into tablets in the customary manner such that each tablet contains 10 mg of active compound.

Example F: coated tablets

Tablets are pressed analogously to Example E and are then coated in the customary manner with a coating of sucrose, potato starch, talc, tragacanth gum and dyestuff.

Example G: capsules

Hard gelatin capsules are filled with 2 kg of active compound of the formula I in the customary manner such that each capsule contains 20 mg of the active compound.

Example H: ampoules

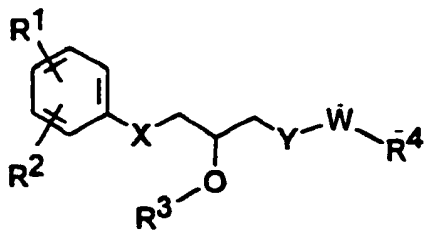
A solution of 1 kg of active compound of the formula I in 60 l of doubly distilled water is subjected to sterile filtration, and ampoules are filled with the solution, lyophilized under sterile conditions and

closed under sterile conditions. Each ampule contains 10 mg of active compound.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

The claims defining the invention are as follows:

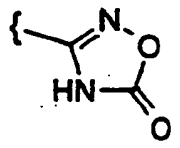
1. Compounds of the formula I



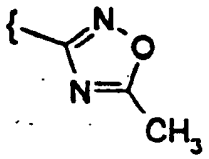
I

in which

R^1 is $-C(=NH)-NH_2$ which can also be mono-substituted by -COA, $-CO-[C(R^5)_2]_m-Ar$, -COOA, -OH or by a conventional amino-protective group,



or



R^2 is H, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NR^5COA, NHCOAr, $NHSO_2A$, $NHSO_2Ar$, $COOR^5$, $CON(R^5)_2$, CONHAr, COR^5, COAr, $S(O)_nA$ or $S(O)_nAr$,

R^3 is R^5 or $-[C(R^5)_2]_m-COOR^5$,

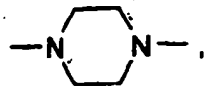
R^3 and X together are also -CO-N-, thus forming a 5-membered ring, where R^3 is -C=O and X is N

R^4 is A, cycloalkyl, $-[C(R^5)_2]_mAr$, $-[C(R^5)_2]_mHet$ or $-CR^5=CR^5-Ar$,

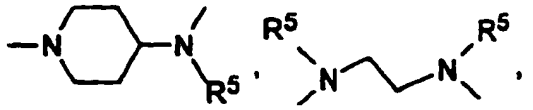
R^5 is H, A or benzyl,

X is O, NR^5 or CH_2,

Y i[redacted]O, NR^5, $N[C(R^5)_2]_m$-Ar, [redacted]$(R^5)_2]_m$-Het,



$N[C(R^5)_2]_m$-$COOR^5$,



$N[C(R^5)_2]_m$-$CON(R^5)_2$, $N[C(R^5)_2]_m$-$CONR^5Ar$ or $N[C(R^5)_2]_m$-$CONAr_2$,

W is a bond, $-SO_2-$, -CO-, or $-CONR^5-$,

A is alkyl having 1-20 C atoms in which one or two CH_2 groups can be replaced by O or S atoms or by $-CR^5=CR^5-$ groups and/or 1-7 H atoms can be replaced by F,

Ar is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, Ar', OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, NHCOAr', $NHSO_2A$, $NHSO_2Ar'$, $COOR^5$, $CON(R^5)_2$, CONHAr', COR^5, COAr', $S(O)_nA$ or $S(O)_nAr$,

Ar' is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, $COOR^5$, $CON(R^5)_2$, COR^5 or $S(O)_nA$,

Het is a mono- or bicyclic saturated or unsaturated heterocyclic ring system which contains one, two, three or four identical or different hetero atoms such as nitrogen, oxygen and sulfur and which is unsubstituted or mono- or polysubstituted by Hal, A, Ar', OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOAr' and/or carbonyl oxygen,

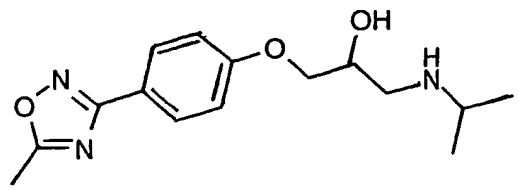
Hal is F, Cl, Br or I,

m is 0, 1, 2, 3 or 4,

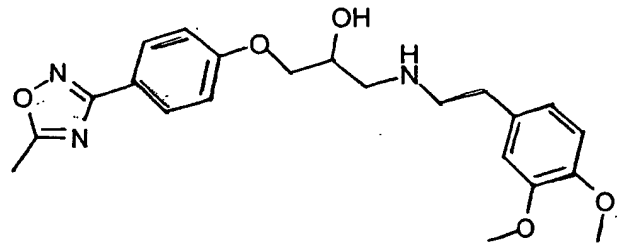
n is 0, 1 or 2,

and salts thereof,

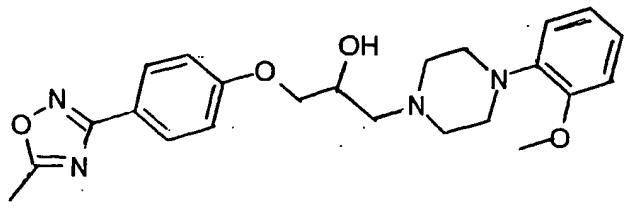
with the proviso that the following compounds are excluded:



1-isopropylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol;



1-[2-(3,4-dimethoxy-phenyl)-ethylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol; and



1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol.

2. Compounds according to Claim 1,

a) 4-{3-[4-(2,6-dichloro-4-methoxybenzene-sulfonyl)piperazin-1-yl]-2-hydroxypropyl-amino}benzamidine;

b) 4-{3-[(4-isopropylbenzenesulfonyl)methyl-amino]-2-hydroxypropylamino}benzamidine;

c) 4-{3-[4-(1-naphthylbenzenesulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine;

d) 3-(4-amidinophenyl)-5-[(3-amidinophenoxy)-methyl]oxazolidin-2-one

and salts thereof.

3. Process for preparing compounds of the formula I according to Claim 1 and salts thereof, characterized in that

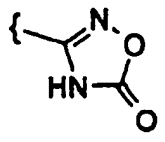
a) they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent, by

i) liberating an amidino group from its oxadiazole derivative by hydrogenolysis,

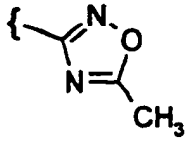
ii) replacing a conventional amino-protective group by treatment with a solvolysing or hydrogenolysing agent with hydrogen or liberating an amino group which is protected by a conventional protective group,

b) that for preparing compounds of the formula I

in which R^1 is

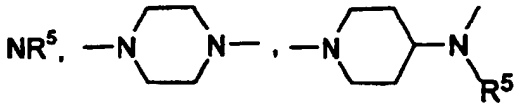


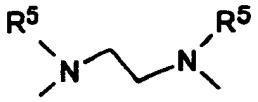
or



,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  or

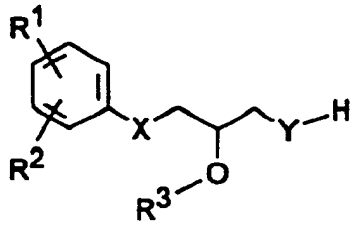


,

W is $-SO_2-$ or -CO-,

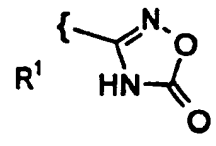
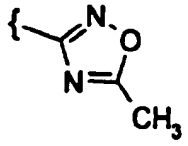
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II

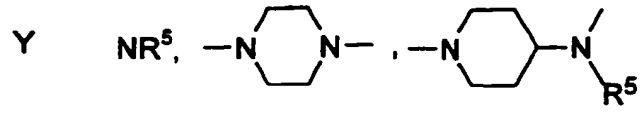


II

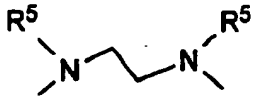
in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is 

or



and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula III

$$R^4\text{-}W\text{-}L \qquad III$$

in which

W is $-SO_2-$ or -CO-,

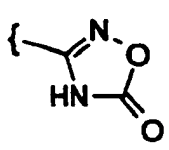
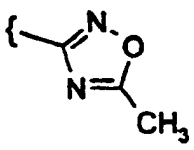
R^4 is as defined in Claim 1,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

or

c) that for preparing compounds of the formula I

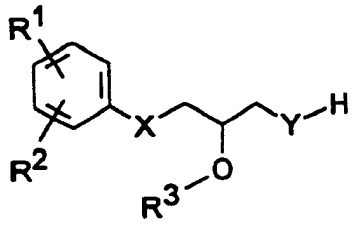
in which R^1 is


or


R^3 and X together are -CO-N-, thus forming a 5-membered ring,
Y is O,
W is a bond,

and R^2 and R^4 are as defined in Claim 1,

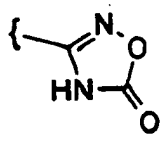
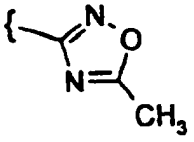
a compound of the formula II



II

in which

R^1 is

R^1 
or


R^3 and X together are -CO-N-, thus forming a 5-membered ring,
Y is O,
and R^2 is as defined in Claim 1,

is reacted with a compound of the formula IV

R^4-W-OH IV

in which

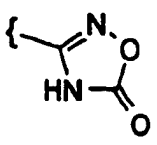
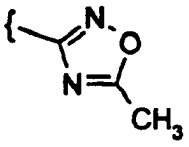
W is a bond,

and R^4 is as defined in Claim 1,

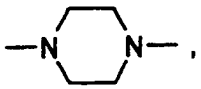
or

d) that for preparing compounds of the formula I

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  ,

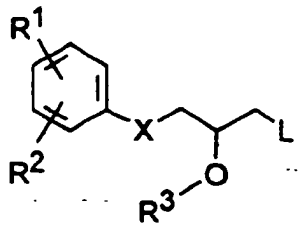
W is a bond,

R^4 is $-[C(R^5)_2]_m Ar$ or $-[C(R^5)_2]_m Het$,

m is 0,

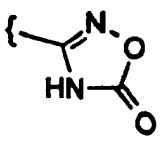
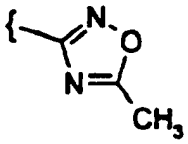
and R^2 is as defined in Claim 1,

a compound of the formula V



V

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

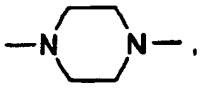
and R^2 is as defined in Claim 1,

is reacted with a compound of the formula VI

$$R^4\text{-}W\text{-}Y\text{-}H \qquad VI$$

in which

W is a bond,

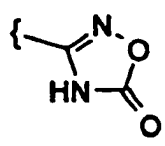
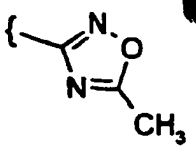
Y is  ,

R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$ and

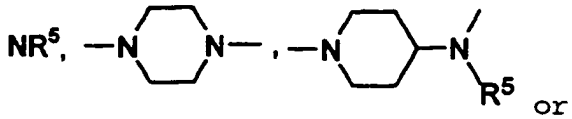
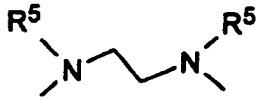
m is 0,

or

e) that for preparing compounds of the formula I in which

R^1 is  or  ,

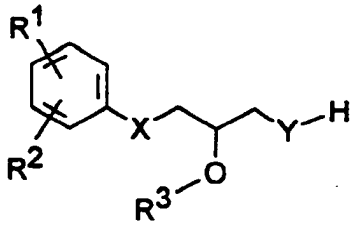
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  or  ,

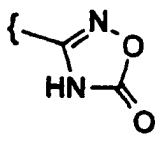
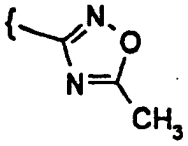
W is -CONH-,

and R^2 and R^4 are as defined in Claim 1,

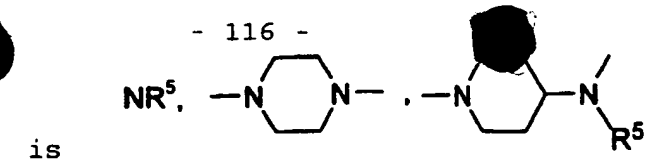
a compound of the formula II

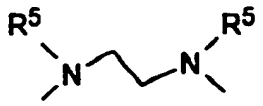
 II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is 

or 

and R^2 and R^5 are as as defined in Claim 1,

is reacted with a compound of the formula VII

$$R^4\text{-}N{=}C{=}O \qquad \text{VII}$$

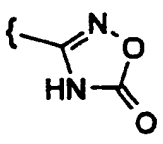
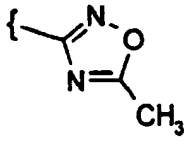
in which

R^4 is as defined in Claim 1,

or

f) that for preparing compounds of the formula I

in which

R^1 is  or  ,

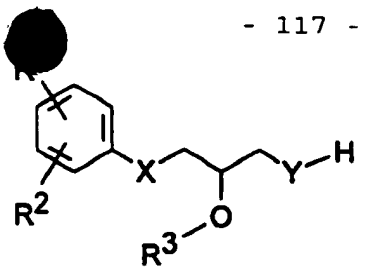
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m\text{-}COOR^5$,

W is SO_2,

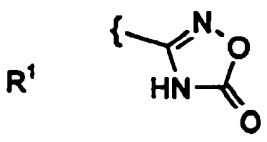
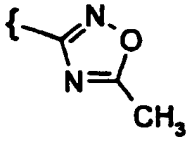
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II



II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$,

and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula VIII

$$R^4\text{-}SO_2\text{-}L \qquad \text{VIII}$$

in which

L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

and R^4 is as defined in Claim 1,

or

g) that for preparing compounds of the formula I

in which

X is NH and

R^3 is H

and R^1, R^2, R^4, Y and W are as defined in Claim 1,

these compounds are liberated from their oxazolidinone derivatives by treatment with a solvolysing or hydrogenolyzing agent,

or

h) that for preparing compounds of the formula I

in which R^1 is $-C(=NH)-NH_2$,

a cyano group is converted into an amidino group,

or

I) in a compound of the formula I, one or more radicals Y, R^1, R^2, R^3 and/or R^4 are converted into one or more radicals R^1, R^2, R^3 and/or R^4,

by, for example,

i) hydrolysing an ester group to give a carboxyl group,

ii) reducing a nitro group,

iii) acylating an amino group,

and/or

k) converting a base or acid of the formula I into one of its salts.

4. Process for preparing pharmaceutical formulations, characterized in that a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts is brought into a suitable dosage form together with at least one solid, liquid or semi-liquid carrier or auxiliary.

5. Pharmaceutical formulation, characterized by a content of at least one compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts together with at least one solid, liquid or semi-liquid carrier or auxiliary.

6. Use of compounds of the formula I according to Claim 1 and their physiologically acceptable salts for combating thromboses, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

7. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts for the preparation of a medicament.

8. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts for the preparation of a medicament for combating thromboses, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

9. Method for combating thromboses, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens which comprises administering to a subject in need of such treatment at least one compound of the formula I according to claim 1 and/or one of its physiologically acceptable salts together with at least one solid, liquid or semi-liquid carrier or auxiliary.

10. Compounds of the formula I, processes for their preparation or pharmaceutical compositions or methods of treatment involving/containing them, substantially as hereinbefore described with reference to the Examples.

DATED this 30th day of April, 2001

MERCK PATENT GMBH

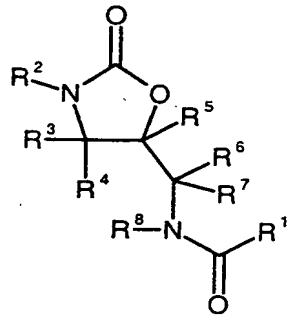
By its Patent Attorneys

DAVIES COLLISON CAVE

Substituted oxazolidinones and their use

Abstract

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



(I),

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

ORIGINAL

533 Rec'd PCT/PTO 24 JUN 2002

FORM PTO-1390 (REV. 12-2001) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY 'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	Le A 34 122
	U S APPLICATION NO (If known, see 37 CFR 1.5) 10/181051

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/12492	11 December 2000 (11.12.00)	24 December 1999 (24.12.99)

TITLE OF INVENTION
Substituted Oxazolidinones and Their Use in the Field of Blood Coagulation

APPLICANT(S) FOR DO/EO/US
Alexander STRAUB, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [X] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [X] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information: **1) Certificate of Mailing under 37 C.F.R. 1.10;**
    2) Transmittal of Information Disclosure Statement under 37 C.F.R. 1.97(b);
    3) Information Disclosure Citation (Modified Form PTO-1449) and copies of references cited therein;
    4) Return Receipt Postcard.

Date of Deposit: JUN 24 2002
Express Mail Label No.: EU054495463US

10/181051 JC20 Rec'd PCT/PTO 24 JUN 2002

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/181051	PCT/EP00/12492	Le A 34 122

21. [X] The following fees are submitted:

	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	15 - 20 =	0	x $18.00	$ 00.00
Independent claims	5 - 3 =	2	x $84.00	$ 168.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable) 0			+ $280.00	$ 00.00

TOTAL OF ABOVE CALCULATIONS =	$ 1,058.00
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2. +	$
SUBTOTAL =	$ 1,058.00
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).	$
TOTAL NATIONAL FEE =	$ 1,058.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +	$
TOTAL FEES ENCLOSED =	$ 1,058.00
Amount to be refunded:	$
charged:	$

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 13-3372 in the amount of $ 1,058.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3372 . A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO **Customer No. 27941**

Jeffrey M. Greenman
Vice President, Patents and Licensing
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West Haven, Connecticut 06516

William F. Gray
SIGNATURE

William F. Gray
NAME

Reg. No. 31,018
REGISTRATION NUMBER

Substituted oxazolidinones and their use

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").

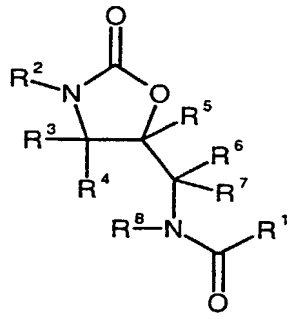
Recently, a novel therapeutic approach for the treatment and prophylaxis of thromboembolic disorders has been described. This novel therapeutic approach aims to inhibit factor Xa (cf. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research **1999**, *93*, 203; F. Al-Obeidi, J.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

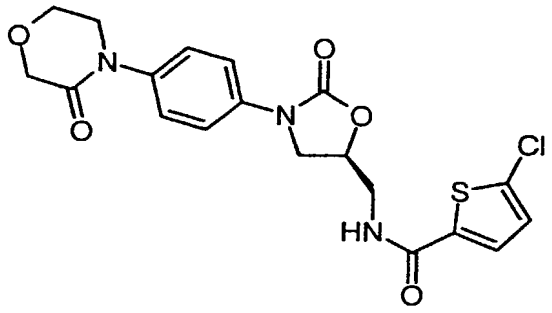
where:
the radical "A" represents phenylene;
the radical "D" represents a saturated 5- or 6-membered heterocycle, which is attached to "A" via a nitrogen atom,
which has a carbonyl group directly adjacent to the linking nitrogen atom and
in which one carbon ring member may be replaced by a heteroatom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