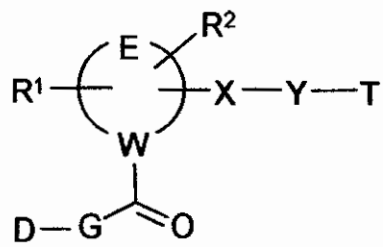
Medicaments comprising carbonyl compounds, and the use thereof

The invention relates to the use of compounds of the formula I



I

in which

R^1 and R^2 each, independently of one another, denote H, =O, Hal, A, ethynyl, OR^3, $N(R^3)_2$, NO_2, CN, N_3, $COOR^3$, $CON(R^3)_2$, $-[C(R^4)_2]_n$-Ar, $-[C(R^4)_2]_n$-Het, $-[C(R^4)_2]_n$-cycloalkyl, $-OCOR^3$, NR^3COA or NR^3SO_2A,

R^1 and R^2 together also denote a bicyclically or spirocyclically bonded 3- to 7-membered carbocyclic or heterocyclic ring having 0 to 3 N, O and/or S atoms,

R^3 denotes H, A, H-C≡C-CH_2-, CH_3-C≡C-CH_2-, -CH_2-CH(OH)-CH_2OH, -CH_2-CH(OH)-CH_2NH_2, -CH_2-CH(OH)-CH_2Het', $-[C(R^4)_2]_n$-Ar', $-[C(R^4)_2]_n$-Het', $-[C(R^4)_2]_n$-cycloalkyl, $-[C(R^4)_2]_n$-COOA or $-[C(R^4)_2]_nN(R^4)_2$,

R^4 denotes H or A,

W denotes N, CR^3 or an sp^2-hybridised carbon atom,

E together with W denotes a 3- to 7-membered saturated carbocyclic or heterocyclic ring having 0 to 3 N, 0 to 2 O and/or 0 to 2 S atoms,

which may contain a double bond,

D denotes a monocyclic or bicyclic, aromatic carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or polysubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$ or $CON(R^3)_2$,

G denotes $-[C(R^4)_2]_n-$, $-[C(R^4)_2]_nNR^3-$, $-[C(R^4)_2]_nO-$, $-[C(R^4)_2]_nS-$ or $-[C(R^4)=C(R^4)]_n-$,

X denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n-$, $-[C(R^4)_2]_nNR^3CO[C(R^4)_2]_n-$, $-[C(R^4)_2]_nNR^3[C(R^4)_2]_n-$, $-[C(R^4)_2]_nO[C(R^4)_2]_n-$, $-[C(R^4)_2]_nCO[C(R^4)_2]_n-$ or $-[C(R^4)_2]_nCOO[C(R^4)_2]_n-$,

Y denotes alkylene, cycloalkylene, Het-diyl or Ar-diyl,

T denotes a monocyclic or bicyclic, saturated or unsaturated carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is monosubstituted or disubstituted by =O, =S, $=NR^3$, =N-CN, $=N-NO_2$, $=NOR^3$, $=NCOR^3$, $=NCOOR^3$ or $=NOCOR^3$ and may furthermore be monosubstituted, disubstituted or trisubstituted by R^3, Hal, A, $-[C(R^4)_2]_n$-Ar, $-[C(R^4)_2]_n$-Het, $-[C(R^4)_2]_n$-cycloalkyl, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, $NR^3CON(R^3)_2$, NR^3SO_2A, COR^3, SO_2NR^3 and/or $S(O)_nA$,

A denotes unbranched or branched alkyl having 1-10 carbon atoms in which one or two CH_2 groups may be replaced by O or S atoms and/or by -CH=CH- groups and/or in addition 1-7 H atoms may be replaced by F,

Ar denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, $NR^3CON(R^3)_2$, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, $S(O)_nA$, $-[C(R^4)_2]_n-COOR^3$ or $-O[C(R^4)_2]_o-COOR^3$,

Ar' denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^4, $N(R^4)_2$, NO_2, CN, $COOR^4$, $CON(R^4)_2$, NR^4COA,

$NR^4CON(R^4)_2$, NR^4SO_2A, COR^4, $SO_2N(R^4)_2$, $S(O)_nA$, $-[C(R^4)_2]_n-COOR^4$ or $-O[C(R^4)_2]_o-COOR^4$,

Het denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 N, O and/or S atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, $-[C(R^4)_2]_n-Ar$, $-[C(R^4)_2]_n-Het'$, $-[C(R^4)_2]_n-$cycloalkyl, OR^3, $N(R^3)_2$, $NR^3CON(R^3)_2$, NO_2, CN, $-[C(R^4)_2]_n-COOR^3$, $-[C(R^4)_2]_n-CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, $S(O)_mA$ and/or carbonyl oxygen,

Het' denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 N, O and/or S atoms which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, =S, $=N(R^4)_2$, Hal, A, OR^4, $N(R^4)_2$, NO_2, CN, $COOR^4$, $CON(R^4)_2$, NR^4COA, $NR^4CON(R^4)_2$, NR^4SO_2A, COR^4, SO_2NR^4 and/or $S(O)_nA$,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

o denotes 1, 2 or 3,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios,

for the preparation of a medicament for the prevention and treatment of thromboembolic diseases and/or thromboses as a consequence of surgery, genetically caused diseases with increased thrombophilia, diseases of the arterial and venous vascular system, cardiac insufficiency, atrial fibrillation, thrombophilia, tinnitus and/or sepsis.

The invention had the object of finding novel uses of the compounds of the formula I, in particular those which can result in the preparation of medicaments.

The compounds of the formula I and salts thereof have very valuable pharmacological properties while being well tolerated. In particular, they exhibit factor Xa-inhibiting properties and can therefore be employed for combating and preventing thromboembolic diseases, such as thrombosis, myocardial infarction, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

The compounds of the formula I may furthermore be inhibitors of the coagulation factors factor VIIa, factor IXa and thrombin in the blood coagulation cascade.

Aromatic amidine derivatives having an antithrombotic action are disclosed, for example, in EP 0 540 051 B1, WO 98/28269, WO 00/71508, WO 00/71511, WO 00/71493, WO 00/71507, WO 00/71509, WO 00/71512, WO 00/71515 and WO 00/71516. Cyclic guanidines for the treatment of thromboembolic diseases are described, for example, in WO 97/08165. Aromatic heterocyclic compounds having a factor Xa inhibitory activity are disclosed, for example, in WO 96/10022. Substituted N-[(aminoiminomethyl)phenylalkyl]azaheterocyclylamides as factor Xa inhibitors are described in WO 96/40679.
Other carboxamide derivatives are disclosed in WO 02/48099 and WO 02/57236, other pyrrolidine derivatives are described in WO 02/100830.

Further heterocyclic derivatives are disclosed in WO 03/045912.

The antithrombotic and anticoagulant effect of the compounds of the formula I is attributed to the inhibitory action against activated coagulation protease, known by the name factor Xa, or to the inhibition of other activated serine proteases, such as factor VIIa, factor IXa or thrombin.

Factor Xa is one of the proteases 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 cross-linking, make an elementary contribution to thrombus formation. Activation of thrombin may result in the occurrence of thromboembolic diseases. However, inhibition of thrombin may inhibit the fibrin formation involved in thrombus formation.

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 the formation of thrombin.

The compounds of the formula I and salts thereof engage in the blood coagulation process by inhibiting factor Xa and thus inhibit the formation of thrombuses.

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

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

Coagulation factor VIIa initiates the extrinsic part of the coagulation cascade after binding to tissue factor and contributes to the activation of factor X to give factor Xa. Inhibition of factor VIIa thus prevents the formation of factor Xa and thus subsequent thrombin formation.

The inhibition of factor VIIa by the compounds of the formula I and the measurement of the anticoagulant and antithrombotic activity can be determined by conventional in-vitro or in-vivo methods. A conventional

method for the measurement of the inhibition of factor VIIa is described, for example, by H. F. Ronning et al. in *Thrombosis Research* **1996**, *84*, 73-81.

Coagulation factor IXa is generated in the intrinsic coagulation cascade and is likewise involved in the activation of factor X to give factor Xa. Inhibition of factor IXa can therefore prevent the formation of factor Xa in a different way.

The inhibition of factor IXa by the compounds of the formula I and the measurement of the anticoagulant and antithrombotic activity can be determined by conventional in-vitro or in-vivo methods. A suitable method is described, for example, by J. Chang et al. in *Journal of Biological Chemistry* **1998**, *273*, 12089-12094.

The compounds of the formula I may furthermore be used for the treatment of tumours, tumour diseases and/or tumour metastases.

A correlation between tissue factor TF / factor VIIa and the development of various types of cancer has been indicated by T.Taniguchi and N.R.Lemoine in Biomed. Health Res. (2000), 41 (Molecular Pathogenesis of Pancreatic Cancer), 57-59.

The publications listed below describe an antitumoural action of TF-VII and factor Xa inhibitors of various types of tumour:

K.M. Donnelly et al. in Thromb. Haemost. 1998; 79: 1041-1047;

E.G. Fischer et al. in J. Clin. Invest. 104: 1213-1221 (1999);

B.M. Mueller et al. in J. Clin. Invest. 101: 1372-1378 (1998);

M.E. Bromberg et al. in Thromb. Haemost. 1999; 82: 88-92.

The compounds of the formula I can be employed as medicament active ingredients in human and veterinary medicine, in particular for the treatment and prevention of thromboembolic diseases, such as thrombosis, myocardial infarction, arteriosclerosis, inflammation, apoplexy, angina

pectoris, restenosis after angioplasty, claudicatio intermittens, venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, unstable angina and strokes based on thrombosis.

The compounds of the formula I are also employed for the treatment or prophylaxis of arteriosclerotic diseases, such as coronary arterial disease, cerebral arterial disease or peripheral arterial disease.

The compounds of the formula I are also employed in combination with other thrombolytic agents in myocardial infarction, furthermore for prophylaxis for reocclusion after thrombolysis, percutaneous transluminal angioplasty (PTCA) and coronary bypass operations.

The compounds of the formula I are furthermore used for the prevention of rethrombosis in microsurgery, furthermore as anticoagulants in connection with artificial organs or in haemodialysis.

The compounds of the formula I are furthermore used in the cleaning of catheters and medical aids in patients *in vivo*, or as anticoagulants for the preservation of blood, plasma and other blood products *in vitro*. The compounds are furthermore used for diseases in which blood coagulation makes a crucial contribution toward the course of the disease or represents a source of secondary pathology, such as, for example, in cancer, including metastasis, inflammatory diseases, including arthritis, and diabetes.

The compounds of the formula I are furthermore used for the treatment of migraine (F.Morales-Asin et al., Headache, 40, 2000, 45-47).

The use of anticoagulants in the therapy of tinnitus is described by R. Mora et al. in International Tinnitus Journal (2003), 9(2), 109-111.

In the treatment of the diseases described, the compounds of the formula I are also employed in combination with other thrombolytically active compounds, such as, for example, with the "tissue plasminogen activator" t-PA, modified t-PA, streptokinase or urokinase. The compounds are ad-

ministered either at the same time as or before or after the other substances mentioned.

Particular preference is given to simultaneous administration with aspirin in order to prevent recurrence of the clot formation.

Surprisingly, it has been found that the compounds of the formula I can be used for the preparation of a medicament for the prevention and treatment of thromboembolic diseases and/or thromboses as a consequence of surgery, genetically caused diseases with increased thrombophilia, diseases of the arterial and venous vascular system, cardiac insufficiency, atrial fibrillation, thrombophilia, tinnitus and/or sepsis.

Preference is given to uses where the surgery is selected from the group thorax operations, operations in the abdominal region, orthopaedic interventions, hip and knee joint replacement, CABG (coronary artery bypass grafting), artificial heart valve replacement, operations with use of a heart-lung machine, vascular surgery, organ transplants and use of central vein catheters.

The invention also relates to the use of the compounds of the formula I for the preparation of a medicament for the prevention and treatment of thromboembolic diseases and/or thromboses in adults and children.

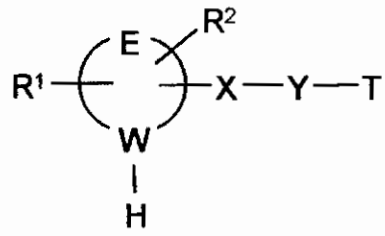
The preparation of the compounds of the formula I and salts thereof is characterised in that ,

a) for the preparation of compounds of the formula I in which

W denotes N and

G denotes NH,

a compound of the formula II



II

in which

R^1, R^2, E, X, Y and T have the meaning indicated in Claim 1,

and W denotes N,

is reacted with a compound of the formula III

$$D\text{-}N{=}C{=}O \qquad III$$

in which

D has the meaning indicated in Claim 1,

or

b) for the preparation of compounds of the formula I in which

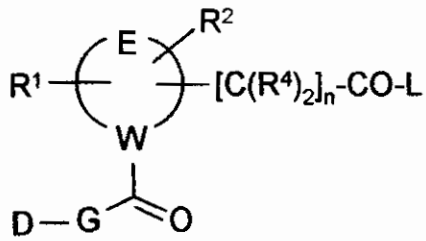
X denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n-$,

a compound of the formula IV

$$HNR^3\text{-}[C(R^4)_2]_n\text{-}Y\text{-}T \qquad IV$$

in which R^3, n, Y and T have the meaning indicated in Claim 1,

is reacted with a compound of the formula V



V

in which

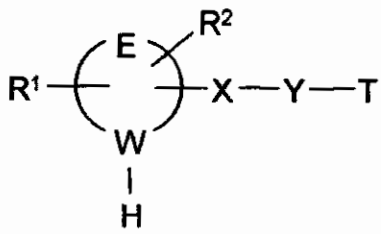
L denotes Cl, Br, I or a free or reactively functionally modified OH group, and

R^1, R^2, R^4, D, E, G, W and n have the meaning indicated in Claim 1,

or

c) for the preparation of compounds of the formula I in which W denotes N,

a compound of the formula II



II

in which

R^1, R^2, E, X, Y and T have the meaning indicated in Claim 1,

and W denotes N,

is reacted with a compound of the formula VI

D-G-CO-L VI

in which D and G have the meaning indicated in Claim 1, and

L denotes Cl, Br, I or a free or reactively functionally modified OH group,

and/or

a base or acid of the formula I is converted into one of its salts.

The formula I also encompasses the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds. The term "solvates of the compounds" is taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

The term "pharmaceutically usable derivatives" is taken to mean, for example, the salts of the compounds of the formula I and so-called prodrug compounds.

The term "prodrug derivatives" is taken to mean compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to form the active compounds.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

The formula I also encompasses mixtures of the compounds of the formula I, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

These are particularly preferably mixtures of stereoisomeric compounds.

Preference is given to the use according to the invention of the pyrrolidine-carboxylic acid derivatives selected from the group

1-N-[(4-chlorophenyl)]-2-N-[(1'-methyl-[1,4']bipiperidinyl-4-yl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl)-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-(4-pyridin-4-ylpiperazine-1-carbonyl)pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-(2-methoxyphenyl)piperazine-1-carbonyl]pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4-fluorophenyl)piperazine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carbonyl]pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-(4-pyridin-2-ylpiperazine-1-carbonyl)pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4-ethylpiperazin-1-yl)piperidine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4,6-dimethylpyrimidin-2-yl)piperazine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-(1-methylpiperidin-4-yl)-piperazine-1-carbonyl]pyrrolidine-1-carboxamide;

1-N-[(4-chlorophenyl)]-2-N-{[2-(2-dimethylaminoethoxy)-4-morpholin-4-ylphenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(2-ethoxy-4-morpholin-4-ylphenyl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(4-morpholin-4-yl-2-propoxyphenyl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

The invention also relates to the use of the cyclopentanecarboxylic acid derivatives selected from the group

N-[4-(3-oxomorpholin-4-yl)phenyl]-(rac)-2-[3-(4-chlorophenyl)ureido]-cyclopentanecarboxamide,

N-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]-(rac)-2-[3-(4-chlorophenyl)ureido]cyclopentanecarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

Particular preference is given to the use according to the invention of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

For all radicals which occur more than once, such as, for example, A, their meanings are independent of one another.

Above and below, the radicals or parameters D, E, G, W, X, Y, T, R^1 and R^2 have the meaning indicated under the formula I, unless expressly stated otherwise.

A denotes alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. A preferably denotes 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, furthermore preferably, for example, trifluoromethyl.

A very particularly preferably denotes alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

Cycloalkyl preferably denotes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Alkylene is preferably methylene, ethylene, propylene, butylene, pentylene or hexylene, furthermore branched alkylene.

R^1 and R^2 each, independently of one another, preferably denote, for example, H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH.

R^1 preferably denotes H, =O, $COOR^3$, such as, for example, COOA, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, such as, for example, methylcarbonyloxy, NHCOA, such as, for example, acetamino, or $NHSO_2A$, such as, for example, methylsulfonylamino; OCH_2COOA, such as, for example, OCH_2COOCH_3; or OCH_2COOH.

R^2 preferably denotes H, =O, OH, OA, such as, for example, methoxy, or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms.

In a further preferred embodiment,

R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA, $NHSO_2A$,

H-C≡C-CH_2-, CH_3-C≡C-CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2, -O-CH_2-CH(OH)-CH_2Het', OCH_2COOCH_3 or OCH_2COOH;

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;

Het' denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, A, OH, NH_2, NO_2, CN, COOA or $CONH_2$.

In another preferred embodiment,

R^1 denotes ethynyl, vinyl, allyloxy, CH_3-C≡C-CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2, -O-CH_2-CH(OH)-CH_2Het', OCH_2COOCH_3 or OCH_2COOH,

R^2 denotes H, A or OH,

Het' denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, A, OH, NH_2, NO_2, CN, COOA or $CONH_2$.

In a further preferred embodiment,

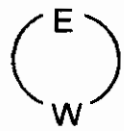
R^1 denotes ethynyl, vinyl, allyloxy, CH_3-C≡C-CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2, -O-CH_2-CH(OH)-CH_2Het', OCH_2COOCH_3 or OCH_2COOH,

R^2 denotes H, A or OH,

Het' denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen.

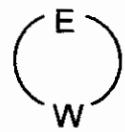
Het' in this connection very particularly preferably denotes pyrrolidine, piperidine or oxazolidine, each of which is unsubstituted or monosubstituted by carbonyl oxygen.

R^1 and R^2 together also denote a 3- to 6-membered carbocyclic or heterocyclic ring having 0 to 3 N, O and/or S atoms which is spirocyclically or bicyclically bonded (fused) to the



ring system. The 3- to 6-membered carbocyclic or heterocyclic ring here is, for example, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyridyl, imidazolyl, piperidinyl or 1,3-dioxolanyl.

R^1 and R^2 together denote in particular a 3- to 6-membered carbocyclic ring which is spirocyclically bonded to the



ring system. The 3- to 6-membered carbocyclic ring here is preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

R^3 preferably denotes H or A, furthermore also phenyl, benzyl or $[C(R^4)_2]_nCOOA$, such as, for example, CH_2COOCH_3.

R^4 preferably denotes H or A, very particularly preferably H.

COR^2, COR^3 and COR^4 are, for example, CHO or -COA.

-COA (acyl) is preferably acetyl, propionyl, furthermore also butyryl, pentanoyl, hexanoyl or, for example, benzoyl.

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

Ar denotes, for example, phenyl, 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-(N-methylaminocarbonyl)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-ethoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N,N-dimethylaminocarbonyl)-phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)-

phenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-(methylsulfonamido)phenyl, o-, m- or p-(methylsulfonyl)phenyl, o-, m- or p-phenoxyphenyl, further 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 preferably denotes, for example, phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^2, OR^3, SO_2A, $COOR^2$ or CN.

Ar particularly preferably denotes, for example, phenyl which is unsubstituted or monosubstituted or disubstituted by Hal, A, OA, phenoxy, SO_2A, SO_2NH_2, $COOR^2$ or CN, such as, for example, phenyl, 2-methylsulfonylphenyl, 2-aminosulfonylphenyl, phenoxyphenyl, 2-, 3- or 4-chlorophenyl, 3,4-dichlorophenyl, 4-methylphenyl, 4-bromophenyl, 3-fluoro-4-methoxyphenyl, 4-trifluoromethoxyphenyl, 4-ethoxyphenyl, 2-methoxyphenyl, 3-cyanophenyl, 4-ethoxycarbonylphenyl, methoxycarbonylphenyl, carboxyphenyl or aminocarbonylphenyl.

Ar very particularly preferably denotes unsubstituted phenyl, 4-chlorophenyl or 2-methylsulfonylphenyl.

G particularly preferably denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-.

X particularly preferably denotes -CONH- or -CON(CH_2COOA)-.

Y preferably denotes cycloalkylene, Het-diyl or Ar-diyl, particularly preferably 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl, furthermore also pyridinediyl, preferably pyridine-2,5-diyl, piperidinediyl or cyclohexylene.

Y denotes in particular pyridinediyl, piperidinediyl, cyclohexylene, or phenylene which is unsubstituted or monosubstituted or disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl.

Het denotes, 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-benzodioxane-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 can thus also denote, 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-dioxaneyl, 1,3-dioxane-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-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

Het' preferably denotes, 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-isoquino-

lyl, 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-benzodioxane-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' can thus 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-dioxaneyl, 1,3-dioxane-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-oxomethylenedioxy)phenyl or also 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

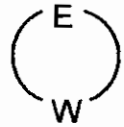
T preferably denotes a monocyclic or bicyclic, saturated or unsaturated heterocyclic ring having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by =O, =S, $=NR^2$, =N-CN, $=N-NO_2$, $=NOR^2$, $=NCOR^2$, $=NCOOR^2$ or $=NOCOR^2$ and may furthermore be monosubstituted or disubstituted by Hal, A or OA.

In a further embodiment, T preferably denotes, for example, 2-iminopiperidin-1-yl, 2-iminopyrrolidin-1-yl, 2-imino-1*H*-pyridin-1-yl, 3-iminomorpholin-4-yl, 4-imino-1*H*-pyridin-1-yl, 2,6-diiminopiperidin-1-yl, 2-iminopiperazin-1-yl, 2,6-diiminopiperazin-1-yl, 2,5-diiminopyrrolidin-1-yl, 2-imino-1,3-oxazolidin-3-yl, 3-imino-2*H*-pyridazin-2-yl, 2-iminoazepan-1-yl, 2-hydroxy-6-iminopiperazin-1-yl or 2-methoxy-6-iminopiperazin-1-yl.

T denotes, in particular, a monocyclic, saturated or unsaturated heterocyclic ring having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by =O, =S or =NH and may furthermore be monosubstituted or disubstituted by Hal, A and/or OA.

T particularly preferably denotes piperidin-1-yl, pyrrolidin-1-yl, pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl, 2-azabicyclo[2.2.2]octan-2-yl, imidazolidinyl, thiazolyl or 1,4-oxazepanyl, each of which is monosubstituted or disubstituted by =O or =NH and where the radicals may also be monosubstituted or disubstituted by Hal, A and/or OA;
very particular preference is given to 3-oxomorpholin-4-yl.
T furthermore preferably also denotes 2-oxo-3-methoxy-1H-pyridin-1-yl.

D preferably denotes phenyl, thienyl, pyridyl, furyl, thiazolyl, pyrrolyl or imidazolyl, each of which is monosubstituted or disubstituted by Hal, particularly preferably phenyl, pyridyl, thienyl, furyl or imidazolyl, each of which is monosubstituted or disubstituted by Hal.

The radical 

preferably denotes pyrrolidine-1,2-diyl, piperidine-1,2- diyl, piperidine-1,3-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-

diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl.

The compounds of the formula I can have one or more centres of chirality and can therefore occur in various stereoisomeric forms. The formula I covers all these forms.

Accordingly, the invention relates, in particular, to the use of those compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following sub-formulae Ia to Iw, which conform to the formula I and in which the radicals not designated in greater detail have the meaning indicated under the formula I, but in which

in Ia	D	denotes a monocyclic or bicyclic, aromatic carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or disubstituted by Hal;
in Ib	D	is phenyl, pyridyl, thienyl, furyl or imidazolyl, each of denotes is monosubstituted or disubstituted by Hal;
in Ic	R^1 and R^2	each, independently of one another, denote H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH;
in Id	G	denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-;
in Ie	X	denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n$-;

in If	X	denotes -CONH- or -CON(CH_2COOA)-;
in Ig	Y	denotes cycloalkylene, Het-diyl or Ar-diyl;
in Ih	Y	denotes pyridinediyl, piperidinediyl, cyclohexylene, or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl;
in Ii	T	denotes a monocyclic, saturated or unsaturated heterocyclic ring having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by =O, =S or =NH and may be monosubstituted or disubstituted by Hal, A and/or OA;
in Ij	T	denotes piperidin-1-yl, pyrrolidin-1-yl, pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl, 2-azabicyclo[2.2.2]-octan-2-yl, imidazolidinyl, thiazolyl or 1,4-oxazepanyl, each of which is monosubstituted or disubstituted by =O or =NH and where the radicals may also be monosubstituted or disubstituted by Hal, A and/or OA;
in Ik	Ar	denotes phenyl which is unsubstituted or monosubstituted or disubstituted by Hal, A, OA, SO_2A, $COOR^2$, SO_2NH_2, CN, COOA, COOH or phenoxy;
in Il	D	denotes a monocyclic or bicyclic, aromatic carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms

which is unsubstituted or monosubstituted or disubstituted by Hal,

R^1 and R^2 each, independently of one another, denote H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H, A, phenyl, benzyl or $[C(R^4)_2]_nCOOA$,

R^4 denotes H or A,

W denotes N, CR^3 or an sp^2-hybridised carbon atom,

E together with W denotes a 3- to 7-membered saturated carbocyclic or heterocyclic ring having 0 to 3 N, 0 to 2 O and/or 0 to 2 S atoms,
which may contain a double bond,

G denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-,

X denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n$-,

Y denotes cycloalkylene, Het-diyl or Ar-diyl,

Ar denotes phenyl which is unsubstituted or monosubstituted or disubstituted by Hal, A, OA, SO_2A, $COOR^2$, SO_2NH_2, CN, COOA, COOH or phenoxy,

T denotes a monocyclic, saturated or unsaturated heterocyclic ring having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by =O, =S or =NH and may be monosubstituted or disubstituted by Hal, A and/or OA,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

in Im

D denotes phenyl, pyridyl, thienyl, furyl or imidazolyl, each of which is monosubstituted or disubstituted by Hal,

R^1 and R^2 each, independently of one another, denote H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H, A or CH_2COOA,

R^4 denotes H or A,

W denotes N, CR^3 or an sp^2-hybridised carbon atom,

E together with W denotes a 3- to 7-membered saturated carbocyclic or heterocyclic ring having 0 to 3 N, 0 to 2 O and/or 0 to 2 S atoms,

which may contain a double bond,

G denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-,

X denotes -CONH- or $-CON(CH_2COOA)$-,

Y denotes pyridinediyl, piperidinediyl, cyclohexylene, or phenylene which is unsubstituted or monosubstituted or disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl,

T denotes piperidin-1-yl, pyrrolidin-1-yl, pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl, 2-azabicyclo[2.2.2]-octan-2-yl, imidazolidinyl, thiazolyl or 1,4-oxazepanyl, each of which is monosubstituted or disubstituted by =O or =NH and where the radicals may also be monosubstituted or disubstituted by Hal, A and/or OA,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

in In D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

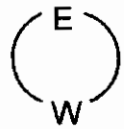
R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA or $NHSO_2A$,

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_nNH$-,

X denotes CONH,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes piperidin-1-yl, pyrrolidin-1-yl, 1*H*-pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, 2*H*-

pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl or 2-aza-bicyclo[2.2.2]octan-2-yl, each of which is monosubstituted or disubstituted by carbonyl oxygen,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

in lo

D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

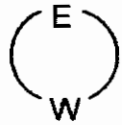
R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA or $NHSO_2A$,

R^2 is H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 denotes atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

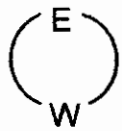
R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_nNH$-,

X denotes CONH,

		Y	denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,
		T	denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,
		A	denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,
		Hal	denotes F, Cl, Br or I,
		n	denotes 0, 1 or 2;
	in Ip	X	denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n-$ or $-[C(R^4)_2]_nCO[C(R^4)_2]_n-$;
	in Iq	X	denotes CONH or $COCH_2$;
	in Ir	D	denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,
		R^1	denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA or $NHSO_2A$,
		R^2	denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,
		R^1 and R^2	together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,
		R^3	denotes H or A,
		R^4	denotes H or A,
			denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-di-

hydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_nNH$-,

X denotes CONH or $COCH_2$,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

in Is

D denotes a monocyclic or bicyclic, aromatic carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or disubstituted by Hal,

R^1 and R^2 each, independently of one another, denote H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA or $NHSO_2A$,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

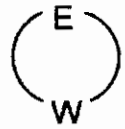
R^4 denotes H or A,

W denotes N, CR^3 or an sp^2-hybridised carbon atom,

E	together with W denotes a 3- to 7-membered saturated carbocyclic or heterocyclic ring having 0 to 3 N, 0 to 2 O and/or 0 to 2 S atoms, which may contain a double bond,
G	denotes $(CH_2)_n$ or $(CH_2)_nNH$-,
X	denotes -$[C(R^4)_2]_nCONR^3[C(R^4)_2]_n$- or -$[C(R^4)_2]_nCO[C(R^4)_2]_n$-,
Y	denotes Ar-diyl,
Ar	denotes phenyl which is unsubstituted or monosubstituted or disubstituted by Hal, A, OA, SO_2A, $COOR^2$, SO_2NH_2 or CN,
T	denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,
A	denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,
Hal	denotes F, Cl, Br or I,
n	denotes 0, 1 or 2;

in it

D	denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,
R^1	denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA, $NHSO_2A$, CH_3-C≡C-CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2 or -O-CH_2-CH(OH)-CH_2Het',
R^2	denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,
R^1 and R^2	together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,
R^3	denotes H or A,

		R^4	denotes H or A,
			denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,
		G	denotes $(CH_2)_n$ or $(CH_2)_nNH$-,
		X	denotes CONH or $COCH_2$,
		Y	denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,
		T	denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,
		Het'	denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, A, OH, NH_2, NO_2, CN, COOA or $CONH_2$,
		A	denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,
		Hal	denotes F, Cl, Br or I,
		n	denotes 0, 1 or 2;
	in Iu	D	denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,
		R^1	denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA, $NHSO_2A$, H-C≡C-CH_2-, CH_3-C≡C-

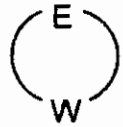
CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2 or -O-CH_2-CH(OH)-CH_2Het',

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_nNH$-,

X denotes CONH, $COCH_2$, CO or COO,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,

Het' denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, A, OH, NH_2, NO_2, CN, COOA or $CONH_2$,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

in Iv

D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

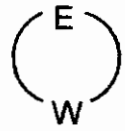
R^1 denotes ethynyl, vinyl, allyloxy, CH_3-C≡C-CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2 or -O-CH_2-CH(OH)-CH_2Het',

R^2 denotes H or OH,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_n$NH-,

X denotes CONH, CO, COO or $COCH_2$,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes piperidin-1-yl, pyrrolidin-1-yl, 1*H*-pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, 2*H*-pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl or 2-azabicyclo[2.2.2]octan-2-yl, each of which is monosubstituted or disubstituted by carbonyl oxygen or OA,

Het' denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsub-

stituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, A, OH, NH_2, NO_2, CN, COOA or $CONH_2$,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

in Iw

D denotes phenyl, pyridyl, thienyl, furyl or imidazolyl, each of which is monosubstituted or disubstituted by Hal,

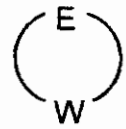
R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH,

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



is pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-,

X denotes CONH, $COCH_2$ or $-CON(CH_2COOA)-$,

Y denotes pyridinediyl, piperidinediyl, cyclohexylene, or phenylene which is unsubstituted or monosubstituted or

disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl,

T denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds of the formula I and also the starting materials for the preparation thereof are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methodn der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

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

The starting compounds of the formulae II, III, IV, V and VI are generally known. If they are novel, they can, however, be prepared by methods known per se.

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

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

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, 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 or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide 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 said solvents.

Compounds of the formula I can furthermore preferably be obtained by reacting compounds of the formula IV with compounds of the formula V.

The reaction is generally carried out in an inert solvent and under conditions as indicated above.

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

Radicals of this type for activation of the carboxyl group in typical acylation reactions 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).

Activated esters are advantageously formed in situ, for example through addition of HOBt or N-hydroxysuccinimide.

The reaction is generally carried out in an inert solvent, in the presence of an acid-binding agent, preferably an organic base, such as DIPEA, triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the carboxyl component of the formula V.

It may also be favourable to add an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium, calcium or caesium.

Depending on the conditions used, the reaction time is between a few minutes and 14 days, and the reaction temperature is between about -30° and 140°, normally between -10° and 90°, in particular between about 0° and about 70°.

Suitable inert solvents are those mentioned above.

Compounds of the formula I can furthermore preferably be obtained by reacting compounds of the formula II with compounds of the formula VI.

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

The term "amino-protecting group" is known in general terms and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protecting groups are removed after the desired reaction (or reaction sequence), their type and size are furthermore not crucial; however, preference is given to those having 1-20, in particular 1-8, carbon atoms. The term "acyl group" is to be understood 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 especially aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl and butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl and tolyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert-butoxycarbonyl) and 2-iodoethoxycarbonyl; aralkoxycarbonyl, such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl and FMOC; and arylsulfonyl, such as Mtr. Preferred amino-protecting groups are BOC and Mtr, furthermore CBZ, Fmoc, benzyl and acetyl.

The term "hydroxyl-protecting group" is likewise known in general terms and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical

of such groups are the above-mentioned unsubstituted or substituted aryl, aralkyl or acyl groups, furthermore also alkyl groups. The nature and size of the hydroxyl-protecting groups are not crucial since they are removed again after the desired chemical reaction or reaction sequence; preference is given to groups having 1-20, in particular 1-10, carbon atoms. Examples of hydroxyl-protecting groups are, inter alia, benzyl, 4-methoxybenzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, where benzyl and tert-butyl are particularly preferred.

The compounds of the formula I are liberated from their functional derivatives – depending on the protecting group used – for example using strong acids, advantageously using TFA or perchloric acid, but also using 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 is not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as DMF, halogenated hydrocarbons, such as dichloromethane, furthermore also alcohols, such as methanol, ethanol or isopropanol, and water. Mixtures of the above-mentioned solvents are furthermore suitable. TFA is preferably used in excess without addition of a further solvent, and perchloric acid is preferably used in the form of a mixture of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are advantageously between about 0 and about 50°, preferably between 15 and 30° (room temperature).

The BOC, OBut and Mtr groups can, for example, preferably be cleaved off using TFA in dichloromethane or using approximately 3 to 5N HCl in dioxane at 15-30°, and the FMOC group can be cleaved off using an

approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

Protecting groups which can be removed hydrogenolytically (for example CBZ, benzyl or the liberation of the amidino group from the oxadiazole derivative thereof) 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, advantageously on a support, such as carbon). Suitable solvents here are those indicated 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° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group succeeds well, for example, on 5 to 10% Pd/C in methanol or using ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, trifluoromethylbenzene, 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 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 said solvents.

Esters can be saponified, for example, using acetic acid or using NaOH or KOH in water, water/THF or water/dioxane, at temperatures between 0 and 100°.

Free amino groups can furthermore be acylated in a conventional manner using an acid chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide or reacted with CH_3-C(=NH)-OEt, advantageously 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°.

Pharmaceutical salts and other forms

The said compounds of the formula I can be used in their final non-salt form. On the other hand, the present invention also relates to the use of these compounds in the form of their pharmaceutically acceptable salts, which can be derived from various organic and inorganic acids and bases by procedures known in the art. Pharmaceutically acceptable salt forms of the compounds of the formula I are for the most part prepared by conventional methods. If the compound of the formula I contains a carboxyl group, one of its suitable salts can be formed by reacting the compound with a suitable base to give the corresponding base-addition salt. Such bases are, for example, alkali metal hydroxides, including potassium hydroxide, sodium hydroxide and lithium hydroxide; alkaline earth metal hydroxides, such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, for example potassium ethoxide and sodium propoxide; and various organic bases, such as piperidine, diethanolamine and N-methylglutamine. The aluminium salts of the compounds of the formula I are likewise included. In the case of certain compounds of the formula I, acid-addition salts can be formed by treating these compounds with pharmaceutically acceptable organic and inorganic acids, for example hydrogen halides, such as hydrogen chloride, hydrogen bromide or hydrogen iodide, other

mineral acids and corresponding salts thereof, such as sulfate, nitrate or phosphate and the like, and alkyl- and monoarylsulfonates, such as ethanesulfonate, toluenesulfonate and benzenesulfonate, and other organic acids and corresponding salts thereof, such as acetate, trifluoroacetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate and the like. Accordingly, pharmaceutically acceptable acid-addition salts of the compounds of the formula I include the following: acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, isobutyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, palmoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate, but this does not represent a restriction.

Furthermore, the base salts of the compounds of the formula I include aluminium, ammonium, calcium, copper, iron(III), iron(II), lithium, magnesium, manganese(III), manganese(II), potassium, sodium and zink salts, but this is not intended to represent a restriction. Of the above-mentioned salts, preference is given to ammonium; the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium. Salts of the compounds of the formula I which are derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines, also including naturally occurring substituted amines, cyclic amines, and basic ion exchanger res-

ins, for example arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris(hydroxymethyl)methylamine (tromethamine), but this is not intended to represent a restriction.

Compounds of the formula I of the present invention which contain basic nitrogen-containing groups can be quaternised using agents such as (C_1-C_4)alkyl halides, for example methyl, ethyl, isopropyl and tert-butyl chloride, bromide and iodide; di(C_1-C_4)alkyl sulfates, for example dimethyl, diethyl and diamyl sulfate; (C_{10}-C_{18})alkyl halides, for example decyl, dodecyl, lauryl, myristyl and stearyl chloride, bromide and iodide; and aryl-(C_1-C_4)alkyl halides, for example benzyl chloride and phenethyl bromide. Both water- and oil-soluble compounds of the formula I can be prepared using such salts.

The above-mentioned pharmaceutical salts which are preferred include acetate, trifluoroacetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate and tromethamine, but this is not intended to represent a restriction.

The acid-addition salts of basic compounds of the formula I are prepared by bringing the free base form into contact with a sufficient amount of the desired acid, causing the formation of the salt in a conventional manner.

The free base can be regenerated by bringing the salt form into contact with a base and isolating the free base in a conventional manner. The free base forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free base forms thereof.

As mentioned, the pharmaceutically acceptable base-addition salts of the compounds of the formula I are formed with metals or amines, such as alkali metals and alkaline earth metals or organic amines. Preferred metals are sodium, potassium, magnesium and calcium. Preferred organic amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methyl-D-glucamine and procaine.

The base-addition salts of acidic compounds of the formula I are prepared by bringing the free acid form into contact with a sufficient amount of the desired base, causing the formation of the salt in a conventional manner. The free acid can be regenerated by bringing the salt form into contact with an acid and isolating the free acid in a conventional manner. The free acid forms differ in a certain respect from the corresponding salt forms thereof with respect to certain physical properties, such as solubility in polar solvents; for the purposes of the invention, however, the salts otherwise correspond to the respective free acid forms thereof.

If a compound of the formula I contains more than one group which is capable of forming pharmaceutically acceptable salts of this type, the formula I also encompasses multiple salts. Typical multiple salt forms include, for example, bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium and trihydrochloride, but this is not intended to represent a restriction.

With regard to that stated above, it can be seen that the term "pharmaceutically acceptable salt" in the present connection is taken to mean an active ingredient which comprises a compound of the formula I in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

Owing to their molecular structure, the compounds of the formula I can be chiral and can accordingly occur in various enantiomeric forms. They can therefore exist in racemic or in optically active form.

Since the pharmaceutical activity of the racemates or 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 can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are 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. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent

(for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents 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 relates to the use of compounds according to one or more of Claims 1-27, in combination with at least one further medicament active ingredient.

The further medicament active ingredients are preferably selected from the group the antithrombotics, antiarrhythmics, contraceptives, phosphodiesterase V inhibitors.

The antithrombotic is preferably selected from the group the vitamin K antagonists, heparin compounds, thrombocyte aggregation inhibitors, enzymes, factor Xa inhibitors, factor VIIa inhibitors, other antithrombotic agents, blood platelet glycoprotein receptor (IIb/IIIa) antagonists, thromboxane antagonists, thrombocyte adhesion inhibitors.

The vitamin K antagonists are preferably selected from the group dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione, tioclomarol.

The heparin compounds are preferably selected from the group heparin, antithrombin III, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, danaparoid, tinzaparin, sulodexide.

The thrombocyte aggregation inhibitors are preferably selected from the group ditazole, cloricromen, picotamide, clopidogrel, ticlopidine, acetyl-

salicylic acid, dipyridamole, calcium carbassalate, epoprostenol, indobufen, iloprost, abciximab, tirofiban, aloxiprin, intrifiban.

The enzymes are preferably selected from the group streptokinase, alteplase, anistreplase, urokinase, fibrinolysin, brinase, reteplase, saruplase.

The other antithrombotic agents are preferably selected from the group defibrotide, desirudin, lepirudin.

The thromboxane antagonists are preferably selected from the group ramatroban, equalen sodium, seratrodast.

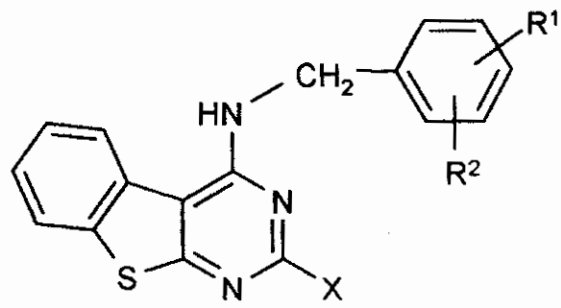
The antiarrhythmics are preferably selected from the group

a) chinidin, disopyramide, ajmaline, detajmium,
b) lidocaine, mexiletine, phenytoin, tocainide,
c) propafenone, flecainide,
d) metoprolol, esmolol, propranolol, atenolol, oxprenolol,
e) amiodarone, sotalol,
f) diltiazem, verapamil, gallopamil,
g) adenosine, orciprenaline, ipratropium,
h) cardiac glycosides.

The contraceptives are preferably selected from the group desogestrel, medroxyprogesterone acetate, levonorgestrel, etonogestrel, norethisterone enantate.

The PDE V inhibitors are preferably selected from the group

a) sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®),
b) the compounds of the formula I described in WO 99/55708



I

in which

R^1, R^2 each, independently of one another, denote H, A, OA, OH or Hal,

R^1 and R^2 together also denote alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

X denotes mono-R^7-substituted R^4, R^5 or R^6,

R^4 denotes linear or branched alkylene having 1-10 C atoms, in which one or two CH_2 groups may be replaced by -CH=CH- groups,

R^5 denotes cycloalkyl or cycloalkylalkylene having 5-12 C atoms,

R^6 denotes phenyl or phenylmethyl,

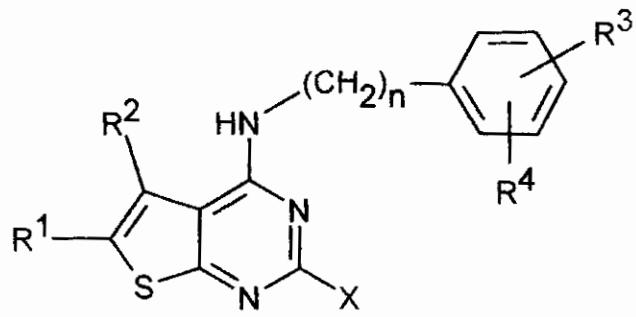
R^7 denotes COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A denotes alkyl having 1 to 6 C atoms and

Hal denotes F, Cl, Br or I,

and/or physiologically acceptable salts and/or solvates thereof,

c) the compounds of the formula I described in WO 99/28325



I

in which

R^1, R^2	each, independently of one another, denote H, A or Hal, where one of the radicals R^1 or R^2 is always ≠ H,	
R^1 and R^2	together also denote alkylene having 3-5 C atoms,	
R^3, R^4	each, independently of one another, denote H, A, OH, OA or Hal,	
R^3 and R^4	together also denote alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,	
X	denotes mono-R^7-substituted R^5 or R^6,	
R^5	denotes linear or branched alkylene having 1-10 C atoms, in which one or two CH_2 groups may be replaced by -CH=CH- groups, or $-C_6H_4-(CH_2)_m-$,	
R^6	denotes cycloalkylalkylene having 6-12 C atoms,	
R^7	denotes COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,	
A	denotes alkyl having 1 to 6 C atoms,	
Hal	denotes F, Cl, Br or I,	
m	denotes 1 or 2 and	
n	denotes 0, 1, 2 or 3,	

and/or physiologically acceptable salts and/or solvates thereof.

Preferred antithrombotics are furthermore the blood platelet glycoprotein receptor (IIb/IIIa) antagonists, which inhibit blood platelet aggregation.

Preferred compounds are described, for example, in EP 0 623 615 B1 on page 2 or in EP 0 741 133 A2, page 2, line 2, to page 4, line 56.

The invention furthermore relates to medicaments comprising 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxamide and/or pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and a further medicament active ingredient selected from the group the antithrombotics, antiarrhythmics, contraceptives, phosphodiesterase V inhibitors.

Preferred groups of the further medicament active ingredients are those described above.

These compositions can be used as medicaments in human and veterinary medicine.

Pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the disease condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process which is generally known in the pharmaceutical art.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

Thus, for example, in the case of oral administration in the form of a tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form, can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may likewise be added in order to improve the availability of the medicament after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinylpyrrolidone, a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acadia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture can be run through a tableting machine, giving lumps of non-uniform shape which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The active ingredients can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a

shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a prespecified amount of the compounds. Syrups can be prepared by dissolving the compounds in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersion of the compounds in a non-toxic vehicle. Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

The compounds of the formula I and salts, solvates and physiologically functional derivatives thereof and the other active ingredients can also be administered in the form of liposome delivery systems, such as, for example, small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from various phospholipids, such as, for example, cholesterol, stearylamine or phosphatidylcholines.

The compounds of the formula I and the salts, solvates and physiologically functional derivatives thereof and the other active ingredients can also be delivered using monoclonal antibodies as individual carriers to which the

compound molecules are coupled. The compounds can also be coupled to soluble polymers as targeted medicament carriers. Such polymers may encompass polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl-methacrylamidophenol, polyhydroxyethylaspartamidophenol or polyethyl-ene oxide polylysine, substituted by palmitoyl radicals. The compounds may furthermore be coupled to a class of biodegradable polymers which are suitable for achieving controlled release of a medicament, for example polylactic acid, poly-epsilon-caprolactone, polyhydroxybutyric acid, poly-orthoesters, polyacetals, polydihydroxypyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration can be administered as independent plasters for extended, close contact with the epidermis of the recipient. Thus, for example, the active ingredient can be delivered from the plaster by iontophoresis, as described in general terms in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical compounds adapted for topical administration can be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For the treatment of the eye or other external tissue, for example mouth and skin, the formulations are preferably applied as topical ointment or cream. In the case of formulation to give an ointment, the active ingredient can be employed either with a paraffinic or a water-miscible cream base. Alternatively, the active ingredient can be formulated to give a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical application to the eye include eye drops, in which the active ingredient is dissolved or suspended in a suitable carrier, in particular an aqueous solvent.

Pharmaceutical formulations adapted for topical application in the mouth encompass lozenges, pastilles and mouthwashes.

Pharmaceutical formulations adapted for rectal administration can be administered in the form of suppositories or enemas.

Pharmaceutical formulations adapted for nasal administration in which the carrier substance is a solid comprise a coarse powder having a particle size, for example, in the range 20-500 microns, which is administered in the manner in which snuff is taken, i.e. by rapid inhalation via the nasal passages from a container containing the powder held close to the nose. Suitable formulations for administration as nasal spray or nose drops with a liquid as carrier substance encompass active-ingredient solutions in water or oil.

Pharmaceutical formulations adapted for administration by inhalation encompass finely particulate dusts or mists, which can be generated by various types of pressurised dispensers with aerosols, nebulisers or insufflators.

Pharmaceutical formulations adapted for vaginal administration can be administered as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions comprising antioxidants, buffers, bacteriostatics and solutes, by means of which the formulation is rendered isotonic with the blood of the recipient to be treated; and aqueous and non-aqueous sterile suspensions, which may comprise suspension media and thickeners. The formulations can be administered in

single-dose or multidose containers, for example sealed ampoules and vials, and stored in freeze-dried (lyophilised) state, so that only the addition of the sterile carrier liquid, for example water for injection purposes, immediately before use is necessary.

Injection solutions and suspensions prepared in accordance with the recipe can be prepared from sterile powders, granules and tablets.

It goes without saying that, in addition to the above particularly mentioned constituents, the formulations may also comprise other agents usual in the art with respect to the particular type of formulation; thus, for example, formulations which are suitable for oral administration may comprise flavours.

A therapeutically effective amount of a compound of the formula I and of the other active ingredient depends on a number of factors, including, for example, the age and weight of the animal, the precise disease condition which requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as an individual dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound *per se*.

The invention furthermore relates to compounds selected from the group

a) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-(4-aminophenoxy)pyrrolidine-1,2-dicarboxamide,

b) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

c) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

d) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-isopropoxypyrrolidine-1,2-dicarboxamide,

e) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,2,2-trifluoroethoxy)pyrrolidine-1,2-dicarboxamide,

f) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

g) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

h) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

The invention also relates to medicaments comprising at least one compound selected from the group

a) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-(4-aminophenoxy)pyrrolidine-1,2-dicarboxamide,

b) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

c) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

d) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-isopropoxypyrrolidine-1,2-dicarboxamide,

e) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,2,2-trifluoroethoxy)pyrrolidine-1,2-dicarboxamide,

f) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

g) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

h) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

and/or pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and optionally excipients and/or adjuvants.

The said compounds are potent factor Xa inhibitors.

The invention thus also relates to the use of compounds selected from the group

a) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-(4-aminophenoxy)pyrrolidine-1,2-dicarboxamide,

b) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

c) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

d) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-isopropoxypyrrolidine-1,2-dicarboxamide,

e) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,2,2-trifluoroethoxy)pyrrolidine-1,2-dicarboxamide,

f) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

g) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

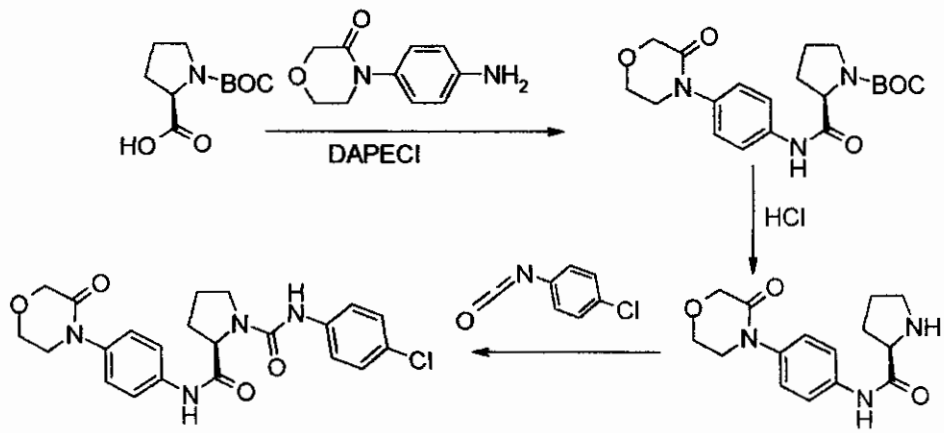
h) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of thromboses, myocardial infarction, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty, claudicatio intermittens, migraine, tumours, tumour diseases and/or tumour metastases,
for the prevention and treatment of thromboembolic diseases and/or thromboses as a consequence of surgery, genetically caused diseases with increased thrombophilia, diseases of the arterial and venous vascular system, cardiac insufficiency, atrial fibrillation, thrombophilia, tinnitus and/or sepsis.

Above and below, all temperatures are indicated in °C. In the following examples, "conventional work-up" means: if necessary, water is added, pH values of between 2 and 10 are set, if necessary, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation. Rf values on silica gel; eluent: ethyl acetate/methanol 9:1.
Mass spectrometry (MS): EI (electron impact ionisation) M^+
FAB (fast atom bombardment) $(M+H)^+$
ESI (electrospray ionisation) $(M+H)^+$ (unless indicated otherwise)

Example 1

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide ("A1") is prepared analogously to the following scheme:



1.1 0.8 g (5.2 mmol) of 1-hydroxybenzotriazole hydrate, 1.12 g (5.2 mmol) of D-Boc-proline, 2 g (10.4 mmol) of N-(3-dimethylamino-propyl)-N'-ethylcarbodiimide hydrochloride (DAPECI) and 1.26 ml of N-methylmorpholine are added successively to a solution of 1.0 g (5.2 mmol) of 4-(4-aminophenyl)morpholin-3-one in 25 ml of dimethyl-formamide, and the resultant solution is stirred at room temperature for 12 hours. The reaction solution is subsequently evaporated to dryness under reduced pressure, the residue is taken up in 10 ml of 5% sodium hydrogencarbonate solution, and the sodium hydrogencarbonate solution is extracted twice with 10 ml of ethyl acetate each time. After the combined organic phases have been dried over sodium sulfate and the solvent has been stripped off, the solid residue is triturated with 20 ml of diethyl ether, giving 1.4 g of *tert*-butyl 2-[4-(3-oxomorpholin-4-yl)phenyl-carbamoyl]pyrrolidine-1-carboxylate as a white powder; ESI 390.

1.2 40 ml of 4N hydrochloric acid in dioxane are added to a solution of 1.4 g (3.60 mmol) of *tert*-butyl 2-[4-(3-oxomorpholin-4-yl)phenylcar-bamoyl]pyrrolidine-1-carboxylate in 20 ml of dioxane, and the mixture is stirred at room temperature for 12 hours. The precipitate is subsequent-ly filtered off with suction and washed successively with 10 ml of di-oxane and 10 ml of diethyl ether and dried under reduced pressure,

giving 1.1 g of *N*-[4-(3-oxomorpholin-4-yl)phenyl]pyrrolidine-2-carboxamide hydrochloride as a white powder; ESI 290.

1.3 95 mg (0.61 mmol) of 4-chlorophenyl isocyanate are added to a solution of 200 mg (0.61 mmol) of *N*-[4-(3-oxomorpholin-4-yl)phenyl]pyrrolidine-2-carboxamide hydrochloride and 1 ml of triethylamine in 5 ml of methylene chloride, and the reaction solution is stirred at room temperature for two hours. The reaction solution is subsequently washed with 5 ml of 1N hydrochloric acid and 5 ml of water, and the methylene chloride solution is dried over sodium sulfate. After the solvent has been stripped off under reduced pressure, the crude product is recrystallised from ethanol/diethyl ether, giving 120 mg of the title compound ("A1") as a white powder; ESI 443; m.p. 227.6°.

The following compounds are obtained analogously:

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 457, m.p. 147° (decomposition);

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 461, m.p. 155°;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 461;

1-N-[(4-chlorophenyl)]-2-N-{[3-trifluoromethyl-4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 511, m.p. 147°;

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-piperidine-1,2-dicarboxamide, ESI 471, m.p. 140°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, m.p. 221°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 438, m.p. 227°;

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(S)-pyrrolidine-1,2-dicarboxamide, ESI 457; m.p. 174°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-4,4-difluoro-(R)-pyrrolidine-1,2-dicarboxamide, ESI 473;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 455;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-3-methoxy-2*H*-pyridin-1-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 467.

Example 1a

N-[4-(3-oxomorpholin-4-yl)phenyl]-(R)-1-(5-chlorothiophene-2-carbonyl)pyrrolidine-2-carboxamide ("AB1")

0.71 g (4.66 mmol) of 1-hydroxybenzotriazole hydrate, 0.76 g (4.66 mmol) of 5-chlorothiophenecarboxylic acid, 1.79 g (9.33 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (DAPECI) and 1.13 ml of N-methylmorpholine are added successively to a solution of 1.35 g (4.66 mmol) of N-[4-(3-oxomorpholin-4-yl)phenyl]-pyrrolidine-2-carboxamide in 30 ml of dimethylformamide, and the resultant solution is stirred at room temperature for 12 hours. The reaction solution is subsequently evaporated to dryness under reduced pressure, the residue is taken up in 10 ml of 5% sodium hydrogencarbonate solution, and the sodium hydrogencarbonate solution is extracted twice with 10 ml of ethyl acetate each time. After the combined organic phases have been dried over sodium sulfate and the solvent has been stripped off, the solid residue is triturated with 20 ml of diethyl ether, giving 1.2 g (59.4%) of "AB1", ESI 434; m.p. 195°.

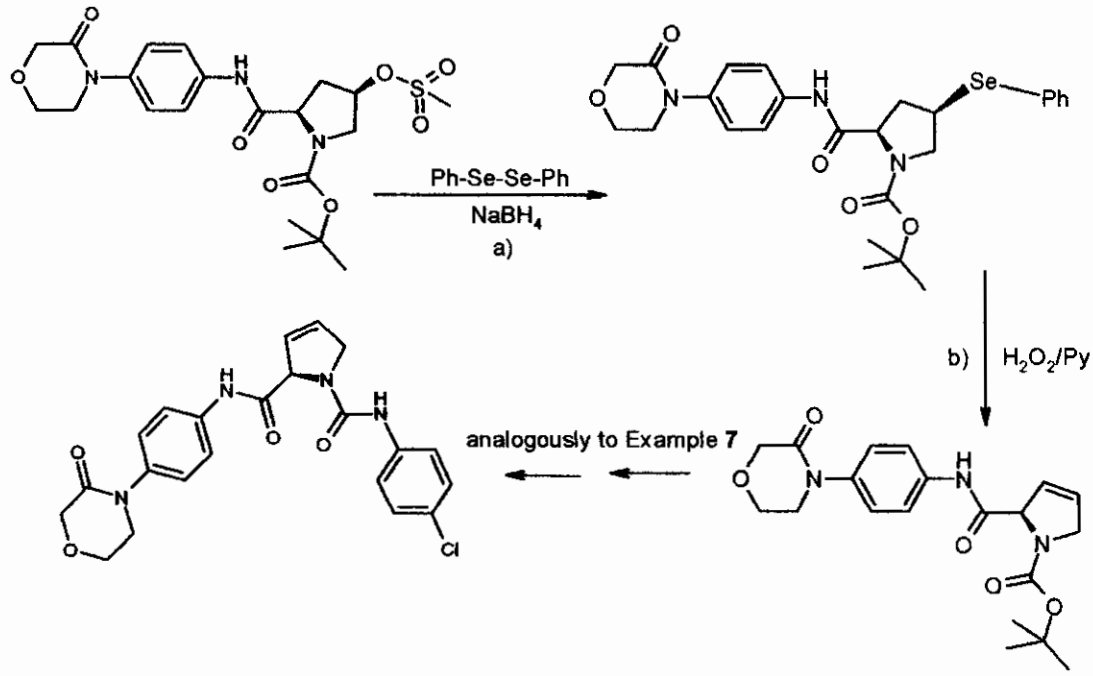
The compound

N-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]-(R)-1-(5-chlorothiophene-2-carbonyl)pyrrolidine-2-carboxamide, ESI 448; m.p. 113° (decomposition)

is obtained analogously.

Example 1b

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide is prepared as follows:



a) 0.19 g (5.1 mmol) of sodium borohydride ($NaBH_4$) is added under nitrogen to the suspension of 0.82 g (2.63 mmol) of diphenyl diselenide in 12 ml of tert-butanol, and the reaction mixture is refluxed for about one hour until the yellow reaction solution becomes colourless. The solution of 1.99 g (4.11 mmol) of *tert*-butyl (2R,4R)-4-methanesulfonyloxy-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate (see Example 9.1) in 12 ml of tert-butanol is subsequently added dropwise at this temperature, and the reaction mixture is then left to reflux for 12 hours with stirring. After the reaction mixture has been cooled, the solvent is stripped

off under reduced pressure, the residue is taken up in 20 ml of ethyl acetate, and the resultant solution is washed with 20 ml of water. Drying of the ethyl acetate phase over sodium sulfate and stripping off of the solvent gives 1.82 g (81.3%) of *tert*-butyl (1R,4R)-2-[4-(3-oxomorpholin-4-yl)-phenylcarbamoyl]-4-phenylselanylpyrrolidine-1-carboxylate, ESI 545.

b) 1 ml of 30% hydrogen peroxide (H_2O_2) is added dropwise at 0°C to the solution of 1.72 g (3.16 mmol) of the selenium compound prepared under a) and 0.4 ml of pyridine in 25 ml of methylene chloride. The reaction mixture is subsequently allowed to come to room temperature over the course of two hours, 10 ml of 5% potassium hydrogensulfate solution are then added, the phases are separated, and the organic phase is washed with 10 ml of saturated sodium hydrogencarbonate solution. After the organic phase has been dried over sodium sulfate and the solvent has been stripped off, the residue is chromatographed on silica gel, giving 0.73 g (59.7%) of *tert*-butyl (R)-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]-2,5-dihydropyrrole-1-carboxylate, ESI 388.

The further reaction is carried out analogously to Example 7, giving 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide, ESI 441, m.p. 245°.

The following compounds are obtained analogously:

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyrazin-1-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

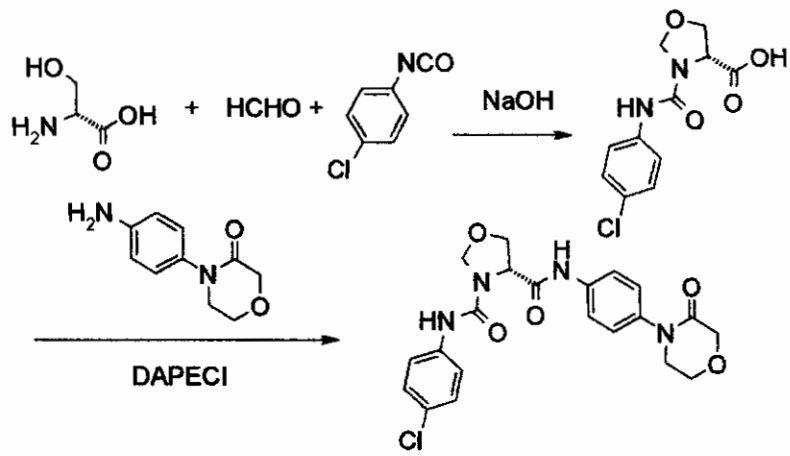
1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide.

Example 2

N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide ("A2") is prepared analogously to the following scheme:



2.1 1.49 ml (20.0 mmol) of 37% aqueous formaldehyde solution are added to a solution of 2.10 g (20.0 mmol) of D-serine in 10 ml of 1N aqueous sodium hydroxide solution. The resultant solution is left at 5°C for 18 hours. The solution is heated to 80°C, 6.14 g (40 mmol) of 4-chlorophenyl isocyanate are added, and the mixture is stirred at this temperature for one hour. The mixture is allowed to cool, and the precipitate formed is filtered off. The filtrate is acidified using 1N HCl, and the precipitate formed is filtered off and dried, giving (R)-3-(4-chlorophenylcarbamoyl)oxazolidine-4-carboxylic acid as a colourless solid; ESI 271.

2.2 498 mg (2.60 mmol) of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (DAPECI) are added to a solution of 541 mg (2.00 mmol) of (R)-3-(4-chlorophenylcarbamoyl)oxazolidine-4-carboxylic acid and 384 mg (2.00 mmol) of 4-(4-aminophenyl)morpholin-3-one in 4 ml

of dimethylformamide (DMF), and the mixture is stirred at room temperature for 18 hours. The reaction mixture is added to saturated sodium hydrogencarbonate solution, and the precipitate formed is filtered off, giving N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide ("A2") as a colourless solid; ESI 461.

The following compounds are obtained analogously:

N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-oxazolidine-3,4-dicarboxamide, ESI 459;

N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(4R,5S)- 5-methyloxazolidine-3,4-dicarboxamide, ESI 459;

N-3-[(4-chlorophenyl)-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide, ESI 473;

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide, ESI 439;

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyridin-1-yl)phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide, ESI 453;

N-3-[(4-chlorophenyl)]-N'-4-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide, ESI 477;

N-3-[(4-chlorophenyl)]-N'-4-{[3-chloro-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide, ESI 477;

N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5R)-5-methyloxazolidine-3,4-dicarboxamide, ESI 473;

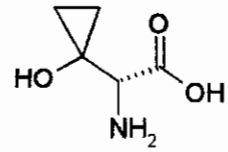
N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyrazin-1-yl)phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide, ESI 454;

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyrazin-1-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide, ESI 440;

N-3-[(4-chlorophenyl)]-N'-4-{[3-chloro-4-(2-oxo-2H-pyridin-1-yl)-phenyl]}-(R)-oxazolidine-3,4-dicarboxamide, ESI 473.

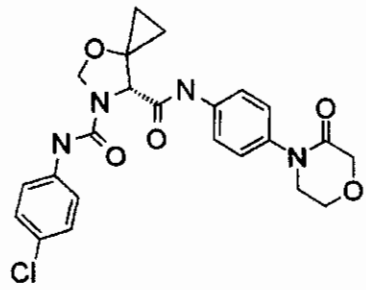
Example 2a

An analogous procedure to Example 2 starting from (R)-cleonine



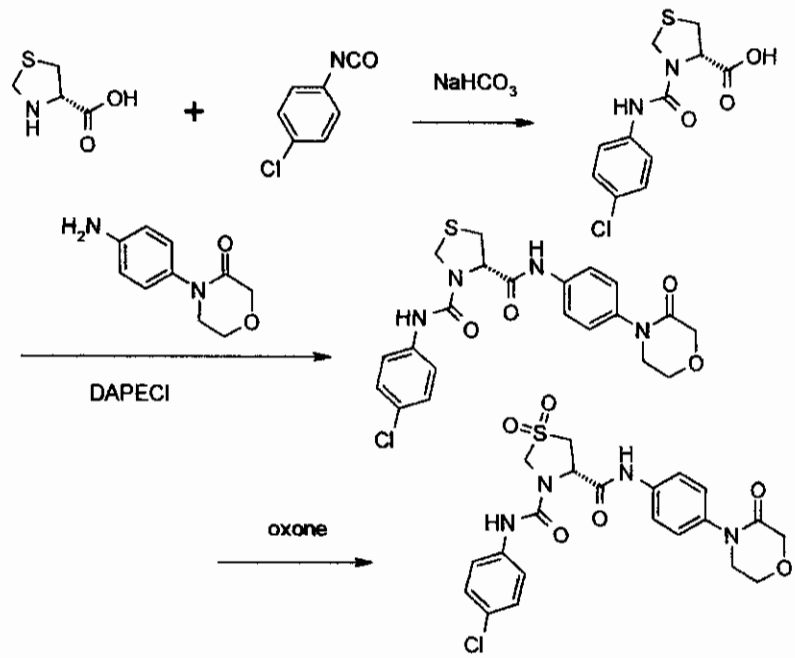
gives the following compound:

N-6-[(4-chlorophenyl)]-N'-7-{[4-(3-oxomorpholin-4-yl)phenyl]}-4-oxa-6-azaspiro[2.4]heptane-6,7-dicarboxamide



Example 3

N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-thiazolidine-3,4-dicarboxamide ("A3") and N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-1,1-dioxo-1λ^6-thiazolidine-3,4-dicarboxamide ("A4") are prepared analogously to the following scheme:



3.1 A solution of 4.54 g (54.0 mmol) of sodium hydrogencarbonate and 3.60 g (27.0 mmol) of 2-(S)-thiazolidine-4-carboxylic acid in 50 ml of water is heated to 80°C, and 8.46 g (54.0 mmol) of 4-chlorophenyl isocyanate are added. The reaction mixture is stirred at this temperature for 1 hour. The mixture is allowed to cool, and the precipitate formed is filtered off. The filtrate is acidified using 1N HCl, and the precipitate formed is filtered off and dried, giving (S)-3-(4-chlorophenylcarbamoyl)thiazolidine-4-carboxylic acid as a colourless solid; ESI 287.

3.2 498 mg (2.60 mmol) of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (DAPECI) are added to a solution of 573 mg (2.00 mmol) of (S)-3-(4-chlorophenylcarbamoyl)thiazolidine-4-carboxylic acid and 384 mg (2.00 mmol) of 4-(4-aminophenyl)morpholin-3-one in 4 ml of dimethylformamide (DMF), and the mixture is stirred at room temperature for 18 hours. The reaction mixture is added to saturated sodium hydrogencarbonate solution, and the precipitate formed is filtered off, giving N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-thiazolidine-3,4-dicarboxamide ("A3") as a colourless solid; ESI 461.

3.3 A solution of 1.9 g of oxone in 30 ml of water is added to a suspension of 450 mg (0.976 mmol) of "A3" in 50 ml of methanol, and the reaction mixture is stirred at room temperature for 24 hours. The reaction mixture is added to water, and the precipitate formed is filtered off and dried, giving N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-1,1-dioxo-1λ^6-thiazolidine-3,4-dicarboxamide ("A4") as a colourless solid; ESI 493.

The following compounds are obtained analogously

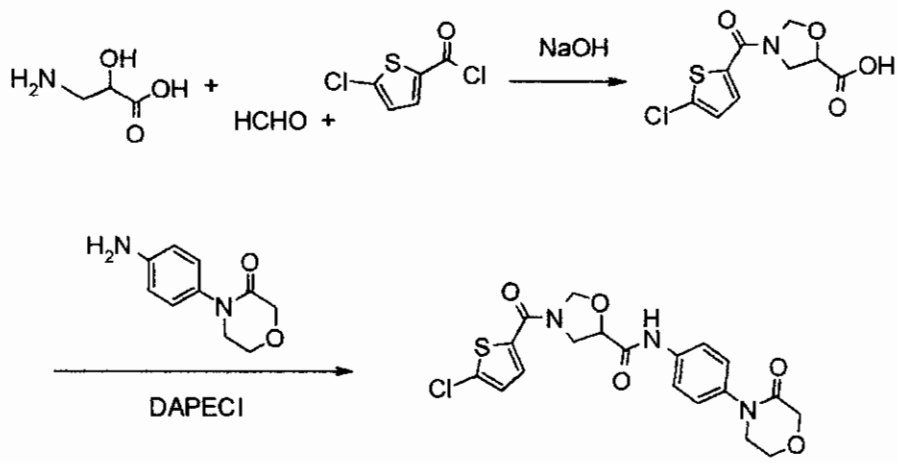
N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(S)-thiazolidine-3,4-dicarboxamide, ESI 475;

N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(S)-1,1-dioxo-1λ^6-thiazolidine-3,4-dicarboxamide, ESI 507;

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyridin-1-yl)phenyl]}-(R)-thiazolidine-3,4-dicarboxamide, ESI 455.

Example 4

N-[4-(3-oxomorpholin-4-yl)phenyl]-3-(5-chlorothiophene-2-carbonyl)-oxazolidine-5-carboxamide ("A5") is prepared analogously to the following scheme:



4.1 1.48 ml (19.9 mmol) of 37% aqueous formaldehyde solution are added to a solution of 2.00 g (19.0 mmol) of DL-isoserine in 10 ml of 1N aqueous sodium hydroxide solution. The resultant solution is left at 5°C for 18 hours. A solution of 3.46 g (19.1 mmol) of 5-chlorothiophenecarbonyl chloride in 10 ml of acetone is added dropwise to this solution at an internal temperature of 0 - 5°C. During the dropwise addition, the pH is held at a value above 7 by addition of solid sodium hydrogencarbonate. When the addition is complete, the mixture is allowed to warm to room temperature, water is added, and the mixture is extracted with tert-butyl methyl ether. The aqueous phase is acidified using 1N HCl and extracted with tert-butyl methyl ether. This organic phase is dried over sodium sulfate and evaporated, giving 3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxylic acid as a colourless solid; ESI 262.

4.2 479 mg (2.50 mmol) of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (DAPECI) are added to a solution of 500 mg (1.91 mmol) of 3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxylic acid and 367 mg (1.91 mmol) of 4-(4-aminophenyl)morpholin-3-one in 5 ml of dimethylformamide (DMF), and the mixture is stirred at room temperature for 18 hours. The reaction mixture is added to saturated sodium hydrogencarbonate solution, and the precipitate formed is filtered off,

giving N-[4-(3-oxomorpholin-4-yl)phenyl]-3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxamide ("A5") as a colourless solid; ESI 436.

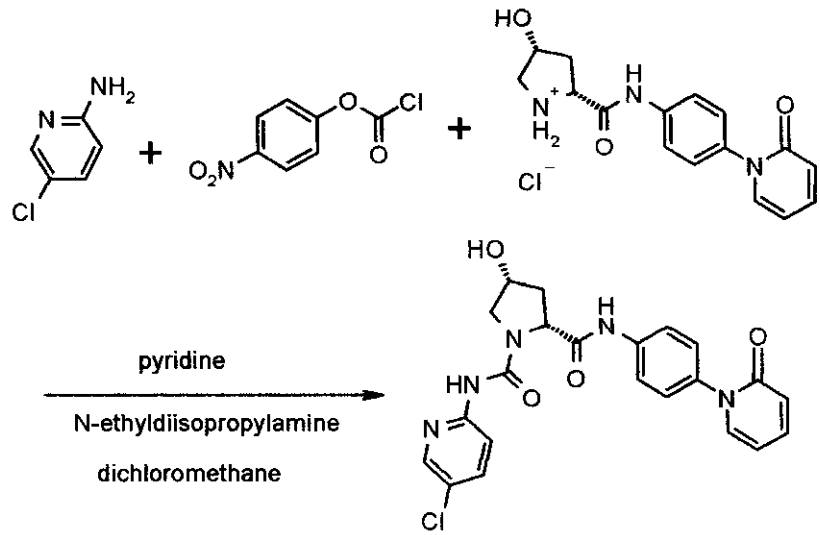
The following compounds are obtained analogously

N-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]-3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxamide, ESI 450;

N-[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]-3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxamide, ESI 430.

Example 5

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide ("A6") is prepared analogously to the following scheme:



894 mg (4.43 mmol) of 4-nitrophenyl chloroformate are added to a solution of 570 mg (4.43 mmol) of 2-amino-5-chloropyridine and 0.73 ml (9.0 mmol) of pyridine in 50 ml of dichloromethane, and the mixture is stirred at room temperature for 1 hour. 1.49 g (4.43 mmol) of (2R,4R)-4-hydroxy-2-[4-(2-oxo-2*H*-pyridin-1-yl)phenylcarbamoyl]pyrrolidinium chloride and 1.5 ml

(9.0 mmol) of N-ethyldiisopropylamine are added to the resultant suspension, and the reaction mixture is stirred at room temperature for 18 hours. The reaction mixture is evaporated, and the residue is chromatographed on a silica-gel column with dichloromethane/methanol 95:5 as eluent, giving 1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide ("A6") as a colourless solid, ESI 454.

The following compounds are obtained analogously:

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 460;

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(2-oxo-2H-pyrazin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 455;

1-N-[(5-chloropyridin-2-yl)]-2-N-{[3-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 472;

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(R)-4,4-dimethoxypyrrolidine-1,2-dicarboxamide, ESI 498;

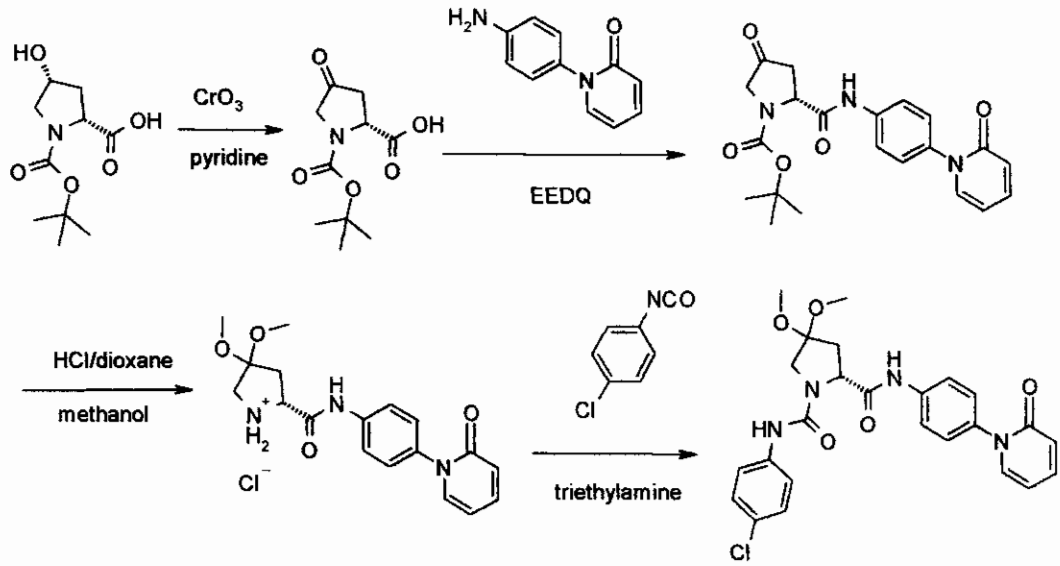
1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-4,4-dimethoxypyrrolidine-1,2-dicarboxamide, ESI 504;

1-N-[(6-chloropyridin-3-yl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 454;

1-N-[(6-chloropyridin-3-yl)]-2-N-{[4-(2-oxo-2H-pyrazin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 455.

Example 6

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2H-pyridin-1-yl)phenyl]}-(R)-4,4-dimethoxypyrrolidine-1,2-dicarboxamide ("A7") is prepared analogously to the following scheme:



6.1 12.2 g (122 mmol) of chromium(VI) oxide are added to a mixture, held at 0°C, of 22 ml of pyridine and 50 ml of dichloromethane, and the mixture is stirred at the same temperature for 30 minutes. The solution is allowed to warm to room temperature, and a solution of 5.00 g of cis-Boc-4-hydroxy-D-proline in 80 ml of dichloromethane is added dropwise over the course of 5 minutes. After stirring at room temperature for 1 hour, the solution is filtered, and the filtrate is evaporated. The residue is partitioned between 1N HCl and tert-butyl methyl ether. The organic phase is dried over sodium sulfate, evaporated and recrystallised from diethyl ether/ petroleum ether, giving Boc-4-keto-D-proline as a colourless solid; ESI 130.

6.2 742 mg (3.00 mmol) of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ) are added to a suspension of 459 mg (2.00 mmol) of Boc-4-keto-D-proline and 372 mg (2.00 mmol) of 1-(4-aminophenyl)-1*H*-pyridin-2-one in 25 ml of toluene, and the mixture is stirred at room temperature for 18 hours. 200 ml of tert-butyl methyl ether are added, and the precipitate formed is filtered off. 200 ml of petroleum ether are added to the filtrate, and the resultant precipitate is filtered off, giving tert-butyl (R)-

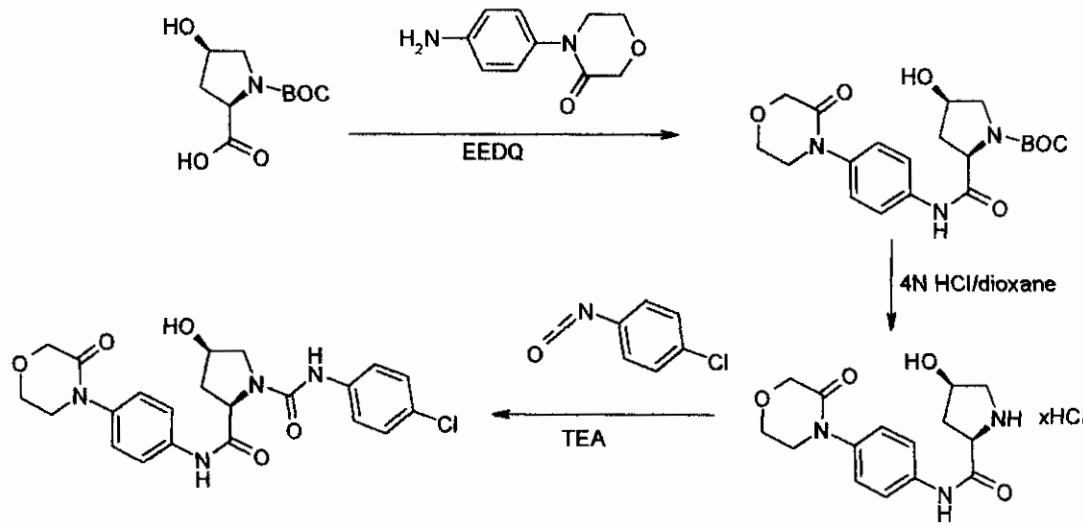
4-oxo-2-[4-(2-oxo-2*H*-pyridin-1-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate as a brownish solid; ESI 398.

6.3 10 ml of methanol are added to a suspension of 400 mg (1.01 mmol) of tert-butyl (R)-4-oxo-2-[4-(2-oxo-2*H*-pyridin-1-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate in 5 ml of 4N HCl in dioxane, and the mixture is stirred at room temperature for one hour. The reaction mixture is evaporated, giving (R)-4,4-dimethoxy-2-[4-(2-oxo-2*H*-pyridin-1-yl)phenylcarbamoyl]pyrrolidinium chloride as a brownish solid; ESI 344.

6.4 0.12 ml of triethylamine and 127 mg (0.830 mmol) of 4-chlorophenyl isocyanate are added to a solution of 250 mg (0.658 mmol) of (R)-4,4-dimethoxy-2-[4-(2-oxo-2*H*-pyridin-1-yl)phenylcarbamoyl]pyrrolidinium chloride in 10 ml of dichloromethane. After stirring at room temperature for one hour, the reaction mixture is evaporated, and the residue is chromatographed on a silica-gel column with dichloromethane/methanol 95:5 as eluent, giving 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2H-pyridin-1-yl)phenyl]}-(R)-4,4-dimethoxypyrrolidine-1,2-dicarboxamide ("A7") as a colourless solid; ESI 497.

Example 7

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide ("A8") is prepared analogously to the following scheme:



7.1 16 g (12.86 mmol) of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ) are added to a suspension of 15 g (64.86 mmol) of cis-N'-BOC-4-hydroxy-D-proline and 12.47 g (64.86 mmol) of 1-(4-aminophenyl)-1*H*-pyridin-2-one in 250 ml of toluene, and the mixture is stirred at room temperature for 18 hours. The precipitated product is subsequently filtered off, washed successively with 50 ml of toluene and 50 ml of diethyl ether and dried in a desiccator, giving 24.5 g (93.2%) of *tert*-butyl (2R,4R)-4-hydroxy-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate as a grey-white powder. ESI 406.

7.2 300 ml of 4N hydrochloric acid in dioxane are added to a solution of 15 g (37 mmol) of *tert*-butyl (2R,4R)-4-hydroxy-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate in 200 ml of dioxane, and the mixture is stirred at room temperature for 12 hours. The precipitate is subsequently filtered off, washed with 50 ml of dioxane and 50 ml of diethyl ether and dried in a desiccator, giving 12.64 g (100%) of N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-4-hydroxypyrrolidine-2-carboxamide hydrochloride as a white powder. ESI 306.

7.3 12.64 g (36.98 mmol) of N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-4-hydroxypyrrolidine-2-carboxamide hydrochloride are suspended in 1200 ml of dichloromethane, and 5.4 ml of triethylamine are added with cooling in an ice bath. The solution of 5.96 g (38.83 mmol) of 4-chlorophenyl isocyanate in 100 ml of dichloromethane is subsequently added dropwise to the mixture at 2°C over the course of 1.5 hours, and the reaction solution is then left to stir for a further 30 minutes with ice cooling. The dichloromethane solution is then washed successively with 100 ml of 1N hydrochloric acid and 100 ml of water and dried over sodium sulfate. After the drying agent has been filtered off and the methylene chloride solution has been evaporated to 1/3 of the original volume in a rotary evaporator, the precipitated product is filtered off, washed with 50 ml of petroleum ether and dried in a desiccator, giving 14.6 g (86%) of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide ("A8") as a white powder, ESI 459; m.p. 216°.

The following compounds are obtained analogously:

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 473; m.p. 250°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 453; m.p. 160°;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 477; m.p. 235°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxopyrazin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 454;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 471;

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,3R)-3-hydroxypyrrolidine-1,2-dicarboxamide,

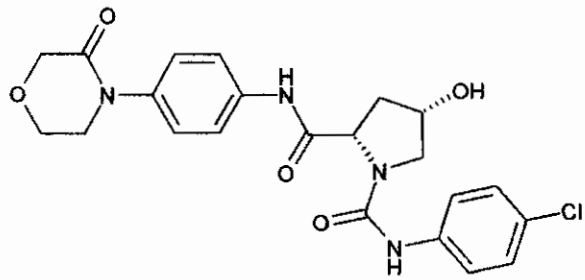
1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,3S)-3-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-3-methoxy-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 483.

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,3S)-3-hydroxypyrrolidine-1,2-dicarboxamide, ESI 459;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 459



;

1-N-[(4-chlorophenyl)]-2-N-{[2-methoxycarbonyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-3-hydroxypyrrolidine-1,2-dicarboxamide, ESI 517, m.p. 119; and therefrom by hydrolysis

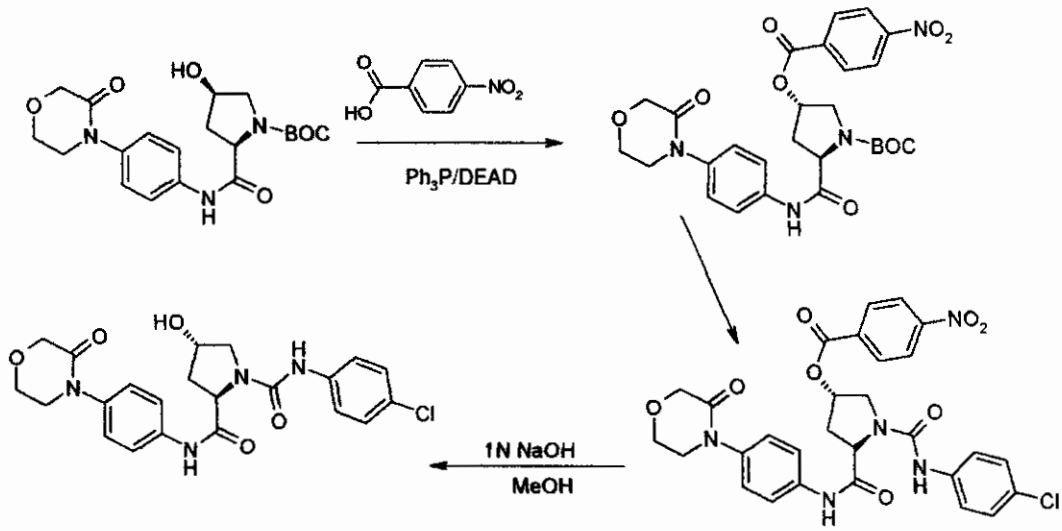
1-N-[(4-chlorophenyl)]-2-N-{[2-carboxy-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-3-hydroxypyrrolidine-1,2-dicarboxamide, ESI 503, m.p. 145°,

1-N-[(4-chlorophenyl)]-2-N-{[2-methoxycarbonyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, and therefrom by hydrolysis

1-N-[(4-chlorophenyl)]-2-N-{[2-carboxy-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide.

Example 8

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-hydroxypyrrolidine-1,2-dicarboxamide is prepared analogously to the following scheme:



8.1 5.51 ml (35 mmol) of diethyl azodicarboxylate (DEAD) are added dropwise at 0°C under nitrogen to a solution of 7.0 g (7.26 mmol) of *tert*-butyl (2R,4R)-4-hydroxy-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate, 5.77 g (34.5 mmol) of p-nitrobenzoic acid and 9.18 g (35 mmol) of triphenylphosphine in 350 ml of tetrahydrofuran. The reaction mixture is subsequently left to stir at room temperature for 12 hours and evaporated to dryness under reduced pressure, 20 ml of methylene chloride are added to the residue, and the methylene chloride solution is washed successively with 10 ml of saturated sodium chloride solution and 10 ml of water and dried over sodium sulfate. After the drying agent has been filtered off and the solvent has been stripped off in a rotary evaporator, the residue is triturated with 30 ml of diethyl ether, giving 8.5 g

(88.8%) of *tert*-butyl (2R,4S)-4-(4-nitrobenzoyloxy)-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate as slightly yellow crystals, ESI 555.

8.2 Analogously to Example 7, reaction of *tert*-butyl (2R,4S)-4-(4-nitrobenzoyloxy)-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate gives the compound (3S,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl 4-nitrobenzoate as yellowish crystals, ESI 608.

8.3 0.075 ml of 1N sodium hydroxide solution is added with ice cooling to the solution of 50 mg (0.082 mmol) of (3S,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl 4-nitrobenzoate in 2 ml of methanol, and the reaction mixture is stirred for 15 minutes. The precipitate is filtered off and washed with 2 ml of methanol and dried, giving 35 mg (93%) of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-hydroxypyrrolidine-1,2-dicarboxamide as colourless crystals, ESI 459, m.p. 243° (decomposition).

An analogous procedure gives

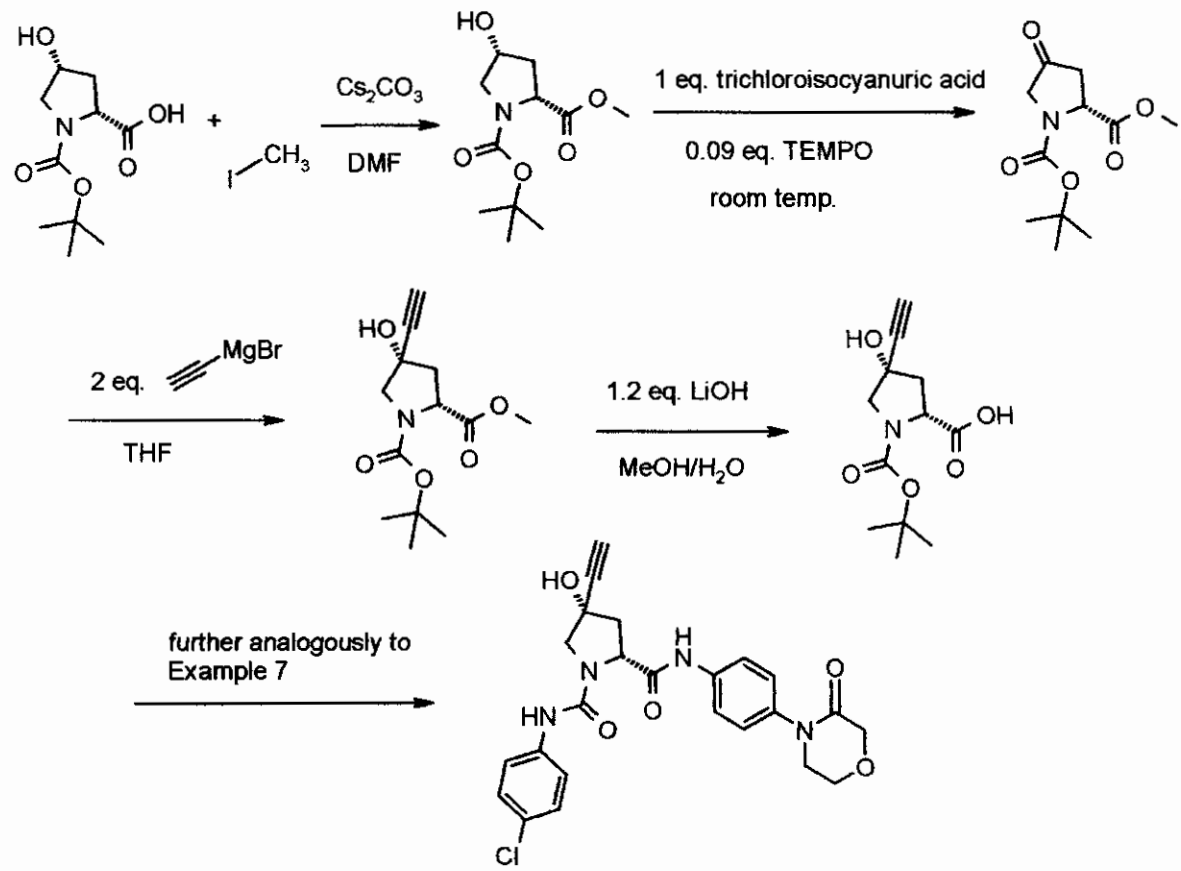
1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R, 3S, 4R)-3,4-dihydroxypyrrolidine-1,2-dicarboxamide, ESI 475, m.p. 247;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 459; m.p. 253°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-3,4-dihydroxypyrrolidine-1,2-dicarboxamide.

Example 8a

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-ethynyl-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 483, is prepared analogously to the following scheme:



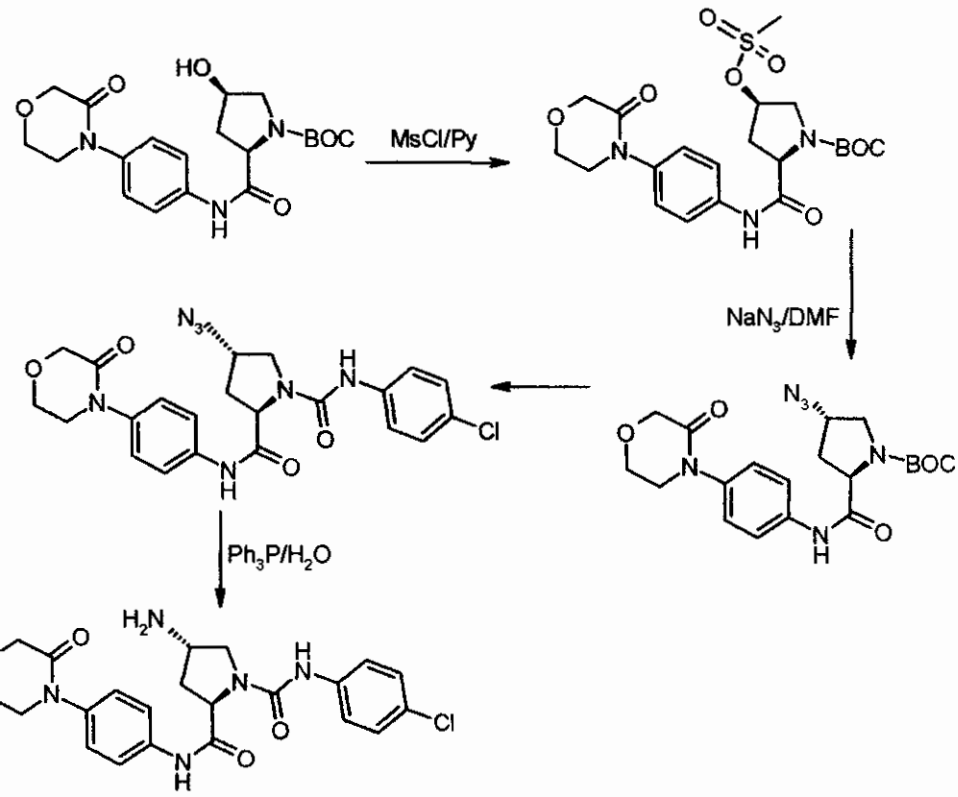
The following compounds are obtained analogously

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-(2R,4S)-4-ethynyl-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 477;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(2R,4S)-4-ethynyl-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 478.

Example 9

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-azidopyrrolidine-1,2-dicarboxamide ("A9") and 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-aminopyrrolidine-1,2-dicarboxamide ("A10") are prepared analogously to the following scheme:



9.1 1.3 ml (16.65 mmol) of methanesulfonyl chloride are added dropwise with ice cooling to a solution of 4.5 g (11.1 mmol) of *tert*-butyl (2R,4R)-4-hydroxy-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate in 20 ml of pyridine, and the reaction solution is stirred at room temperature for 12 hours. The pyridine is subsequently stripped off under reduced pressure, 10 ml of saturated citric acid solution are added to the residue, and the acidic solution is extracted twice with 10 ml of methylene chloride each time. The combined organic phases are then

washed with 10 ml of saturated sodium chloride solution and dried over sodium sulfate. Removal of the drying agent by filtration and stripping-off of the solvent gives 5.4 g (100%) of *tert*-butyl (2R,4R)-4-methanesulfonyl-oxy-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate as a yellow oil, ESI 484.

9.2 A mixture of 5.4 g (11.7 mmol) of *tert*-butyl (2R,4R)-4-methanesulfonyloxy-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate and 3.69 g (56.8 mmol) of sodium azide in 50 ml of dimethylformamide (DMF) is stirred at 60°C for 12 hours. The insoluble matter is subsequently filtered off, and the filtrate is evaporated to dryness under reduced pressure. The residue is then dissolved in 20 ml of water, and the aqueous solution is extracted twice with 10 ml of methylene chloride each time. The combined methylene chloride extracts are finally washed once with 10 ml of saturated sodium chloride solution and dried over sodium sulfate. Removal of the drying agent by filtration and stripping-off of the solvent gives 4.8 g (100%) of *tert*-butyl (2R,4S)-4-azido-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate as slightly yellow crystals, ESI 431.

9.3 Analogously to Example 7, reaction of *tert*-butyl (2R,4S)-4-azido-2-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidine-1-carboxylate gives the compound 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-azidopyrrolidine-1,2-dicarboxamide ("A9") as a white powder, ESI 459, m.p. 145°.

9.4 A solution of 25 mg (0.052 mmol) of "A9" and 20.46 mg (0.08 mmol) of triphenylphosphine in a mixture of 0.5 ml of tetrahydrofuran and 0.5 ml of water is stirred at room temperature for 12 hours. After the precipitated triphenylphosphine oxide has been filtered off, the filtrate is evaporated to dryness, and the residue is purified by preparative HPLC

(acetonitrile/water/0.1% trifluoroacetic acid), giving 12 mg (40%) of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-amino-pyrrolidine-1,2-dicarboxamide ("A10") as colourless crystals, ESI 458.

An analogous procedure gives the compounds

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-azidopyrrolidine-1,2-dicarboxamide, ESI 484, m.p. 125°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-aminopyrrolidine-1,2-dicarboxamide, ESI 458, m.p. 110°;

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-aminopyrrolidine-1,2-dicarboxamide, ESI 472, m.p. 218°.

Starting from the 4-amino compounds,

a) reaction with acetyl chloride gives the compounds

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-acetaminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-acetaminopyrrolidine-1,2-dicarboxamide, ESI 458;

and analogously

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-acetaminopyrrolidine-1,2-dicarboxamide, ESI 514, m.p. 170°;

b) reaction with mesyl chloride gives the compounds

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-methylsulfonylaminopyrrolidine-1,2-dicarboxamide and

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methylsulfonylaminopyrrolidine-1,2-dicarboxamide;

c) reaction with butylsulfonyl chloride gives the compounds

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-butylsulfonylaminopyrrolidine-1,2-dicarboxamide,

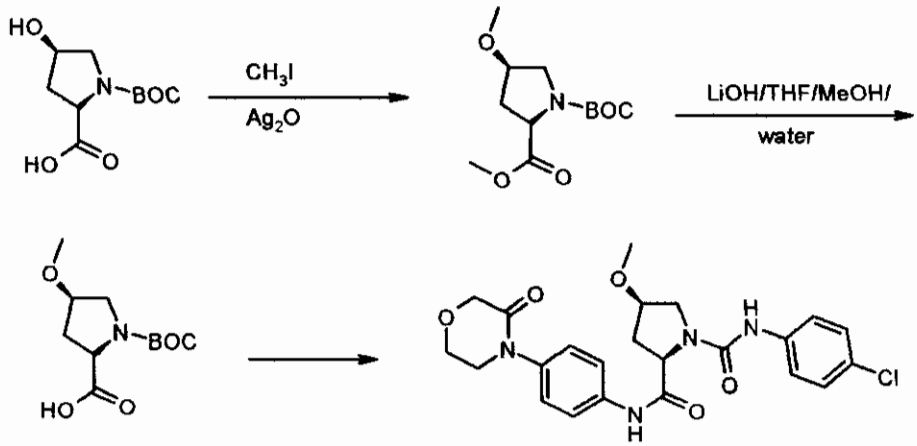
1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-butylsulfonylaminopyrrolidine-1,2-dicarboxamide, ESI 592;

d) reaction with isobutyryl chloride gives the compound

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-(2-methylpropanoylamino)pyrrolidine-1,2-dicarboxamide, ESI 542; m.p.169°.

Example 10

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide ("A11") is prepared analogously to the following scheme:



10.1 0.94 ml (15.1 mmol) of methyl iodide is added under nitrogen to a mixture of 1 g (4.32 mmol) of cis-N'-BOC-4-hydroxy-D-proline and 3.31 g (14.27 mmol) of silver oxide in 15 ml of acetone, and the reaction mixture is stirred at room temperature for 48 hours. The precipitate is subsequently filtered off, and the filtrate is evaporated to dryness under reduced pressure, giving 1 g (89.2%) of cis-N'-BOC-4-methoxy-D-

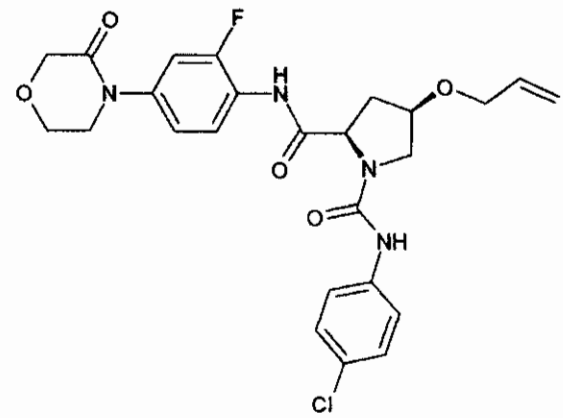
proline methyl ester as a colourless oil, which is reacted further without further purification, ESI 260.

10.2 25 ml of methanol, 25 ml of water and 0.28 g (11.57 mmol) of lithium hydroxide are added to a solution of 1 g (3.85 mmol) of cis-N'-BOC-4-methoxy-D-proline methyl ester in 75 ml of tetrahydrofuran (THF), and the reaction solution is stirred at room temperature for 5 hours. The methanol and the THF are subsequently stripped off in a rotary evaporator, and the aqueous solution is extracted once by shaking with 10 ml of methylene chloride and acidified to pH 2 by means of saturated citric acid solution, and the acidic solution is extracted twice with 10 ml of methylene chloride each time. Drying of the combined organic phases over sodium sulfate and stripping-off of the solvent gives 0.5 g (53%) of cis-N'-BOC-4-methoxy-D-proline as a pale oil, which gradually crystallises, ESI 246.

10.3 Analogously to Example 7, reaction of cis-N'-BOC-4-methoxy-D-proline gives the compound 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide ("A11") as a white powder, ESI 473, m.p. 133°.

The following compounds are obtained analogously

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-allyloxypyrrolidine-1,2-dicarboxamide, ESI 517, m.p. 106°



;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 487, m.p. 136°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-propoxypyrrolidine-1,2-dicarboxamide, ESI 501, m.p. 106°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-allyloxypyrrolidine-1,2-dicarboxamide, ESI 499, m.p. 100° and as by-product

2-N-{allyl-[4-(3-oxomorpholin-4-yl)phenyl]}-1-N-[(4-chlorophenyl)]-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 499;

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 487, m.p. 140°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 467, m.p. 133°;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 491, m.p. 109°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 468, m.p. 127°;

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 491, m.p. 99°;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 485;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 482, m.p.132°;

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 505, m.p. 131°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(prop-2-ynyloxy)pyrrolidine-1,2-dicarboxamide, ESI 497, m.p. 120°;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(but-2-ynyloxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-(prop-2-ynyloxy)pyrrolidine-1,2-dicarboxamide, ESI 515, m.p. 108°;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-(prop-2-ynyloxy)pyrrolidine-1,2-dicarboxamide, ESI 515, m.p. 92°;

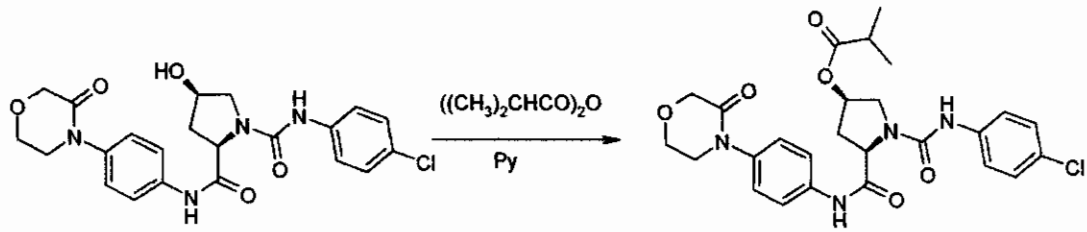
1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(methoxycarbonylmethoxy)pyrrolidine-1,2-dicarboxamide, ESI 531, m.p. 106°; and therefrom by hydrolysis

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(carboxymethoxy)pyrrolidine-1,2-dicarboxamide, ESI 517, m.p. 134°;

1-N-[(4-bromophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 536, m.p. 103°.

Example 11

(3R,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl isobutyrate ("A12") is prepared analogously to the following scheme:



A solution of 0.2 g (0.44 mmol) of "A8" and 0.146 ml of isobutyric anhydride in 1 ml of pyridine is stirred at room temperature for 12 hours. 10 ml of ethyl acetate are subsequently added to the reaction mixture, and the ethyl acetate solution is washed successively with 5 ml of 1N hydrochloric acid and 5 ml of saturated sodium chloride solution and dried over sodium sulfate. Removal of the drying agent by filtration and stripping-off of the solvent gives 183 mg (79.3%) of (3R,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl isobutyrate ("A12") as white crystals, ESI 529, m.p. 129°.

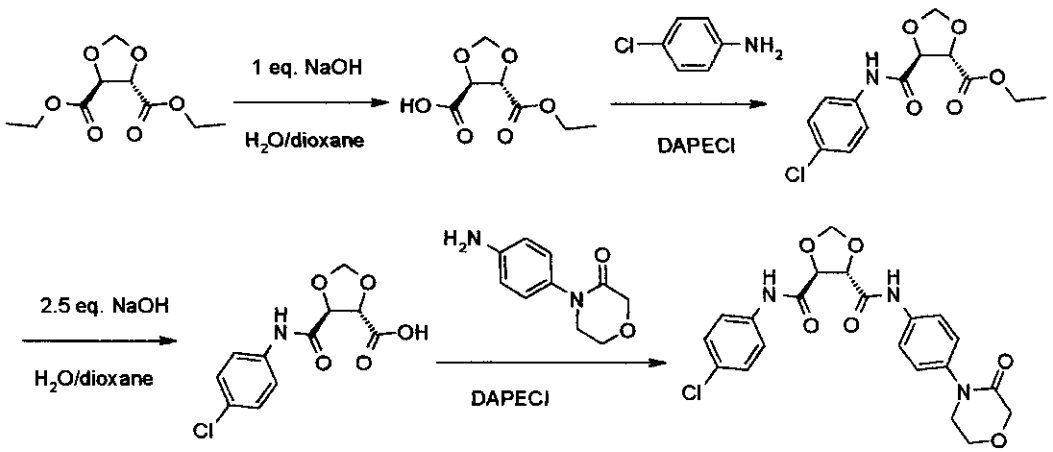
The following compounds are obtained analogously

(3R,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl propionate, ESI 515;

(3R,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl acetate, ESI 501, m.p. 148°.

Example 12

N-4-[(4-chlorophenyl)]-N'-5-{[4-(3-oxomorpholin-4-yl)phenyl]}-1,3-dioxolane-4,5-dicarboxamide is prepared analogously to the following scheme:



The following compounds are obtained analogously

N-4-[(4-chlorophenyl)]-N'-5-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-1,3-dioxolane-4,5-dicarboxamide,

N-4-[(4-chlorophenyl)]-N'-5-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-1,3-dioxolane-4,5-dicarboxamide, ESI 440;

N-4-[(4-chlorophenyl)]-N'-5-{[4-(3-oxomorpholin-4-yl)phenyl]}-1,3-dioxolane-2,2-dimethyl-4,5-dicarboxamide, ESI 474;

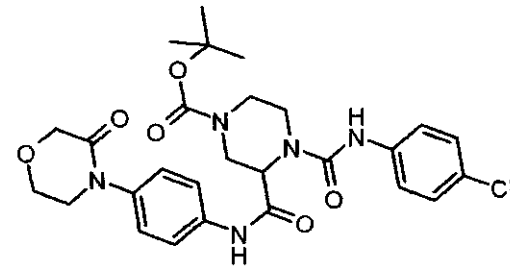
N-4-[(4-chlorophenyl)]-N'-5-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-1,3-dioxolane-2,2-dimethyl-4,5-dicarboxamide, ESI 488;

N-4-[(4-chlorophenyl)]-N'-5-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-1,3-dioxolane-2,2-dimethyl-4,5-dicarboxamide, ESI 468.

Example 13

Analogously to Example 7, reaction of N-[4-(3-oxomorpholin-4-yl)phenyl]-1-BOC-piperazine-2-carboxamide with 4-chlorophenyl isocyanate gives the compound

1-N-[4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-1-BOC-piperazine-1,2-dicarboxamide



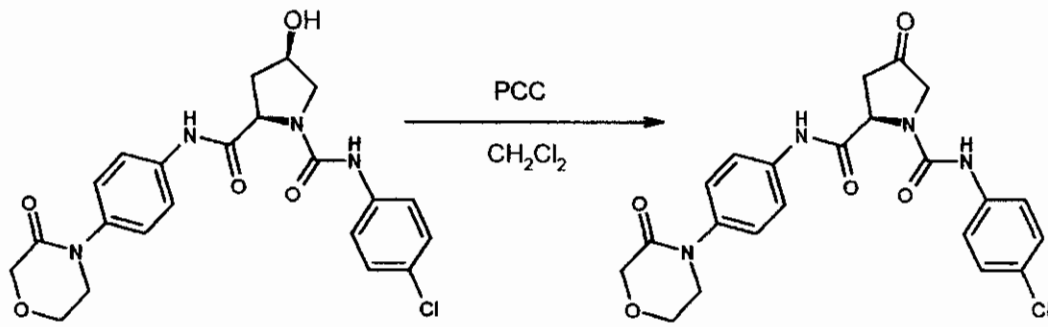
Removal of the BOC group gives 1-N-[4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-piperazine-1,2-dicarboxamide.

Analogous reaction of 4-chlorophenyl isocyanate with N-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazinane-4-carboxamide gives the compound

1-N-[4-chlorophenyl]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-1,3-oxazinane-3,4-dicarboxamide.

Example 13 - 1

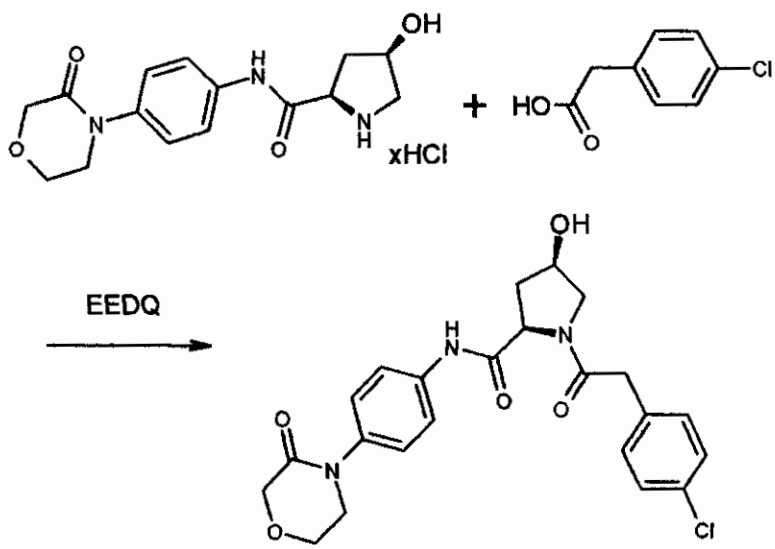
1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-4-oxo-pyrrolidine-1,2-dicarboxamide is prepared analogously to the following scheme:



0.21 g (0.98 mmol) of pyridinium chlorochromate (PCC) is added to the solution of 0.3 g (0.65 mmol) of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(1R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide (Example 7) in 15 ml of methylene chloride, and the reaction mixture is stirred at room temperature for 48 hours. The precipitate is subsequently filtered off, and the filtrate is washed three times with 20 ml of water each time and dried over sodium sulfate. After the solvent has been stripped off, the residue is purified by preparative HPLC, giving 140 mg (47%) of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-4-oxopyrrolidine-1,2-dicarboxamide as a white powder, ESI 457, m.p. 154°.

Example 13 - 2

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[2-(4-chlorophenyl)acetyl]-4-hydroxypyrrolidine-2-carboxamide is prepared analogously to the following scheme:



0.25 g (1.46 mmol) of 4-chlorophenylacetic acid and 0.36 g (1.46 mmol) of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ) are added successively at room temperature to a solution of 0.5 g (1.46 mmol) of N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-4-hydroxypyrrolidine-2-carboxamide (Example 7.2) and 0.2 ml of triethylamine in 20 ml of toluene. The resultant reaction mixture is subsequently left to stir at room temperature for 12 hours, then washed successively with 10 ml of 1N hydrochloric acid and 10 ml of saturated sodium hydrogencarbonate solution, and the organic phase is dried over sodium sulfate. After the solvent has been stripped off, the crude product is purified by preparative HPLC, giving 0.31 g (46.4%) of N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[2-(4-chlorophenyl)acetyl]-4-hydroxypyrrolidine-2-carboxamide as a white powder, ESI 458, m.p. 141°.

The following compounds are obtained analogously

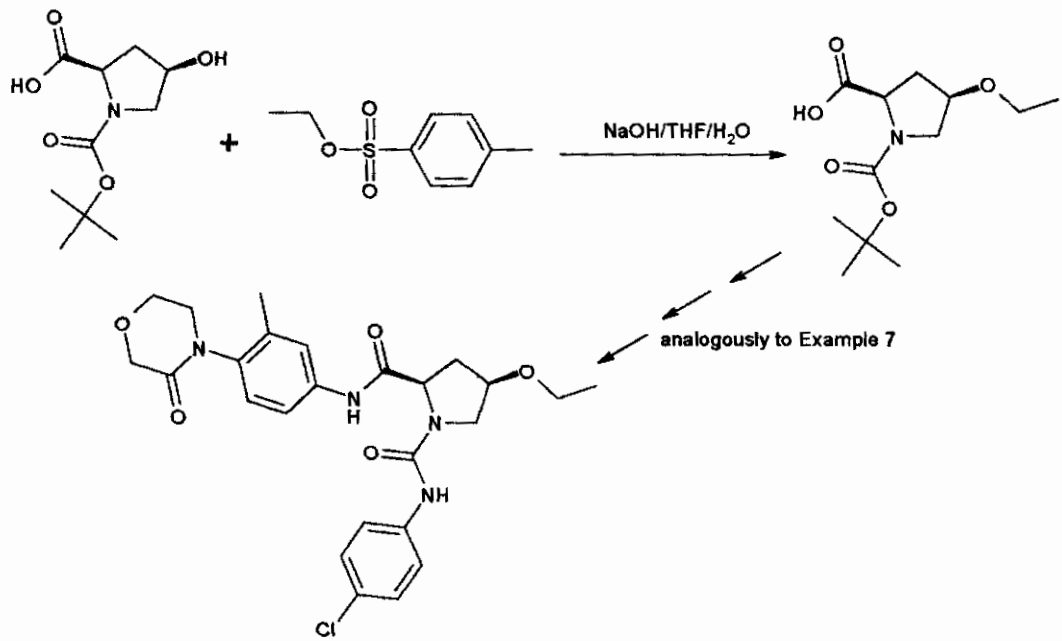
N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-(4-chlorobenzoyl)-4-hydroxypyrrolidine-2-carboxamide, ESI 444, m.p. 216°;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-(1-1*H*-indol-3-yl-methanoyl)-4-hydroxypyrrolidine-2-carboxamide, ESI 449, m.p. 283°;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-(1-1*H*-indol-6-yl-methanoyl)-4-hydroxypyrrolidine-2-carboxamide, ESI 449, m.p. 148°.

Example 13 - 3

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide is prepared analogously to the following scheme:



A solution of 2.94 g (73.5 mmol) of sodium hydroxide in 5 ml of water is added to a suspension of 5 g (21.62 mmol) of cis-N'-Boc-4-hydroxy-D-proline and 8.66 g (43.24 mmol) of ethyl 4-toluenesulfonate in 5 ml of tetrahydrofuran (THF). The reaction mixture is then stirred at 40°C for 12 hours and subsequently evaporated in a rotary evaporator, and the residue is taken up in 10 ml of water. The aqueous solution is then washed twice with 10 ml of methylene chloride each time and acidified using 2N hydrochloric acid. The resultant acidic solution is extracted three times

with 20 ml of methylene chloride each time. Drying of the combined methylene chloride extracts over sodium sulfate and stripping-off of the solvent gives 4.87 g (86.9%) of cis-N'-Boc-4-ethoxy-D-proline as a colourless oil. ESI: 232.

Analogously to Example 7, reaction of cis-N'-Boc-4-ethoxy-D-proline gives the compound

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 501, m.p. 117°.

The compounds

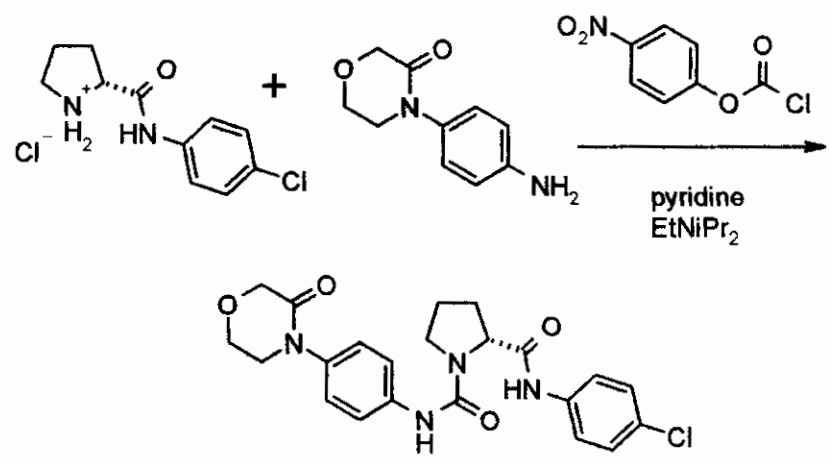
1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 481, m.p. 209°;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 505, m.p. 187°;

are obtained analogously.

Example 13 - 4

2-N-[(4-chlorophenyl)]-1-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide is prepared analogously to the following scheme:

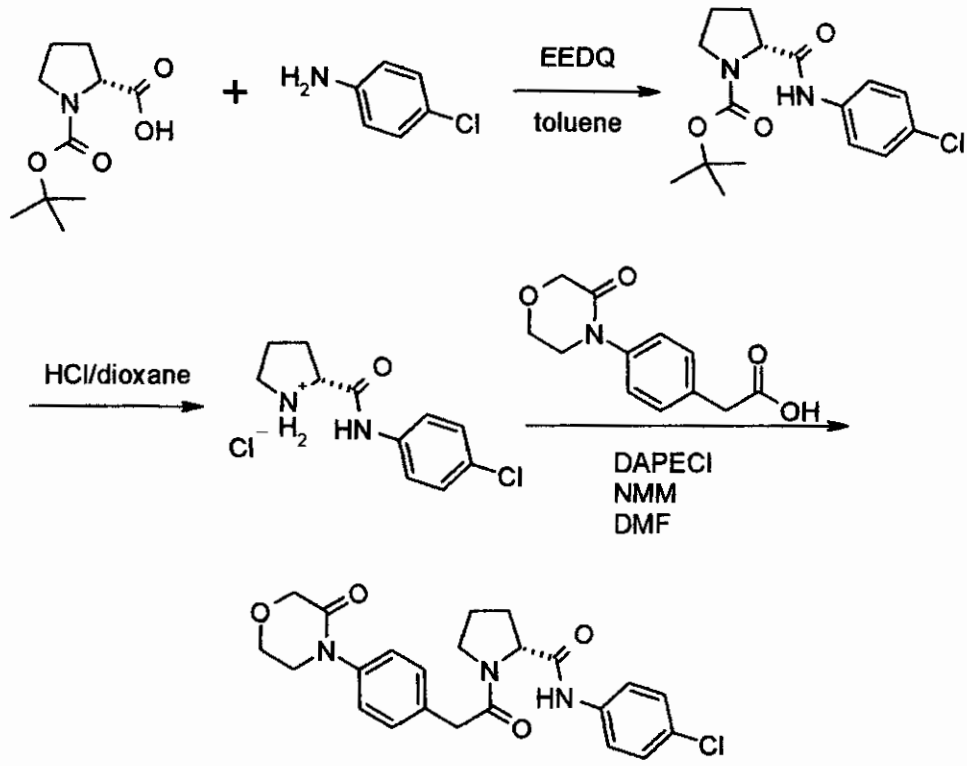


1.01 g (5.00 mmol) of 4-nitrophenyl chloroformate and 0.404 ml (5.00 mmol) of pyridine are added to a solution of 961 mg (5.00 mmol) of 4-(4-aminophenyl)morpholin-3-one in 10 ml of dichloromethane, and the mixture is stirred at room temperature for 1 hour. 1.31 g (5.00 mmol) of (R)-2-(4-chlorophenylcarbamoyl)pyrrolidinium chloride and 2.55 ml (15.0 mmol) of N-ethyldiisopropylamine are added to the suspension. The reaction mixture is stirred at room temperature for 12 hours and then evaporated, and the residue is chromatographed on a silica-gel column, giving 2-N-[(4-chlorophenyl)]-1-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide as a yellowish solid, ESI 443.

2-N-[(4-chlorophenyl)]-1-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-pyrrolidine-1,2-dicarboxamide, ESI 443,
is obtained analogously.

Example 13 - 5

N-(4-chlorophenyl)-(R)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]acetyl}pyrrolidine-2-carboxamide is prepared analogously to the following scheme:



4.82 g (19.5 mmol) of ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate (EEDQ) are added to a suspension of 2.80 g (13.0 mmol) of N-Boc-D-proline and 1.66 g (13.0 mmol) of 4-chloroaniline in 50 ml of toluene, and the mixture is stirred at room temperature for 3 hours. The reaction mixture is filtered, and petroleum ether is added to the filtrate. The precipitate formed is filtered off and dried, giving tert-butyl (R)-2-(4-chlorophenylcarbamoyl)pyrrolidine-1-carboxylate as colourless crystals; ESI 325.

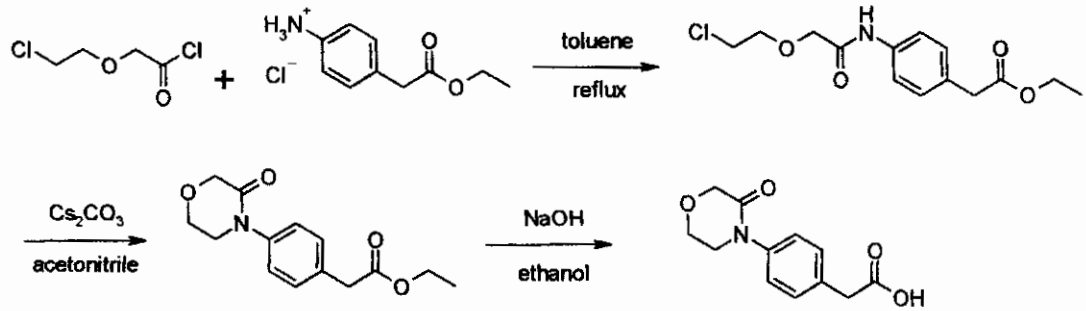
4.00 g (12.3 mmol) of tert-butyl (R)-2-(4-chlorophenylcarbamoyl)pyrrolidine-1-carboxylate are dissolved in 20 ml of 4N HCl in dioxane and left at room temperature for 2 hours. The reaction mixture is evaporated and dried, giving (R)-2-(4-chlorophenylcarbamoyl)pyrrolidinium chloride as a slightly brownish solid; ESI 225.

0.26 ml (2.4 mmol) of 4-methylmorpholine and 230 mg (1.2 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (DAPECI) are

added to a solution of 261 mg (1.00 mmol) of (R)-2-(4-chlorophenylcarbamoyl)pyrrolidinium chloride and 235 mg (1.00 mmol) of 4-(3-oxomorpholin-4-yl)phenylacetic acid in 2 ml of DMF, and the mixture is stirred at room temperature for 18 hours. The reaction mixture is introduced into water, and the precipitate formed is filtered off, giving N-(4-chlorophenyl)-(R)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]acetyl}pyrrolidine-2-carboxamide as a slightly brownish solid; ESI 442.

N-(4-chlorophenyl)-(S)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]acetyl}pyrrolidine-2-carboxamide, ESI 442, is obtained analogously.

Preparation of the carboxylic acid unit



14.6 g (92.7 mmol) of (2-chloroethoxy)acetyl chloride are added to a suspension of 20.0 g (92.7 mmol) of ethyl 4-aminophenylacetate hydrochloride in 25 ml of toluene, and the mixture is heated at the boil for 24 hours. The reaction mixture is evaporated and dried, giving ethyl {4-[2-(2-chloroethoxy)acetylamino]phenyl}acetate as a yellowish solid; ESI 300.

43.4 g (133 mmol) of caesium carbonate are added to a solution of 26.6 g (88.8 mmol) of ethyl {4-[2-(2-chloroethoxy)acetylamino]phenyl}acetate in 100 ml of acetonitrile, and the mixture is stirred at room temperature for 18 hours. The reaction mixture is filtered, and the filtrate is evaporated, giving

ethyl [4-(3-oxomorpholin-4-yl)phenyl]acetate as a yellowish oil: ESI 264.

20.2 g (76.8 mmol) of ethyl [4-(3-oxomorpholin-4-yl)phenyl]acetate are dissolved in a solution of 3.37 g of sodium hydroxide in 40 ml of ethanol, and the reaction solution is stirred at room temperature for 18 hours. The reaction mixture is evaporated, and the residue is dissolved in water and acidified to a pH of 3 using 1N hydrochloric acid. The mixture is extracted with ethyl acetate, and the organic phase is dried over sodium sulfate and evaporated, giving 4-(3-oxomorpholin-4-yl)phenylacetic acid as a yellowish solid; ESI 236.

The following compounds are obtained analogously to Example 13-5:

N-(4-chlorophenyl)-(2R,4R)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]-acetyl}-4-methoxypyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(2R,4S)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]-acetyl}-4-methoxypyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(2S,4R)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]-acetyl}-4-methoxypyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(S)-1-{2-[4-(2-oxo-1H-pyridin-1-yl)phenyl]acetyl}-pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(S)-1-{2-[4-(2-oxopyrrolidin-1-yl)phenyl]acetyl}-pyrrolidine-2-carboxamide,

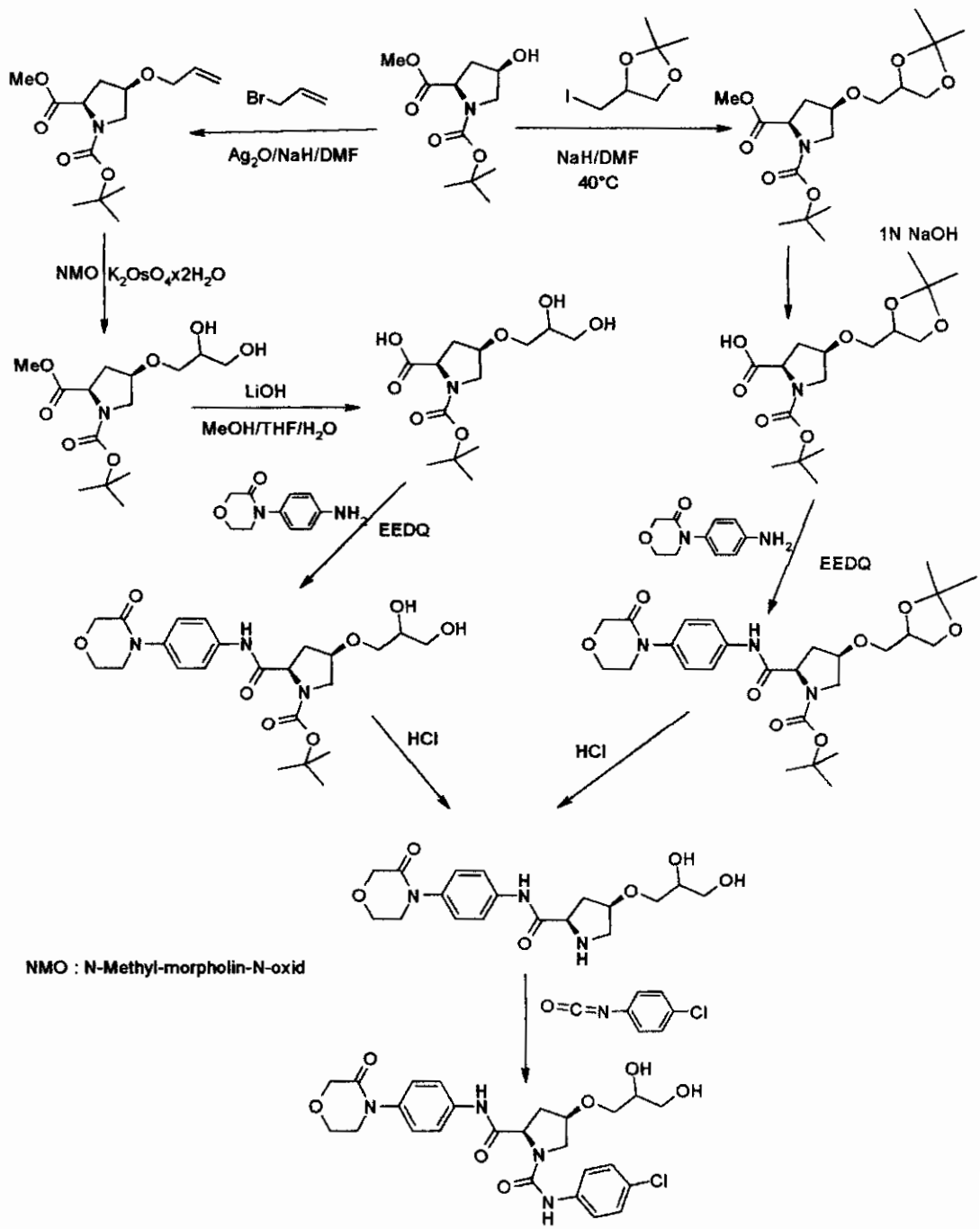
N-(4-chlorophenyl)-(R)-1-{2-[4-(2-oxopyrrolidin-1-yl)phenyl]acetyl}-pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(R)-1-[4-(2-oxopiperidin-1-yl)benzoyl]pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(R)-1-[4-(2-oxopiperidin-1-yl)phenyloxycarbonyl]-pyrrolidine-2-carboxamide.

Example 13 - 6

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,3-dihydroxypropoxy)pyrrolidine-1,2-dicarboxamide is prepared analogously to the following scheme:



NMO : N-Methyl-morpholin-N-oxid

1.55 g (38.6 mmol) of sodium hydride are added in portions under nitrogen to the solution of 10.3 g (42 mmol) of 1-*tert*-butyl 2-methyl (2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate and 36.34 ml (420 mmol) of 3-bromo-1-propene in 100 ml of dimethylformamide (DMF), and the mixture is subsequently stirred at room temperature for 15 minutes. 9.73 g (42 mmol) of silver oxide are then added in portions to the reaction mixture, and the reaction mixture is left to stir at room temperature for a further 12 hours. The reaction mixture is then filtered, the filtrate is evaporated to dryness under reduced pressure, and the residue is taken up in 20 ml of saturated citric acid solution. After the precipitate has been filtered off, the filtrate is extracted twice with 20 ml of ethyl acetate each time. Drying of the combined organic phases over sodium sulfate and stripping-off of the solvent gives 11.6 g of 1-*tert*-butyl 2-methyl (2R,4R)-4-allyloxypyrrolidine-1,2-dicarboxylate as a red-brown oil; ESI 286.

6.16 g (52.6 mmol) of N-methylmorpholine N-oxide (NMO) and 193.7 mg of potassium osmate dihydrate are added successively at room temperature to the solution of 5 g (17.52 mmol) of 1-*tert*-butyl 2-methyl (2R,4R)-4-allyloxypyrrolidine-1,2-dicarboxylate in 60 ml of water, 25 ml of acetone and 10 ml of tert-butanol, and the mixture is stirred for 48 hours. 6.6 g (52.6 mmol) of sodium sulfite are subsequently added to the reaction mixture, which is stirred at room temperature for a further hour. The reaction mixture is then evaporated under reduced pressure, the residue is taken up in 50 ml of water, and the aqueous solution is extracted twice with 20 ml of ethyl acetate each time. Drying of the combined organic phases over sodium sulfate and stripping-off of the solvent gives 4.7 g of 1-*tert*-butyl 2-methyl (2R,4R)-4-(2,3-dihydroxypropoxy)pyrrolidine-1,2-dicarboxylate as a yellowish oil; ESI 320. 1.06 g of lithium hydroxide are added to the solution of 4.6 g of this methyl ester in 40 ml of tetrahydrofuran, 10 ml of methanol and 10 ml of water, and the reaction mixture is stirred at

room temperature for 12 hours. The reaction mixture is subsequently evaporated under reduced pressure, 10 ml of saturated citric acid solution are added to the aqueous solution which remains, and the mixture is extracted three times with 20 ml of ethyl acetate each time. Drying of the combined organic phases over sodium sulfate and stripping-off of the solvent gives 4.3 g of *tert*-butyl (2R,4R)-4-(2,3-dihydroxypropoxy)pyrrolidine-1,2-dicarboxylate as a yellow powder; ESI 306. Analogously to Example 7, this acid gives the compound 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,3-dihydroxypropoxy)pyrrolidine-1,2-dicarboxamide; ESI 533.

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,3-dihydroxypropoxy)pyrrolidine-1,2-dicarboxamide; ESI 551, is obtained analogously.

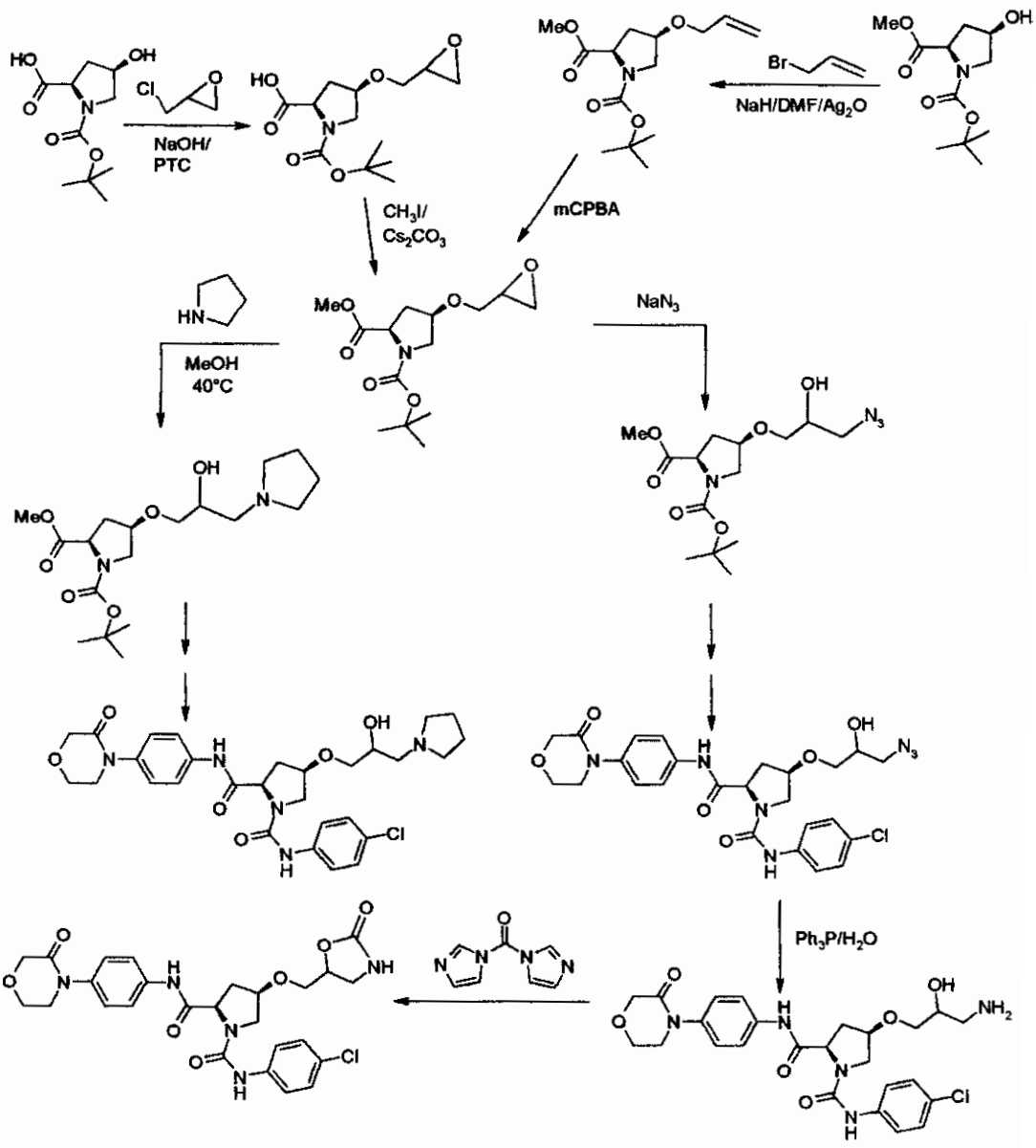
Example 13 - 7

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2-oxooxazolidin-5-ylmethoxy)pyrrolidine-1,2-dicarboxamide and

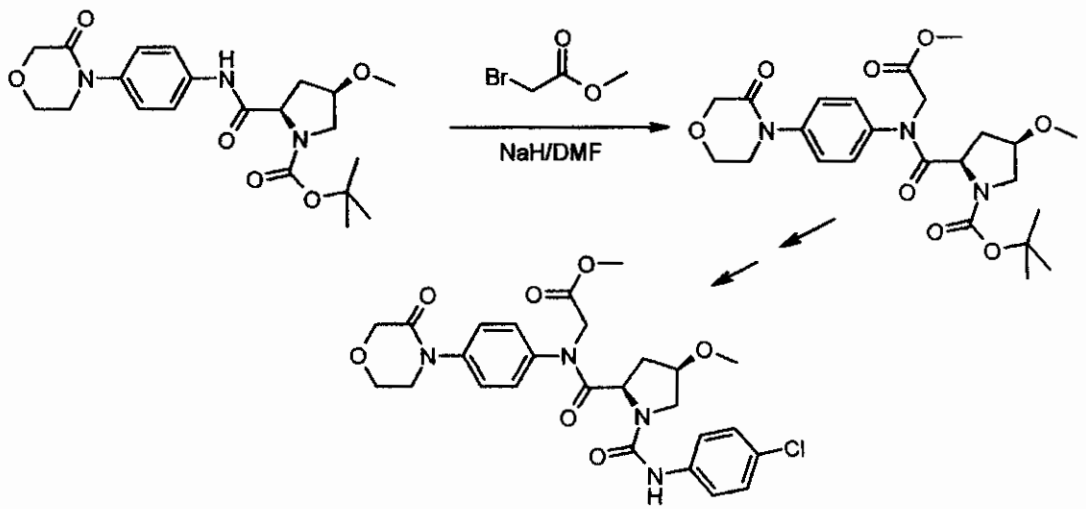
1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(3-amino-2-hydroxypropoxy)pyrrolidine-1,2-dicarboxamide, ESI 532, m.p. 115°;

are prepared analogously to the following scheme:



Example 13 - 8

1-N-[(4-chlorophenyl)]-2-N-{N-methoxycarbonylmethyl-N'-[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide is prepared analogously to the following scheme:



61 mg (2.54 mmol) of sodium hydride are added to the solution of 1 g (2.31 mmol) of *tert*-butyl (2R,4R)-4-methoxy-2-[4-(3-oxomorpholin-4-yl)-phenylcarbamoyl]pyrrolidine-1-carboxylate (prepared analogously to Example 7.1) in 20 ml of dimethylformamide, and the mixture is stirred at room temperature for 30 minutes. 0.22 mg (2.31 mmol) of methyl bromoacetate is subsequently added to the reaction mixture, which is then left to stir at room temperature for 12 hours. The reaction mixture is then evaporated under reduced pressure, the residue is taken up in 20 ml of water, and the aqueous solution is extracted three times with 20 ml of methylene chloride each time. Drying of the combined organic phases over sodium sulfate and stripping-off of the solvent gives 1.1 g of *tert*-butyl (2R,4R)-4-methoxy-2-{methoxycarbonylmethyl-[4-(3-oxomorpholin-4-yl)phenyl]carbamoyl}pyrrolidine-1-carboxylate as a yellow oil; ESI (M-BOC) 392.

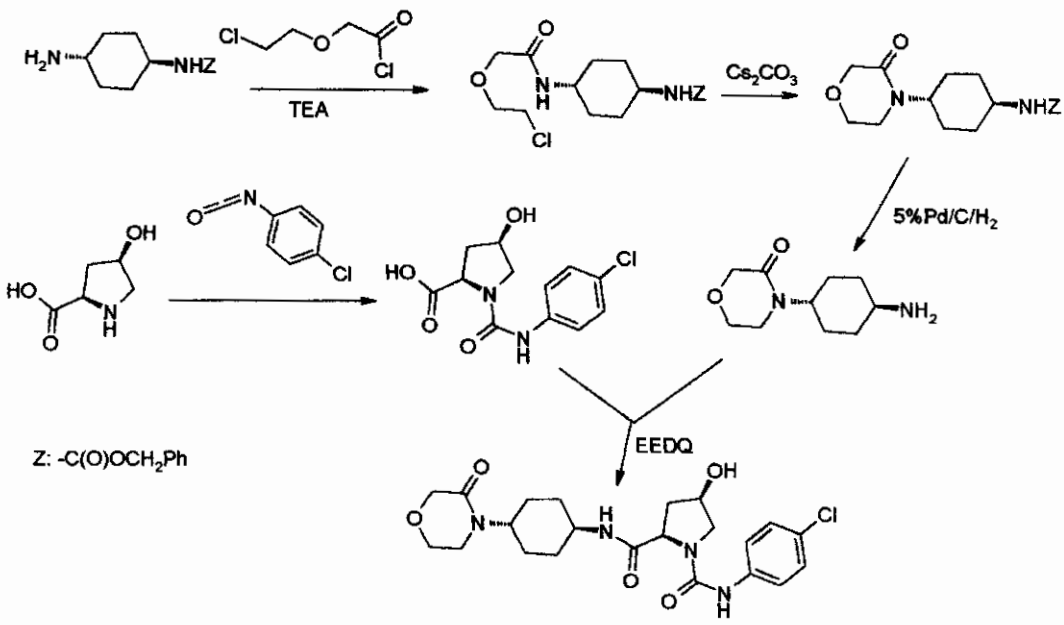
Removal of the BOC group gives 1-N-[(4-chlorophenyl)]-2-N-{N-methoxycarbonylmethyl-N'-[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 545, m.p. 106°.

The compound

1-N-[(4-chlorophenyl)]-2-N-{N-methoxycarbonylmethyl-N'-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, ESI 563, m.p. 100°,
is obtained analogously.

Example 13 - 9

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)cyclohexan-1-yl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide is prepared analogously to the following scheme:



13-9.1 6.32 g (40.3 mmol) of (2-chloroethoxy)acetyl chloride are added to the solution of 10 g (40.3 mmol) of benzyl (4-aminocyclohexyl)carbamate and 6.2 ml of triethylamine (TEA) in 300 ml of tetrahydrofuran, and the mixture is subsequently stirred at room temperature for 20 hours. The reaction mixture is then evaporated under reduced pressure, the residue is taken up in 20 ml of water, and the aqueous solution is extracted three times with 20 ml of ethyl acetate each time. After the combined organic

phases have been dried over sodium sulfate and the solvent has been stripped off, the residue is taken up in 20 ml of acetonitrile, and 2.3 g of caesium carbonate are added to the resultant solution. The reaction mixture is then left to stir at room temperature for 48 hours and then evaporated under reduced pressure, the residue is taken up in 20 ml of water, and the aqueous solution is extracted four times with 20 ml of ethyl acetate each time. After the combined organic phases have been dried over sodium sulfate and the solvent has been stripped off, the residue is taken up in 50 ml of tetrahydrofuran, 0.3 g of 5% palladium/carbon is added to the resultant solution, and the mixture is hydrogenated until the take-up of hydrogen ceases. The catalyst is subsequently filtered off, and the filtrate is evaporated to dryness under reduced pressure, giving 1.5 g of 4-(4-aminocyclohexyl)morpholin-3-one as a colourless oil; ESI 199.

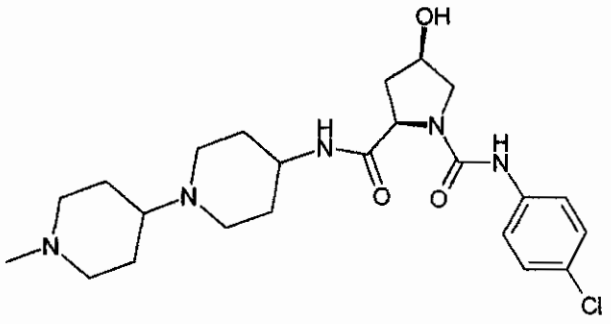
13-9.2 Analogously to Example 7.3, reaction of cis-N'-BOC-4-hydroxy-D-proline and 4-chlorophenyl isocyanate gives the compound (2R,4R)-1-(4-chlorophenylcarbamoyl)-4-hydroxypyrrolidine-2-carboxylic acid; ESI 285; m.p. 132°.

13-9.3 Analogously to Example 7.1, reaction of the amine 13-9.1 and the acid 13-9.2 gives the compound 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)cyclohexan-1-yl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 465; m.p. 245°.

Example 13 - 10

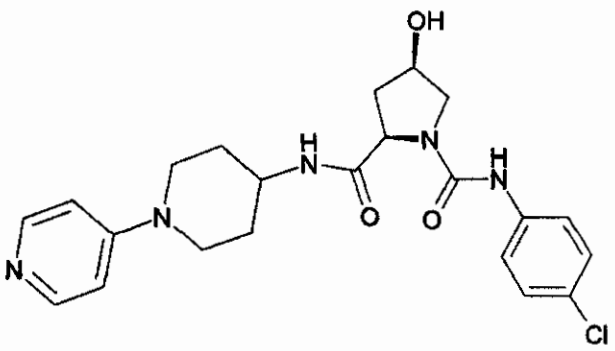
The following compounds are obtained analogously to Example 7:

1-N-[(4-chlorophenyl)]-2-N-[(1'-methyl-[1,4']bipiperidinyl-4-yl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 464; m.p. 78°



;

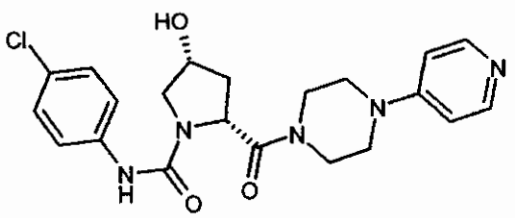
1-N-[(4-chlorophenyl)]-2-N-[(3,4,5,6-tetrahydro-2*H*-[1,4']bipyridinyl-4-yl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 444



;

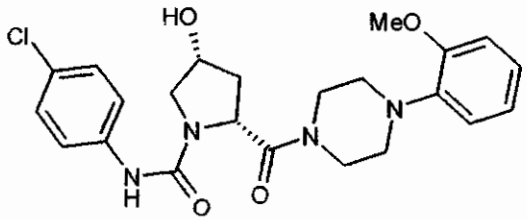
1-N-[(4-chlorophenyl)]-2-N-[(3,4,5,6-tetrahydro-2H-1,4'-bipyridinyl-4-yl)-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 472;

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-(4-pyridin-4-ylpiperazine-1-carbonyl)pyrrolidine-1-carboxamide, ESI 430



;

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-(2-methoxyphenyl)-piperazine-1-carbonyl]pyrrolidine-1-carboxamide, ESI 459



;

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4-fluorophenyl)piperazine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide, ESI 447;

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carbonyl]pyrrolidine-1-carboxamide, ESI 456;

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-(4-pyridin-2-ylpiperazine-1-carbonyl)pyrrolidine-1-carboxamide, ESI 430;

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4-ethylpiperazin-1-yl)piperidine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide, ESI 465;

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4,6-dimethylpyrimidin-2-yl)-piperazine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide, ESI 459;

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-(1-methylpiperidin-4-yl)-piperazine-1-carbonyl]pyrrolidine-1-carboxamide; ESI 450;

1-N-[(4-chlorophenyl)]-2-N-{[2-(2-dimethylaminoethoxy)-4-morpholin-4-ylphenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 532;

1-N-[(4-chlorophenyl)]-2-N-[(2-ethoxy-4-morpholin-4-ylphenyl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 489;

1-N-[(4-chlorophenyl)]-2-N-[(4-morpholin-4-yl-2-propoxyphenyl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 504;

Example 13 - 11

The following compounds are obtained analogously to Example 7:

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-iminopyrrolidin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 442;

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(2-iminopyrrolidin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 456;

1-N-[(4-chlorophenyl)]-2-N-[4-{2-[(E)-cyanimino]imidazolidin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 468;

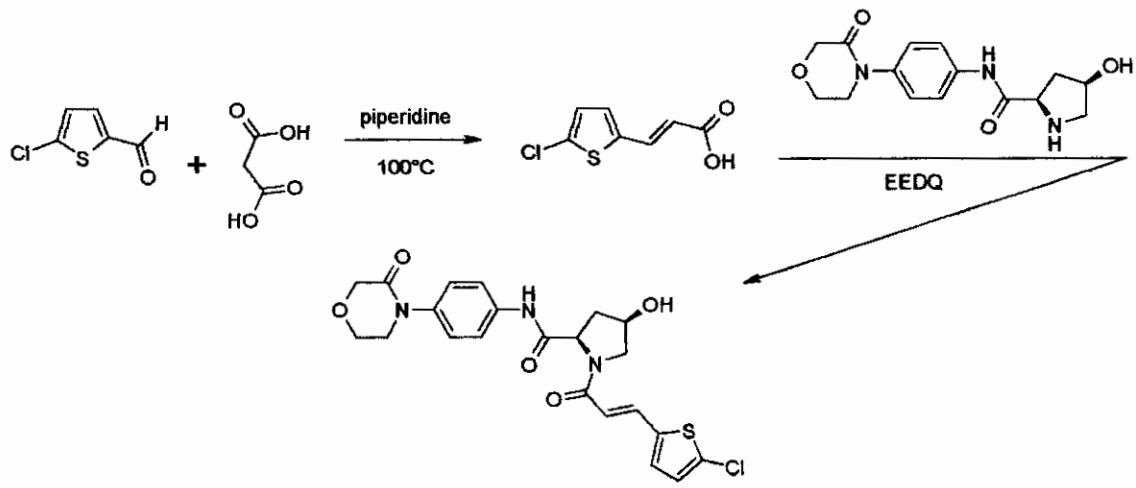
1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methylthiazol-3-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 473;

1-N-[(4-chlorophenyl)]-2-N-{[2-aminocarbonyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 502;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxy-2-methylpyrrolidine-1,2-dicarboxamide, ESI 457.

Example 13 - 12

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide is prepared analogously to the following scheme:



The solution of 1 g (6.62 mmol) of 5-chloro-2-thiophenecarboxaldehyde and 1.38 g (13.23 mmol) of malonic acid in 0.07 ml of piperidine and 5 ml of pyridine is refluxed for 2 hours. The reaction solution is subsequently

allowed to cool, then poured into 20 ml of water and acidified to pH 1 using 2N hydrochloric acid. The product which precipitates in the process is filtered off with suction and dried in a drying cabinet at 80°C, giving 1.02 g of (E)-3-(5-chlorothiophen-2-yl)acrylic acid as brown crystals, ESI 189. Analogously to Example 7.1, reaction between the compound of Example 7.2 and (E)-3-(5-chlorothiophen-2-yl)acrylic acid gives the compound N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide as colourless crystals, ESI 476, m.p. 151°.

The following compounds are obtained analogously:

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-thiophen-3-yl-acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 442, m.p. 137°;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(2E,4E)-5-phenyl-penta-2,4-dienyloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 462, m.p. 127°;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-methylfuran-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 440, m.p. 133°;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-thiophen-2-yl-acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 442;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 508;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 494, m.p. 111°;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)-acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 470;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichloro-phenyl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 504;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)-acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 484;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 518;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 426;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 490;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 460;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 474;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)-acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 498;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 532;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 488;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 504;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 488;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 522;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 478;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 492;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 502;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 536;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 516;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 550;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 506;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 522;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-yl-acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 454;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 444;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 458;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 472;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 455;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 465;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 469;

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 483;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 437;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 451;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-4-ylacryl-oyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 437;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-4-ylacryl-oyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 465;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-yl-acryloyl]-4-methoxypyrrolidine-2-carboxamide, ESI 440;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-bromothio-phen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 521;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-bromothio-phen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 549;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-bromothio-phen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide, ESI 521;

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-bromothio-phen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide, ESI 549.

Example 13 - 13

The following compounds are obtained analogously to Example 7:

N-(4-chlorophenyl)-(R)-1-[4-(2-oxopiperidin-1-yl)benzoyl]pyrrolidine-2-carboxamide, ESI 426;

N-(4-chlorophenyl)-(S)-1-[4-(2-oxopiperidin-1-yl)benzoyl]pyrrolidine-2-carboxamide, ESI 426;

1-N-[(4-chlorophenyl)]-2-N-{[4-(5-oxo-1,4-oxazepan-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide, ESI 457;

1-N-[(4-chlorophenyl)]-2-N-{[4-(5-oxo-1,4-oxazepan-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 473;

1-N-[(4-chlorophenyl)]-2-N-{[4-((S)-2-methyl-3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 473;

1-N-[(4-chlorophenyl)]-2-N-{[4-((S)-2-methyl-3-oxomorpholin-4-yl)-phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide, ESI 457;

1-N-[(4-chlorophenyl)]-2-N-{[4-((R)-2-methyl-3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 473;

1-N-[(4-chlorophenyl)]-2-N-{[4-((R)-2-methyl-3-oxomorpholin-4-yl)-phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide, ESI 457;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)-2-phenoxy-phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide, ESI 535;

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-((R)-2-methyl-3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 491;

1-N-[(4-chlorophenyl)]-N'-3-{[4-(3-oxomorpholin-4-yl)phenyl]}-piperidine-1,3-dicarboxamide, ESI 457;

1-N-[(4-chlorophenyl)]-N'-3-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}piperidine-1,3-dicarboxamide, ESI 471;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxo-1,4-oxazepan-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 473;

1-N-[(4-chlorophenyl)]-2-N-{[2-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 473;

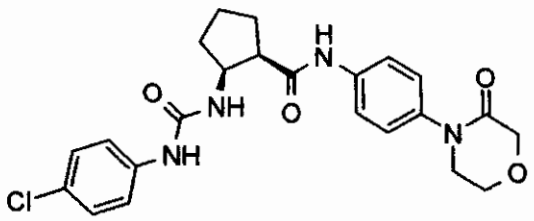
1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 459;

1-N-[(4-chlorophenyl)]-2-N-{[2-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide, ESI 459.

Example 13 - 14

The following compounds are obtained analogously to Example 7:

N-[4-(3-oxomorpholin-4-yl)phenyl]-(rac)-2-[3-(4-chlorophenyl)ureido]-cyclopentanecarboxamide, ESI 457

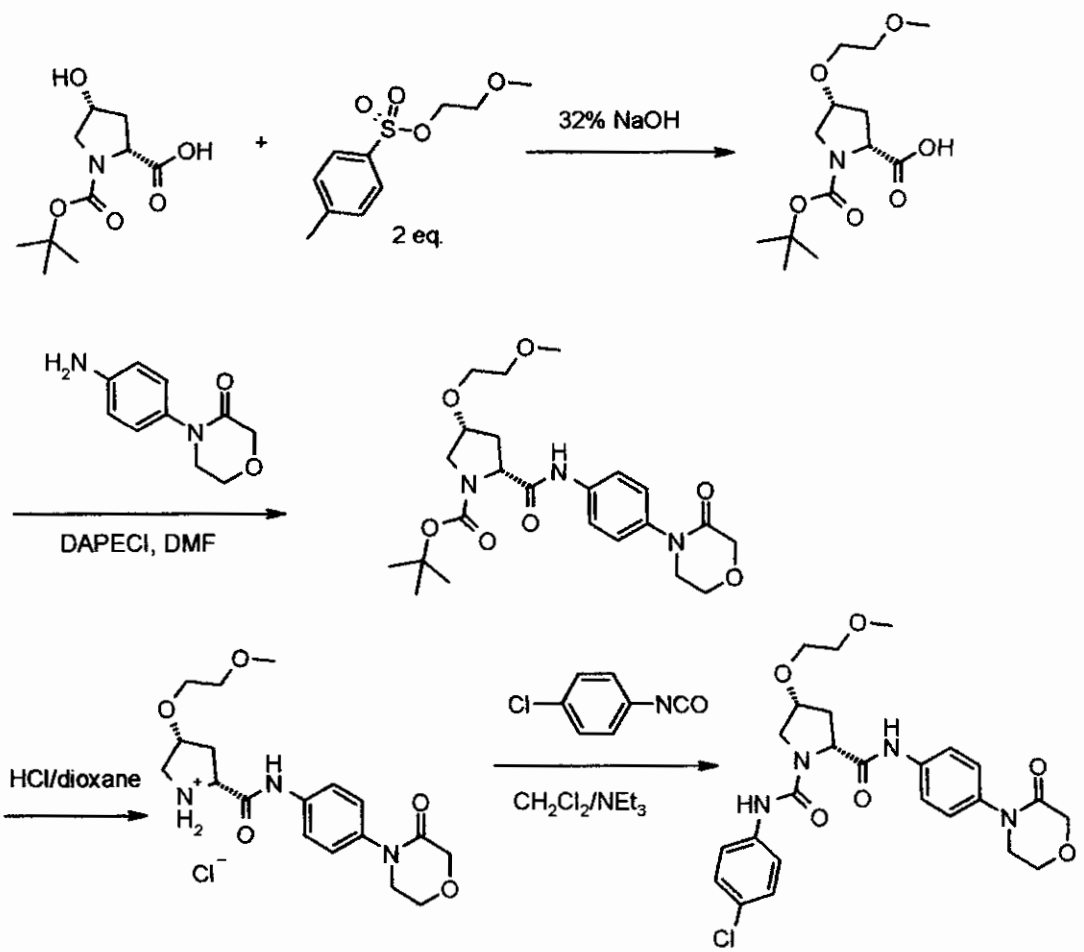


;

N-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]-(rac)-2-[3-(4-chloro-phenyl)ureido]cyclopentanecarboxamide, ESI 471.

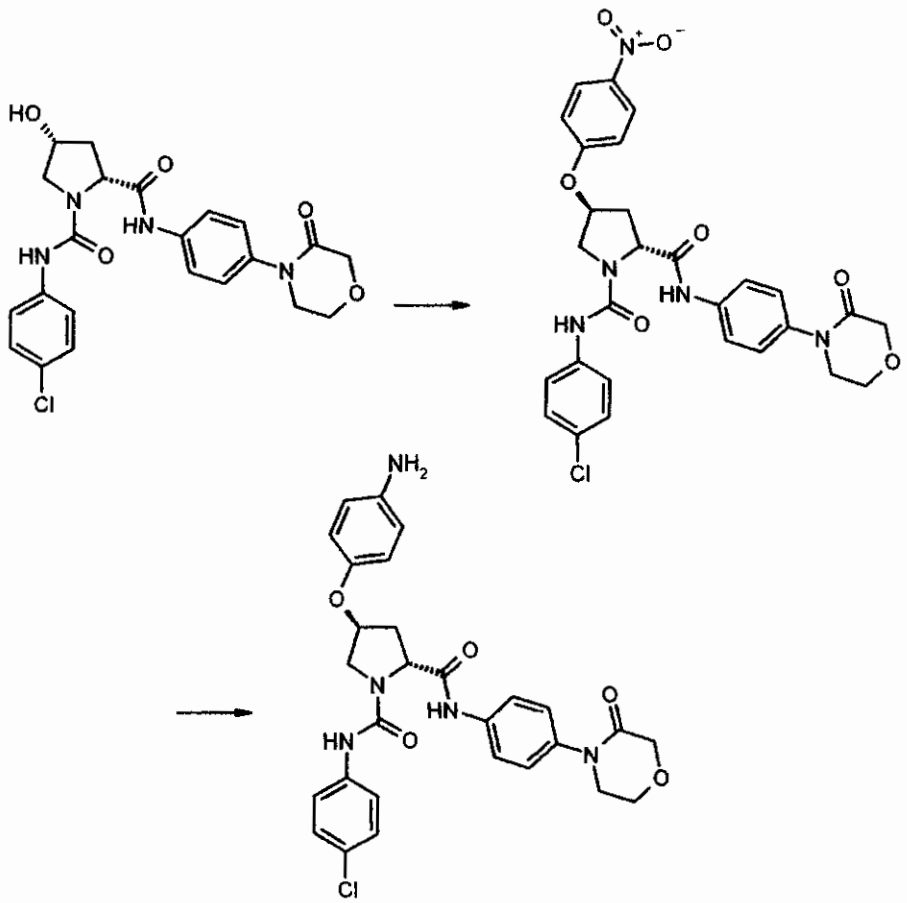
Example 13 - 15

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2-methoxyethoxy)pyrrolidine-1,2-dicarboxamide, ESI 517, is prepared as described below.



Example 13 - 16

Preparation of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-(4-aminophenoxy)pyrrolidine-1,2-dicarboxamide



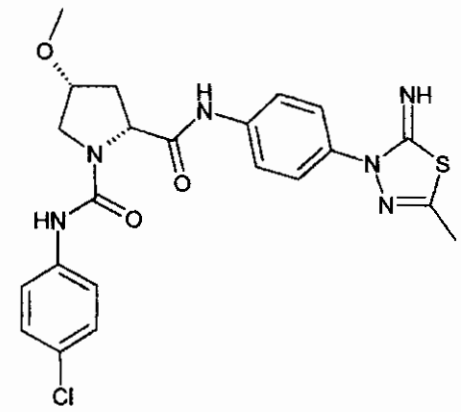
1 g of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide are suspended in 40 ml of THF, and 1.14 g of triphenylphosphine and 0.6 g of 4-nitrophenol are added successively. After cooling to 0°C in an ice bath, 0.69 ml of diethyl azodicarboxylate are added dropwise. The mixture is allowed to warm to RT and, after 16 hours, is worked up by standard methods. Preparative chromatography gives 470 mg of slightly yellowish 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-(4-nitrophenoxy)pyrrolidine-1,2-dicarboxamide. Hydrogenation on Raney nickel then gives 410 mg of end product, ESI 551;

$IC_{50}(Xa) = 2.5 \times 10^{-8}$ M.

Example 13 - 17

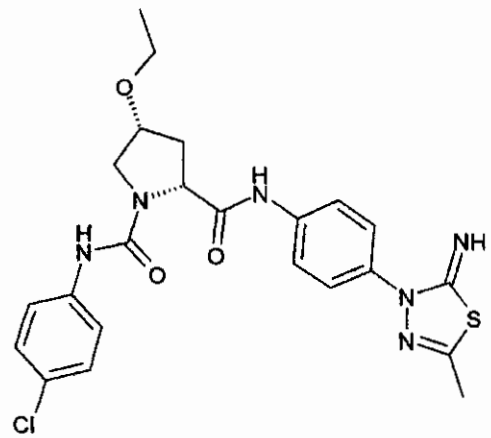
The compounds listed below are obtained analogously to Example 7

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide, trifluoroacetate, ESI 487; $IC_{50}(Xa) = 6.1 \times 10^{-9}$ M



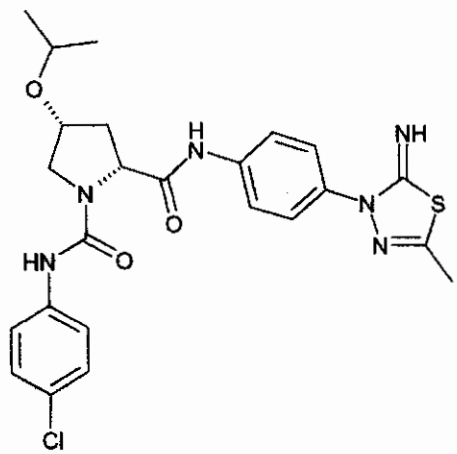
;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, trifluoroacetate, ESI 501; $IC_{50}(Xa) = 4.8 \times 10^{-9}$ M



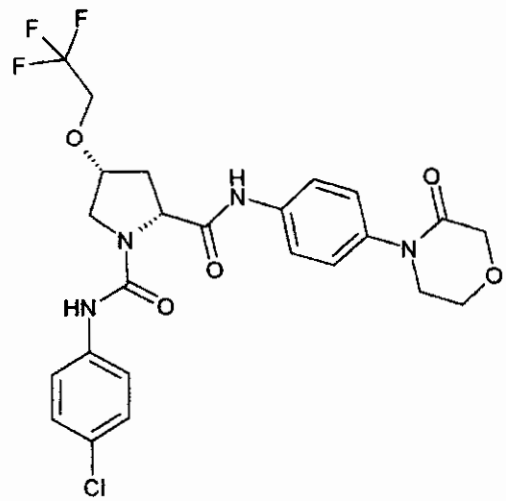
;

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-isopropoxypyrrolidine-1,2-dicarboxamide, trifluoroacetate, ESI 515; IC_{50}(Xa) = 3 x 10^{-9} M

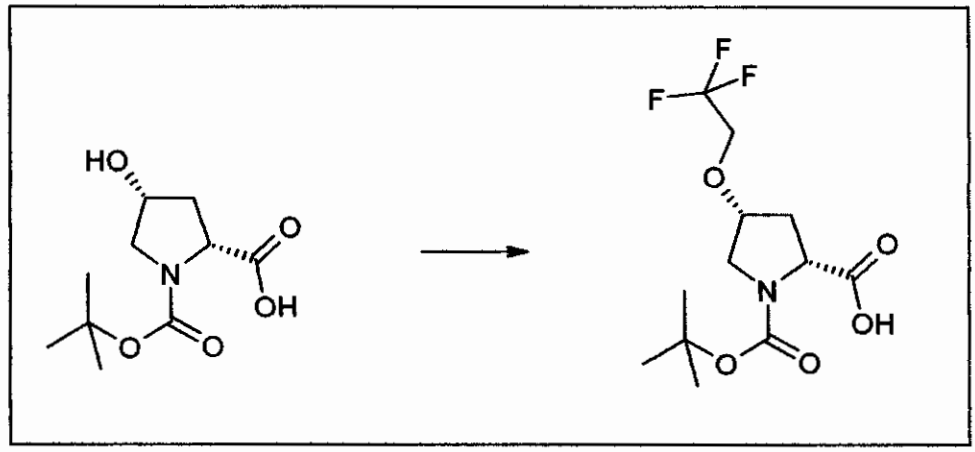


Example 13 - 18

Preparation of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-(2,2,2-trifluoroethoxy)pyrrolidine-1,2-dicarboxamide, ESI 541; IC_{50}(Xa) = 9.7 x 10^{-9} M



Preparation of the precursor 1-tert-butyl (2R,4R)-4-(2,2,2-trifluoroethoxy)-pyrrolidine-1,2-dicarboxylate



9.1 g of 1-tert-butyl (2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate are suspended in 9 ml of THF, and 10 g of 2,2,2-trifluoroethyl toluene-4-sulfonate are added. A solution of 22.46 g of caesium hydroxide in 9 ml of water is subsequently added dropwise, and the reaction mixture is warmed to 40°C. After 16 hours, the mixture is worked up by standard methods, giving 3.1 g of an oily crude product, which was reacted further without purification.

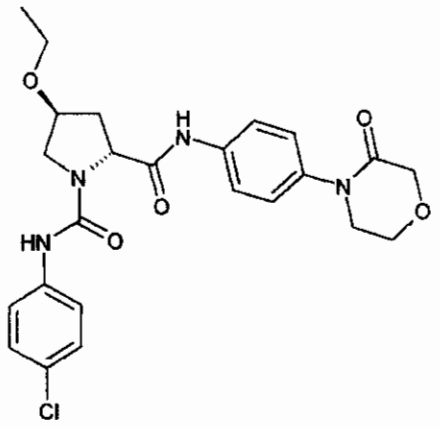
The further conversion to the end product is carried out analogously to Example 7.

Example 13 - 19

The compounds listed below are obtained analogously to Example 13-3

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 487;

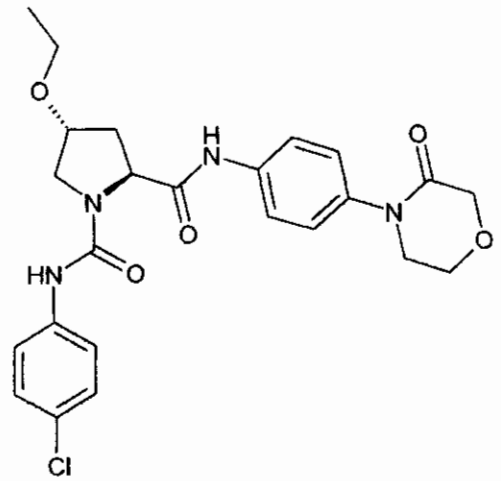
$IC_{50}(Xa) = 8.7 \times 10^{-7}$



;

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 487;

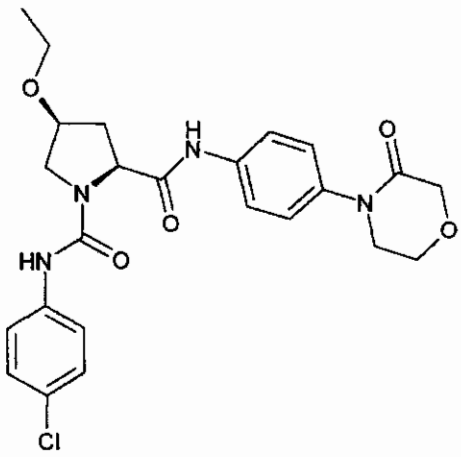
$IC_{50}(Xa) = 9 \times 10^{-6}$



;

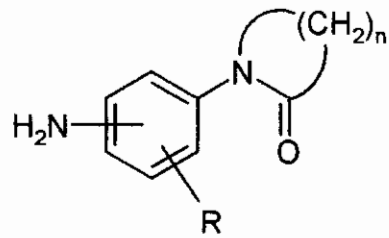
1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide, ESI 487;

$IC_{50}(Xa) = 3.9 \times 10^{-6}$



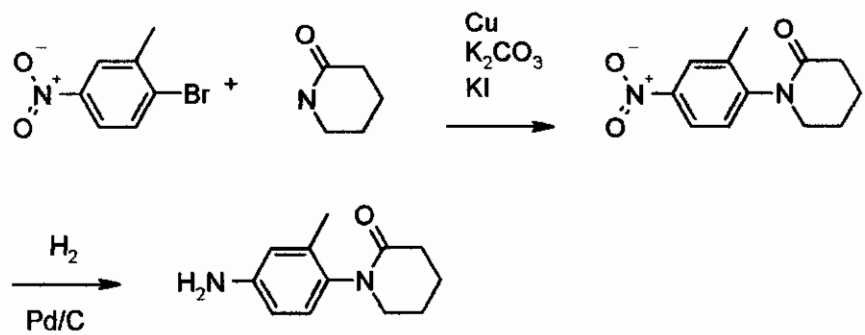
14. Examples of the preparation of intermediate compounds

14.1 **All** compounds of the following formula VI (where R = H or methyl; n = 3, 4 or 5) can be synthesised in accordance with the following scheme.

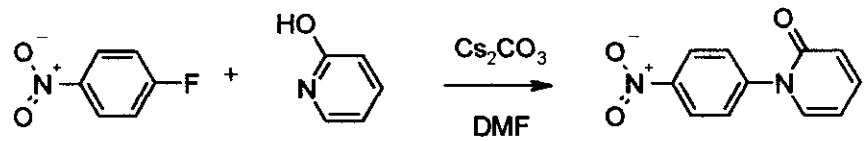


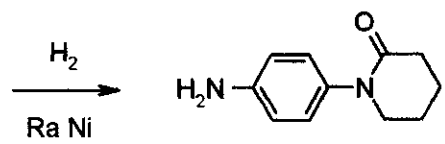
VI

For example, synthesis of 1-(4-amino-2-methylphenyl)piperidin-2-one:

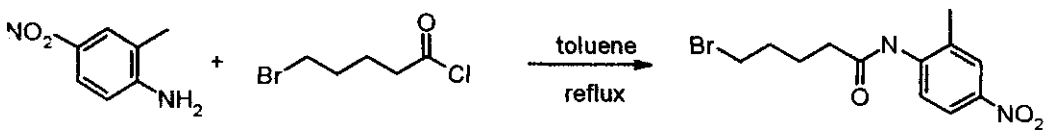


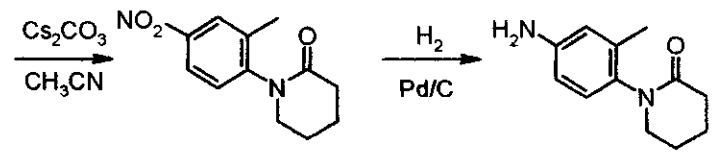
14.2 Synthesis of the phenylpiperidone unit without a methyl group:



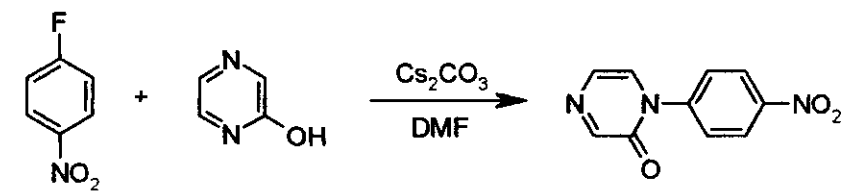


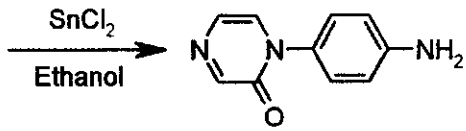
1-(4-Amino-2-methylphenyl)piperidin-2-one is prepared, for example, as indicated below:



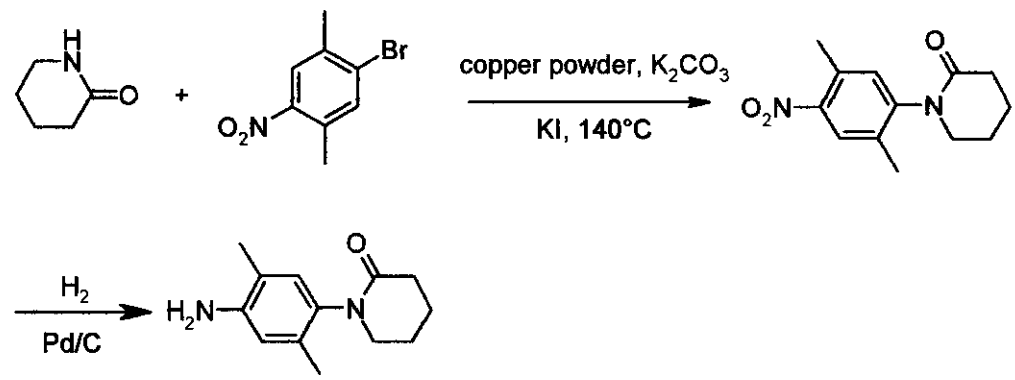


14.3 1-(4-Aminophenyl)-1*H*-pyrazin-2-one

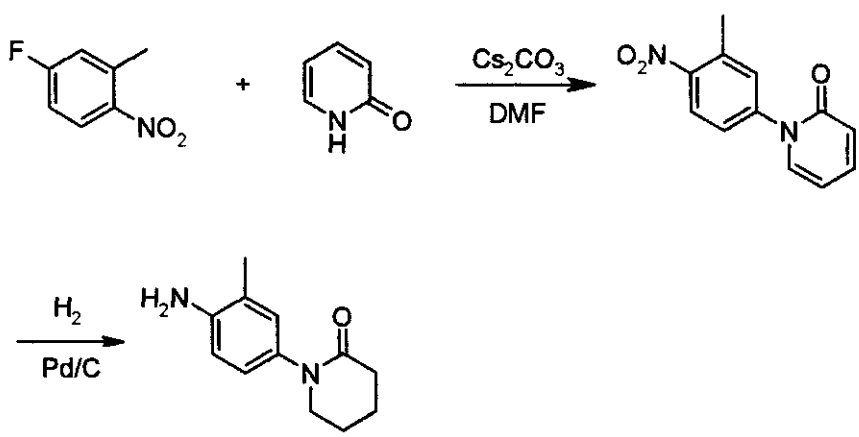




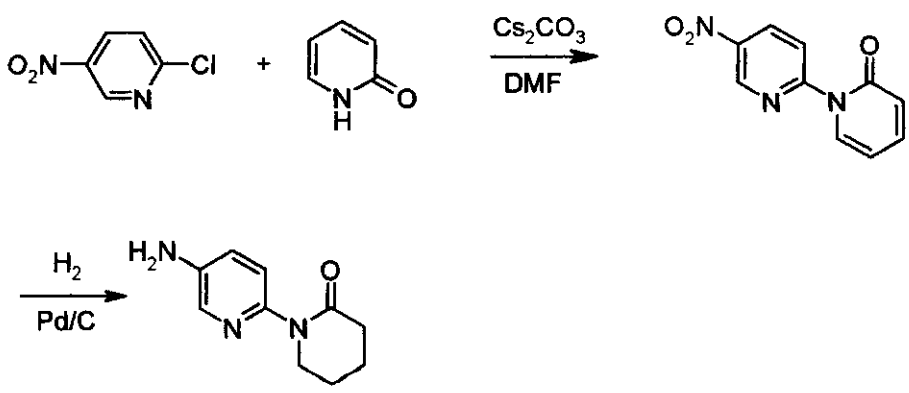
14.4 1-(4-Amino-2,5-dimethylphenyl)piperidin-2-one



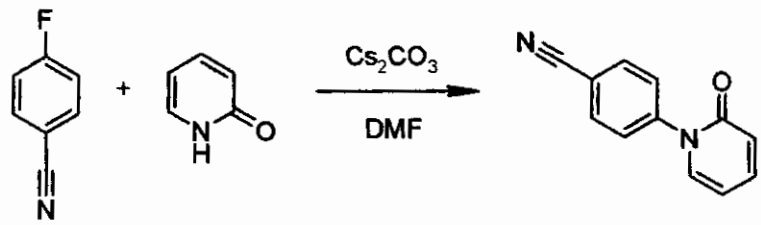
14.5 1-(4-Amino-3-methylphenyl)piperidin-2-one

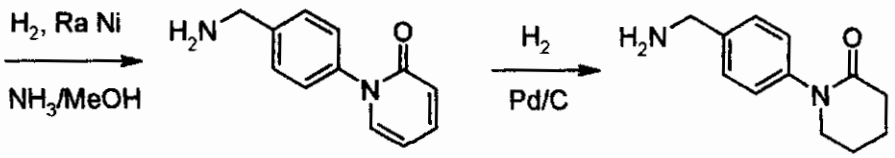


14.6 1-(5-Aminopyridin-2-yl)piperidin-2-one

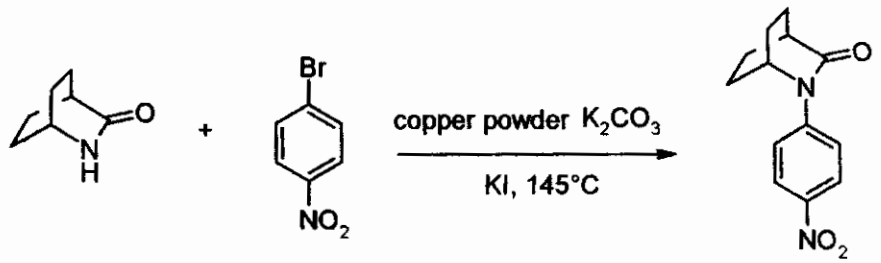


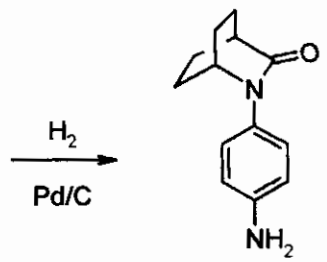
14.7 1-(4-Aminomethylphenyl)piperidin-2-one





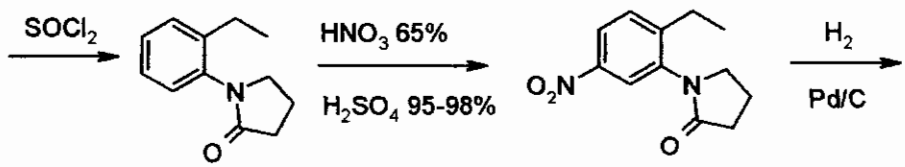
14.8 2-(4-Aminophenyl)-2-azabicyclo[2.2.2]octan-3-one

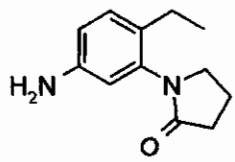




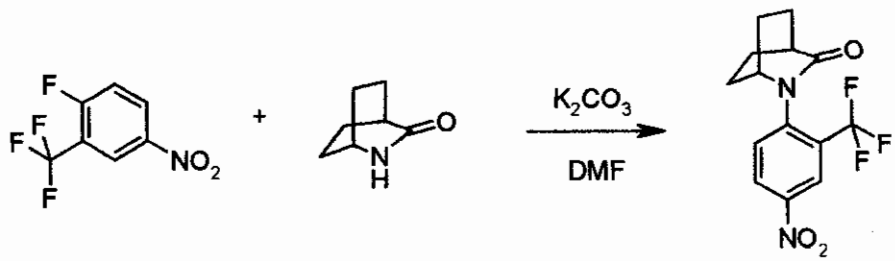
14.9 1-(3-Amino-6-ethylphenyl)pyrrolidin-2-one

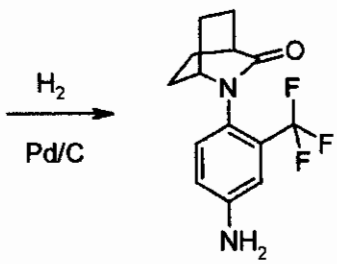




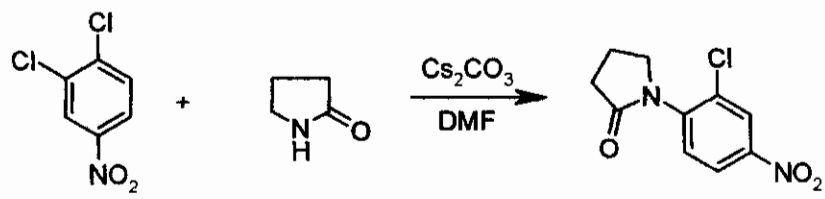


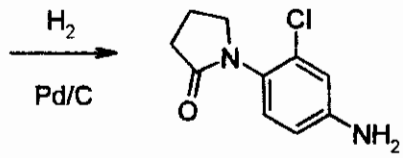
14.10 2-(4-Amino-2-trifluoromethylphenyl)-2-azabicyclo[2.2.2]octan-3-one



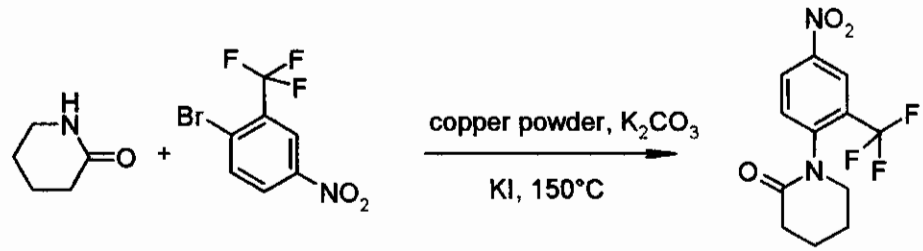


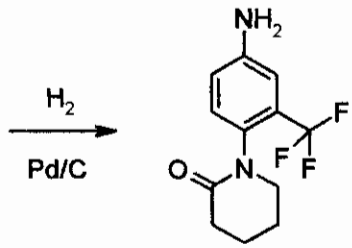
14.11 1-(4-Amino-3-chlorophenyl)pyrrolidin-2-one



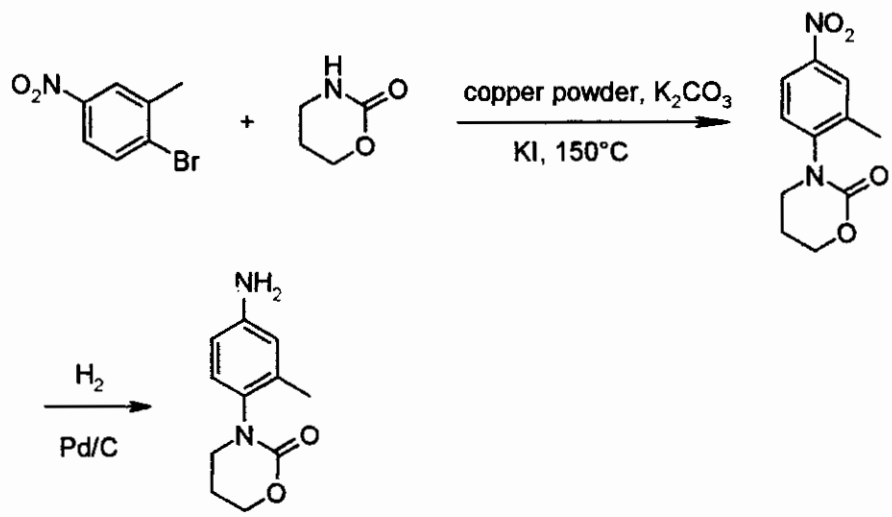


14.12 1-(4-Amino-2-trifluoromethylphenyl)piperidin-2-one

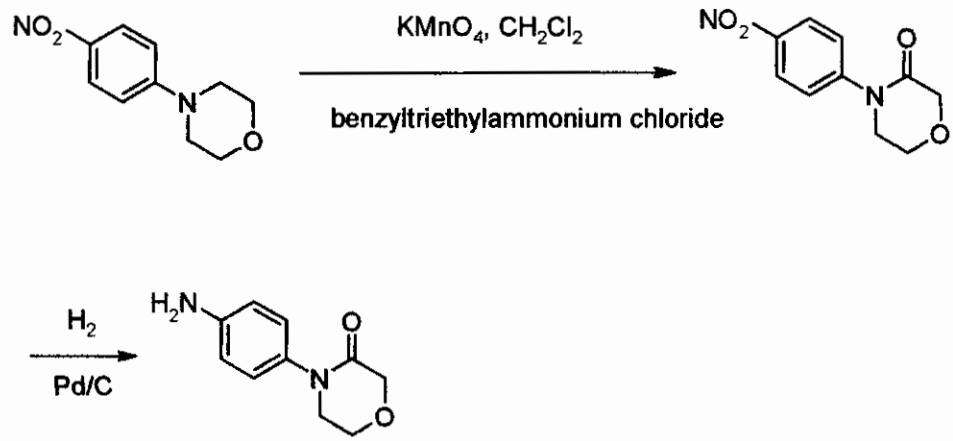




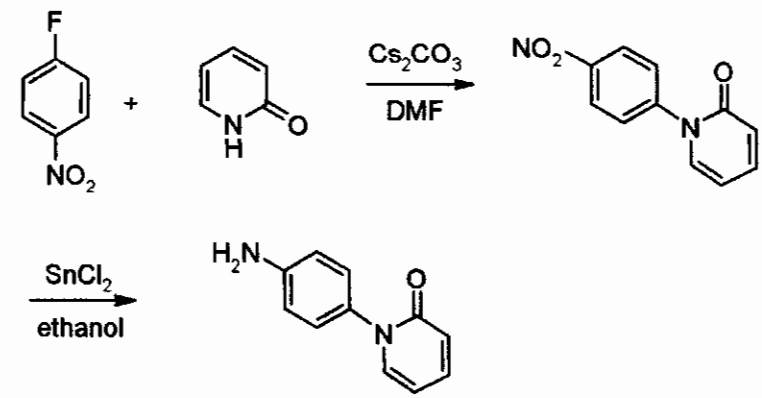
14.13 3-(4-Amino-2-methylphenyl)-1,3-oxazinan-2-one



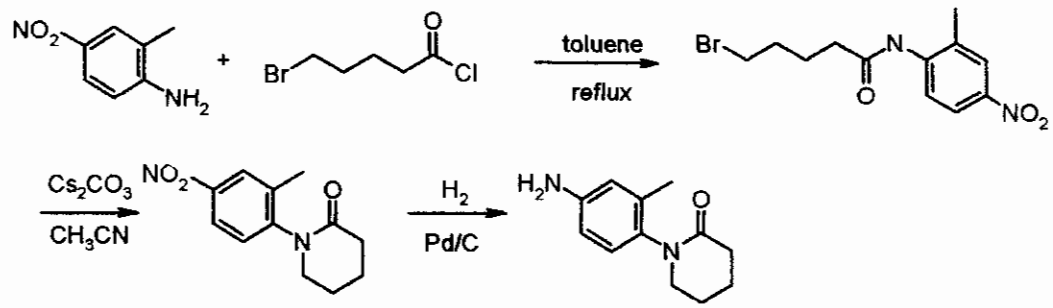
14.14 4-(4-Aminophenyl)morpholin-3-one



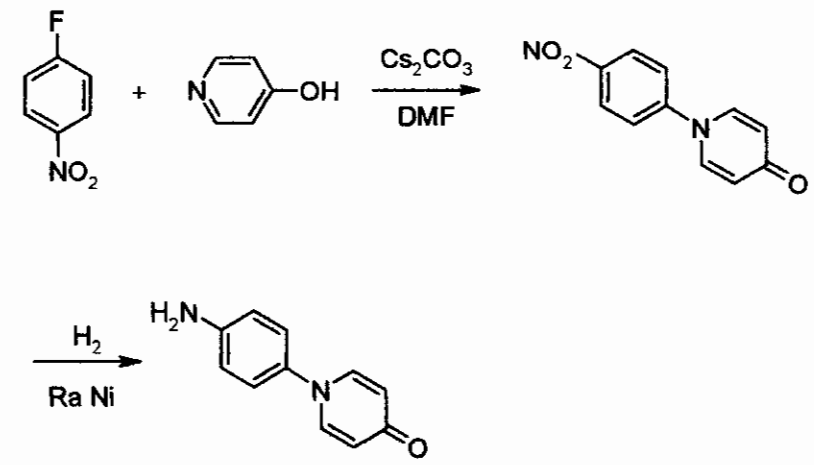
14.15 1-(4-Aminophenyl)pyridin-2-one



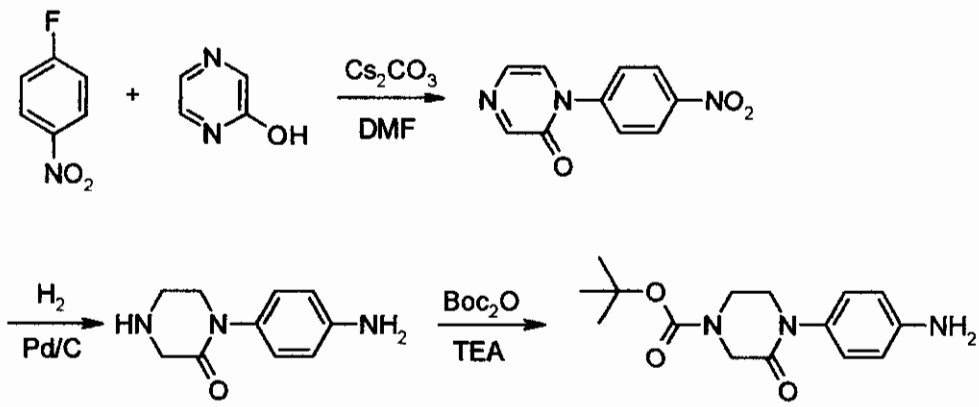
14.16 1-(4-Amino-2-methylphenyl)piperidin-2-one



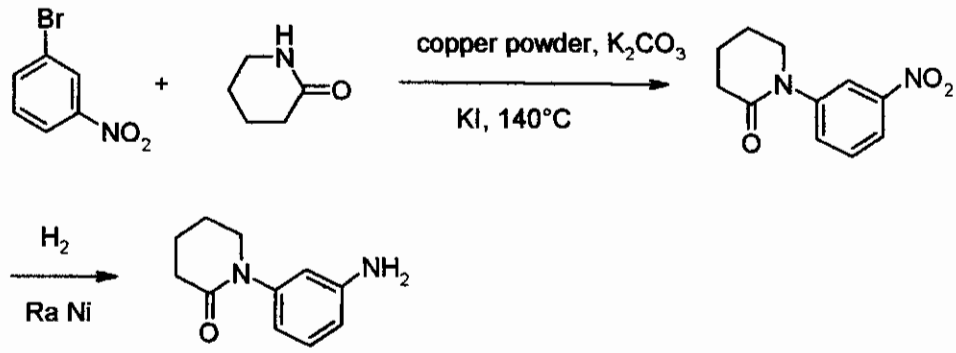
14.17 1-(4-Aminophenyl)-1*H*-pyridin-4-one



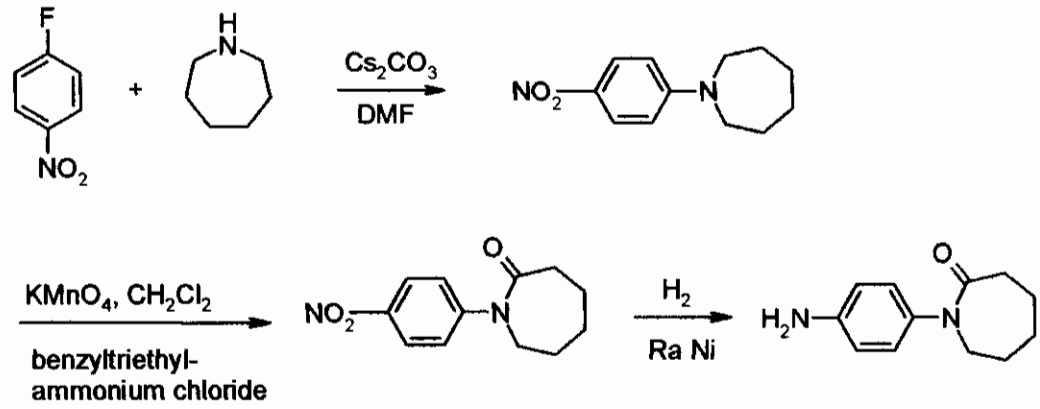
14.18 1-(4-Aminophenyl)-4-tert-butyloxycarbonylpiperazin-2-one



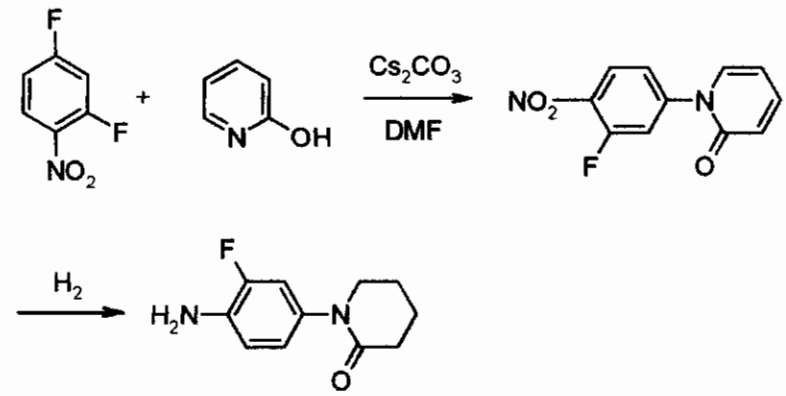
14.19 1-(3-Aminophenyl)piperidin-2-one



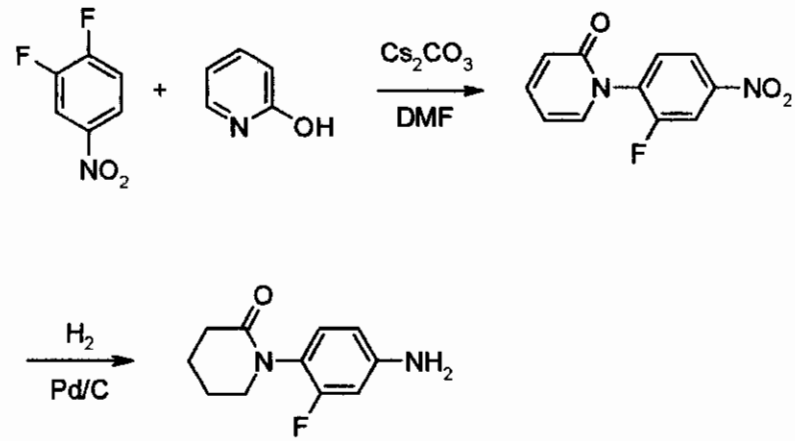
14.20 1-(4-Aminophenyl)-2-caprolactam



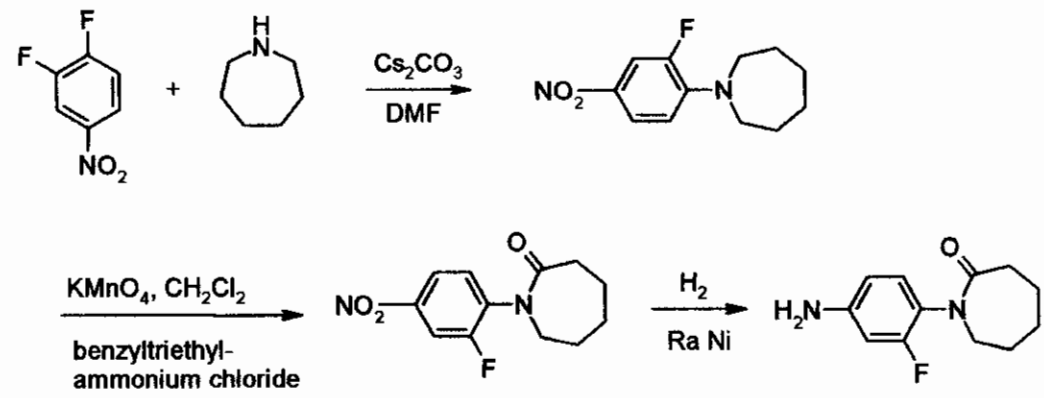
14.21 1-(4-Amino-3-fluorophenyl)piperidin-2-one



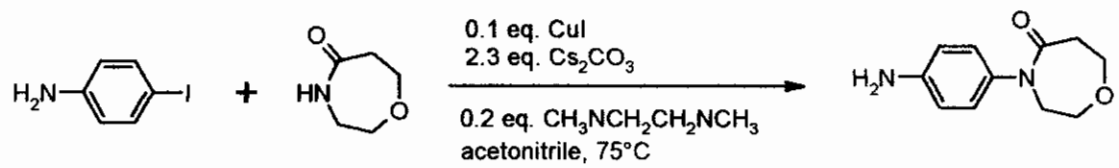
14.22 1-(4-Amino-2-fluorophenyl)piperidin-2-one



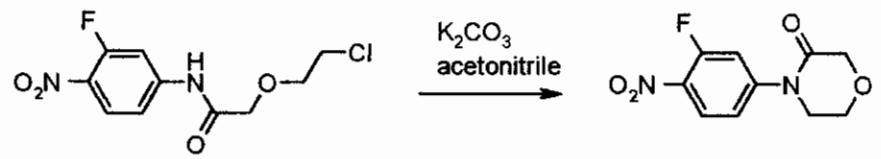
14.23 1-(4-Amino-2-fluorophenyl)-2-caprolactam

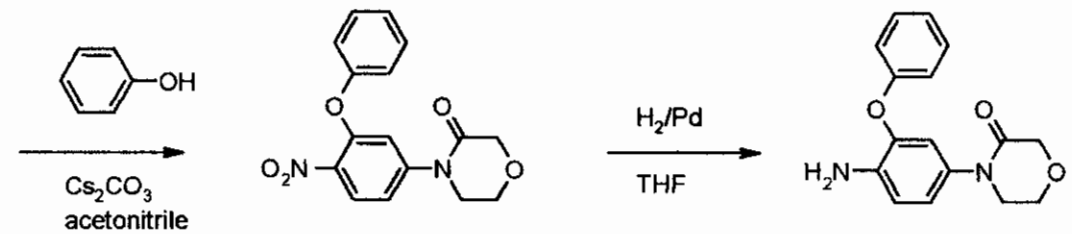


14.24 4-(4-Amino-2-fluorophenyl)-1,4-oxazepan-5-one

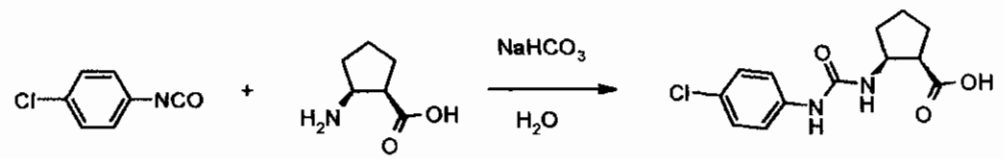


14.25 4-(4-Amino-3-phenoxyphenyl)morpholin-3-one

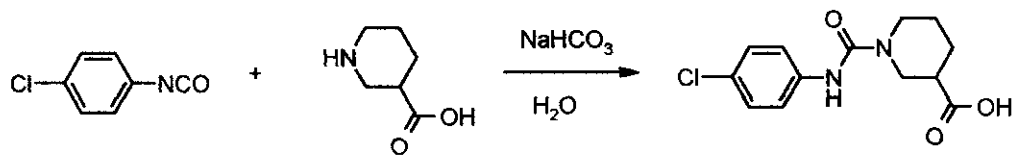




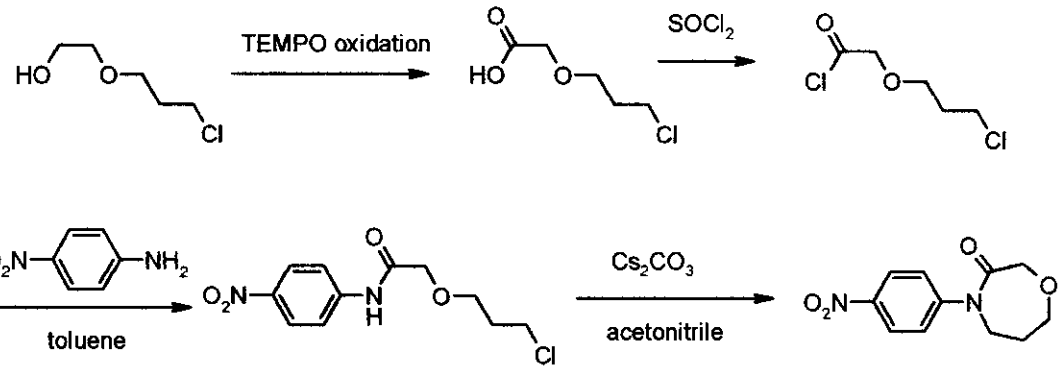
14.26 2-[3-(4-Chlorophenyl)ureido]cyclopentanecarboxylic acid



14.27 1-(4-Chlorophenylcarbamoyl)piperidine-3-carboxylic acid



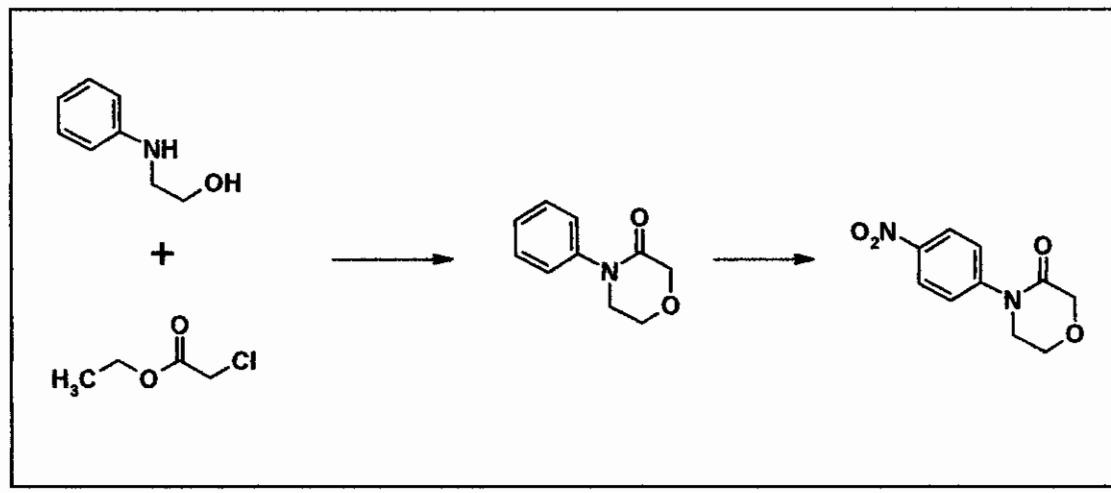
14.28 4-(4-Aminophenyl)-1,4-oxazepan-3-one



The TEMPO oxidation is carried out in accordance with the following literature:

L. DeLuca et al., J. Org. Chem. 68, 4999-5001 (2003).

14.29 Preparation of 4-(4-nitrophenyl)morpholin-3-one:



1. Preparation of 4-phenylmorpholin-3-one:

1.4 g (10 mmol) of N-phenylethanolamine are added dropwise to a solution of 1.12 g (10 mmol) of potassium *tert*-butoxide in 10 ml of THF. 1.27 g (10 mmol) of ethyl chloroacetate are subsequently added dropwise to the brown solution, and the mixture is stirred at room temperature for a number of hours. Extractive work-up and drying under reduced pressure gives 1.4 g of 4-phenylmorpholin-3-one as crude product.

2. Preparation of 4-(4-nitrophenyl)morpholin-3-one:

0.6 ml of concentrated nitric acid are added dropwise with ice cooling to a solution of 1 g (5.64 mmol) of 4-phenylmorpholin-3-one in 2 ml of concentrated sulfuric acid, and the mixture is stirred at room temperature for a further 1 hour. Aqueous work-up and drying gives 1.2 g of yellow 4-(4-nitrophenyl)morpholin-3-one.

Pharmacological data

Affinity to receptors

Table 1

Compound No.	FXa-IC_{50} [M]
"A1"	1.8×10^{-8}
"A2"	2.7×10^{-8}
"AB1"	1.8×10^{-6}
"A6"	3.7×10^{-9}

The following examples relate to pharmaceutical compositions:

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 g of an active ingredient 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 ingredient.

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active ingredient 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 ingredient 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 to give tablets in a conventional manner in such a way that each tablet contains 10 mg of active ingredient.

Example F: Coated tablets

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

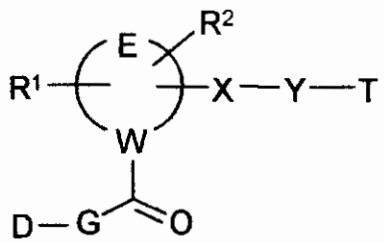
2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Patent Claims

1. Use of compounds of the formula I



I

in which

R^1 and R^2 each, independently of one another, denote H, =O, Hal, A, ethynyl, OR^3, $N(R^3)_2$, NO_2, CN, N_3, $COOR^3$, $CON(R^3)_2$, $-[C(R^4)_2]_n$-Ar, $-[C(R^4)_2]_n$-Het, $-[C(R^4)_2]_n$-cycloalkyl, $-OCOR^3$, $-OCON(R^3)_2$, NR^3COA or NR^3SO_2A,

R^1 and R^2 together also denote a bicyclically or spirocyclically bonded 3- to 7-membered carbocyclic or heterocyclic ring having 0 to 3 N, O and/or S atoms,

R^3 denotes H, A, H-C≡C-CH_2-, CH_3-C≡C-CH_2-, -CH_2-CH(OH)-CH_2OH, -CH_2-CH(OH)-CH_2NH_2, -CH_2-CH(OH)-CH_2Het', $-[C(R^4)_2]_n$-Ar', $-[C(R^4)_2]_n$-Het', $-[C(R^4)_2]_n$-cycloalkyl, $-[C(R^4)_2]_n$-COOA or $-[C(R^4)_2]_nN(R^4)_2$,

R^4 denotes H or A,

W denotes N, CR^3 or an sp^2-hybridised carbon atom,

E together with W denotes a 3- to 7-membered saturated carbocyclic or heterocyclic ring having 0 to 3 N, 0 to 2 O and/or 0 to 2 S atoms,
which may contain a double bond,

D denotes a monocyclic or bicyclic, aromatic carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or polysubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$ or $CON(R^3)_2$,

G	denotes $-[C(R^4)_2]_n-$, $-[C(R^4)_2]_nNR^3-$, $-[C(R^4)_2]_nO-$, $-[C(R^4)_2]_nS-$ or $-[C(R^4)=C(R^4)]_n-$,
X	denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n-$, $-[C(R^4)_2]_nNR^3CO[C(R^4)_2]_n-$, $-[C(R^4)_2]_nNR^3[C(R^4)_2]_n-$, $-[C(R^4)_2]_nO[C(R^4)_2]_n-$, $-[C(R^4)_2]_nCO[C(R^4)_2]_n-$ or $-[C(R^4)_2]_nCOO[C(R^4)_2]_n-$,
Y	denotes alkylene, cycloalkylene, Het-diyl or Ar-diyl,
T	denotes a monocyclic or bicyclic, saturated or unsaturated carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is monosubstituted or disubstituted by =O, =S, $=NR^3$, =N-CN, $=N-NO_2$, $=NOR^3$, $=NCOR^3$, $=NCOOR^3$ or $=NOCOR^3$ and may furthermore be monosubstituted, disubstituted or trisubstituted by R^3, Hal, A, $-[C(R^4)_2]_n-Ar$, $-[C(R^4)_2]_n-Het$, $-[C(R^4)_2]_n-cycloalkyl$, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, $NR^3CON(R^3)_2$, NR^3SO_2A, COR^3, SO_2NR^3 and/or $S(O)_nA$,
A	denotes unbranched or branched alkyl having 1-10 carbon atoms in which one or two CH_2 groups may be replaced by O or S atoms and/or by -CH=CH- groups and/or in addition 1-7 H atoms may be replaced by F,
Ar	denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, $NR^3CON(R^3)_2$, NR^3SO_2A, COR^3, $SO_2N(R^3)_2$, $S(O)_nA$, $-[C(R^4)_2]_n-COOR^3$ or $-O[C(R^4)_2]_o-COOR^3$,
Ar'	denotes phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^4, $N(R^4)_2$, NO_2, CN, $COOR^4$, $CON(R^4)_2$, NR^4COA, $NR^4CON(R^4)_2$, NR^4SO_2A, COR^4, $SO_2N(R^4)_2$, $S(O)_nA$, $-[C(R^4)_2]_n-COOR^4$ or $-O[C(R^4)_2]_o-COOR^4$,

Het denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 N, O and/or S atoms which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, -[C(R^4)$_2$]$_n$-Ar, -[C(R^4)$_2$]$_n$-Het', -[C(R^4)$_2$]$_n$-cycloalkyl, OR^3, N(R^3)$_2$, $NR^3CON(R^3)_2$, NO_2, CN, -[C(R^4)$_2$]$_n$-$COOR^3$, -[C(R^4)$_2$]$_n$-$CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, S(O)$_m$A and/or carbonyl oxygen,

Het' denotes a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic ring having 1 to 4 N, O and/or S atoms which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, =S, =N(R^4)$_2$, Hal, A, OR^4, N(R^4)$_2$, NO_2, CN, $COOR^4$, $CON(R^4)_2$, NR^4COA, $NR^4CON(R^4)_2$, NR^4SO_2A, COR^4, SO_2NR^4 and/or S(O)$_n$A,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

o denotes 1, 2 or 3,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios,

for the preparation of a medicament for the prevention and treatment of thromboembolic diseases and/or thromboses as a consequence of surgery, genetically caused diseases with increased thrombophilia, diseases of the arterial and venous vascular system, cardiac insufficiency, atrial fibrillation, thrombophilia, tinnitus and/or sepsis.

2. Use according to Claim 1, where the surgery is selected from the group

thorax operations, operations in the abdominal region, orthopaedic interventions, hip and knee joint replacement, CABG (coronary artery bypass grafting), artificial heart valve replacement, operations using

a heart-lung machine, vascular surgery, organ transplants and use of central vein catheters.

3. Use according to Claim 1 or 2 of compounds according to Claim 1 in which

D denotes a monocyclic or bicyclic, aromatic carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or disubstituted by Hal,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

4. Use of compounds according to one or more of Claims 1-3 in which

D denotes phenyl, pyridyl, thienyl, furyl or imidazolyl, each of which is monosubstituted or disubstituted by Hal,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

5. Use of compounds according to one or more of Claims 1-4 in which

R^1 and R^2 each, independently of one another, denote H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

6. Use of compounds according to one or more of Claims 1-5 in which

G denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

7. Use of compounds according to one or more of Claims 1-6 in which

X denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n-$,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

8. Use of compounds according to one or more of Claims 1-7 in which

X denotes -CONH- or $-CON(CH_2COOA)-$,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

9. Use of compounds according to one or more of Claims 1-8 in which

Y denotes cycloalkylene, Het-diyl or Ar-diyl,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

10. Use of compounds according to one or more of Claims 1-9 in which

Y denotes pyridinediyl, piperidinediyl, cyclohexylene, or phenylene which is unsubstituted or monosubstituted or disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

11. Use of compounds according to one or more of Claims 1-10 in which

T denotes a monocyclic, saturated or unsaturated heterocyclic ring having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by =O, =S or =NH and may be monosubstituted or disubstituted by Hal, A and/or OA,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

12. Use of compounds according to one or more of Claims 1-11 in which

T denotes piperidin-1-yl, pyrrolidin-1-yl, pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl, 2-azabicyclo[2.2.2]octan-2-yl, imidazolidinyl, thiazolyl or 1,4-oxazepanyl, each of which is monosubstituted or disubstituted by =O or =NH and where the radicals may also be monosubstituted or disubstituted by Hal, A and/or OA,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

13. Use of compounds according to one or more of Claims 1-12 in which

Ar denotes phenyl which is unsubstituted or monosubstituted or disubstituted by Hal, A, OA, SO_2A, $COOR^2$, SO_2NH_2, CN, COOA, COOH or phenoxy,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

14. Use of compounds according to one or more of Claims 1-13 in which

D denotes a monocyclic or bicyclic, aromatic carbocyclic or heterocyclic ring having 0 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or disubstituted by Hal,

R^1 and R^2 each, independently of one another, denote H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H, A, phenyl, benzyl or $[C(R^4)_2]_nCOOA$,

R^4 denotes H or A,

W denotes N, CR^3 or an sp^2-hybridised carbon atom,

E together with W denotes a 3- to 7-membered saturated carbocyclic or heterocyclic ring having 0 to 3 N, 0 to 2 O and/or 0 to 2 S atoms, which may contain a double bond,

G denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-,

X denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n$-,

Y denotes cycloalkylene, Het-diyl or Ar-diyl,

Ar denotes phenyl which is unsubstituted or monosubstituted or disubstituted by Hal, A, OA, SO_2A, $COOR^2$, SO_2NH_2, CN, COOA, COOH or phenoxy,

T denotes a monocyclic, saturated or unsaturated heterocyclic ring having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by =O, =S or =NH and may be monosubstituted or disubstituted by Hal, A and/or OA,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

15. Use of compounds according to one or more of Claims 1-14 in which

D denotes phenyl, pyridyl, thienyl, furyl or imidazolyl, each of which is monosubstituted or disubstituted by Hal,

R^1 and R^2 each, independently of one another, denote H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH,

R^1 and R^2	together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,
R^3	denotes H, A or CH_2COOA,
R^4	denotes H or A,
W	denotes N, CR^3 or an sp^2-hybridised carbon atom,
E	together with W denotes a 3- to 7-membered saturated carbocyclic or heterocyclic ring having 0 to 3 N, 0 to 2 O and/or 0 to 2 S atoms, which may contain a double bond,
G	denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-,
X	denotes -CONH- or -CON(CH_2COOA)-,
Y	denotes pyridinediyl, piperidinediyl, cyclohexylene, or phenylene which is unsubstituted or monosubstituted or disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl,
T	denotes piperidin-1-yl, pyrrolidin-1-yl, pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl, 2-azabicyclo[2.2.2]-octan-2-yl, imidazolidinyl, thiazolyl or 1,4-oxazepanyl, each of which is monosubstituted or disubstituted by =O or =NH and where the radicals may also be monosubstituted or disubstituted by Hal, A and/or OA,
A	denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,
Hal	denotes F, Cl, Br or I,
n	denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

16. Use of compounds according to one or more of Claims 1-15 in which

D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

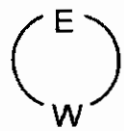
R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA or $NHSO_2A$,

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_nNH$-,

X denotes CONH,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes piperidin-1-yl, pyrrolidin-1-yl, 1*H*-pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, 2*H*-pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl or 2-aza-bicyclo[2.2.2]octan-2-yl, each of which is monosubstituted or disubstituted by carbonyl oxygen,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

17. Use of compounds according to one or more of Claims 1-16 in which

D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

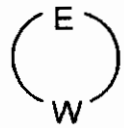
R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA or $NHSO_2A$,

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_nNH$-,

X denotes CONH,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2;

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

18. Use of compounds according to one or more of Claims 1-17 in which

X denotes $-[C(R^4)_2]_nCONR^3[C(R^4)_2]_n-$ or $-[C(R^4)_2]_nCO[C(R^4)_2]_n-$,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

19. Use of compounds according to one or more of Claims 1-18 in which

X denotes CONH or $COCH_2$,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

20. Use of compounds according to one or more of Claims 1-19 in which

D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

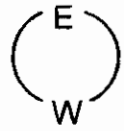
R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, $-OCOR^3$, NHCOA or $NHSO_2A$,

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_nNH$-,

X denotes CONH or $COCH_2$,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

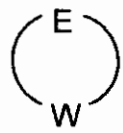
n denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

21. Use of compounds according to one or more of Claims 1-20 in which

D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy,

		-$OCOR^3$, NHCOA, $NHSO_2A$, H-C≡C-CH_2-, CH_3-C≡C-CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2 or -O-CH_2-CH(OH)-CH_2Het',
	R^2	denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,
	R^1 and R^2	together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,
	R^3	denotes H or A,
	R^4	denotes H or A,
		denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,
	G	denotes $(CH_2)_n$ or $(CH_2)_n$NH-,
	X	denotes CONH or $COCH_2$,
	Y	denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,
	T	denotes morpholin-4-yl which is monosubstituted or disubstituted by carbonyl oxygen,
	Het'	denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, A, OH, NH_2, NO_2, CN, COOA or $CONH_2$,
	A	denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,
	Hal	denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

22. Use of compounds according to one or more of Claims 1-21 in which

D denotes phenyl, pyridyl or thienyl, each of which is monosubstituted or disubstituted by Hal,

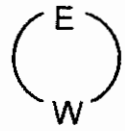
R^1 denotes ethynyl, vinyl, allyloxy, CH_3-C≡C-CH_2-O-, -O-CH_2-CH(OH)-CH_2OH, -O-CH_2-CH(OH)-CH_2NH_2 or -O-CH_2-CH(OH)-CH_2Het',

R^2 denotes H or OH,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazinane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$ or $(CH_2)_n$NH-,

X denotes CONH, CO, COO or $COCH_2$,

Y denotes 1,3- or 1,4-phenylene which is unsubstituted or monosubstituted or disubstituted by methyl, trifluoromethyl, ethyl, propyl, Cl or F,

T denotes piperidin-1-yl, pyrrolidin-1-yl, 1*H*-pyridin-1-yl, morpholin-4-yl, piperazin-1-yl, 1,3-oxazolidin-3-yl, 2*H*-pyridazin-2-yl, pyrazin-1-yl, azepan-1-yl or

2-azabicyclo[2.2.2]octan-2-yl, each of which is monosubstituted or disubstituted by carbonyl oxygen or OA,

Het' denotes a saturated 3-6-membered heterocyclic ring having 1 to 3 N and/or O atoms, which may be unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, Hal, A, OH, NH_2, NO_2, CN, COOA or $CONH_2$,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

23. Use of compounds according to one or more of Claims 1-22 in which

D denotes phenyl, pyridyl, thienyl, furyl or imidazolyl, each of which is monosubstituted or disubstituted by Hal,

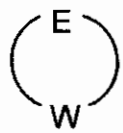
R^1 denotes H, =O, $COOR^3$, OH, OA, NH_2, alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, N_3, ethynyl, vinyl, allyloxy, NHCOA, $NHSO_2A$, OCH_2COOA or OCH_2COOH,

R^2 denotes H, =O, OH, OA or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

R^1 and R^2 together also denote a spirocyclically bonded 3- to 6-membered carbocyclic ring,

R^3 denotes H or A,

R^4 denotes H or A,



denotes pyrrolidine-1,2-diyl, piperidine-1,2-diyl, oxazolidine-3,4- or -3,5-diyl, thiazolidine-3,4-diyl, 2,5-dihydro-1*H*-pyrrole-1,5-diyl, 1,3-dioxolane-4,5-diyl, 1,3-oxazi-

nane-3,4-diyl, piperazine-1,4-diyl, tetrahydrofuran-3,4-diyl or azetidine-1,2-diyl,

G denotes $(CH_2)_n$, $(CH_2)_nNH$-, -CH=CH- or -CH=CH-CH=CH-,

X denotes CONH, $COCH_2$ or -CON(CH_2COOA)-,

Y denotes pyridinediyl, piperidinediyl, cyclohexylene, or phenylene which is unsubstituted or monosubstituted or disubstituted by A, OA, Cl, F, $COOCH_3$, COOH, phenoxy or aminocarbonyl,

T denotes morpholin-4-yl which is monosubstituted or di-substituted by carbonyl oxygen,

A denotes unbranched or branched alkyl having 1-10 carbon atoms and in which 1-7 H atoms may be replaced by F,

Hal denotes F, Cl, Br or I,

n denotes 0, 1 or 2,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

24. Use according to Claim 1 or 2 of compounds according to Claim 1 selected from the group

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-trifluoromethyl-4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-piperidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(R)-1-(5-chlorothiophene-2-carbonyl)pyrrolidine-2-carboxamide,

N-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]-(R)-1-(5-chloro-thiophene-2-carbonyl)pyrrolidine-2-carboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-oxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyridin-1-yl)phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[3-chloro-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(4R,5R)-5-methyloxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyrazin-1-yl)phenyl]}-(4R,5S)-5-methyloxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyrazin-1-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[3-chloro-4-(2-oxo-2H-pyridin-1-yl)phenyl]}-(R)-oxazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-thiazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-1,1-dioxo-1λ^6-thiazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(S)-thiazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(S)-1,1-dioxo-1λ^6-thiazolidine-3,4-dicarboxamide,

N-3-[(4-chlorophenyl)]-N'-4-{[4-(2-oxo-2H-pyridin-1-yl)-phenyl]}-(R)-thiazolidine-3,4-dicarboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxamide,

N-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]-3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxamide,

N-[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]-3-(5-chlorothiophene-2-carbonyl)oxazolidine-5-carboxamide,

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(2-oxo-2H-pyrazin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(5-chloropyridin-2-yl)]-2-N-{[3-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(R)-4,4-dimethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(5-chloropyridin-2-yl)]-2-N-{[4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-4,4-dimethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2H-pyridin-1-yl)phenyl]}-(R)-4,4-dimethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxopyrazin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,3R)-3-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,3S)-3-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-3,4-dihydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-azidopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-aminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-azidopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-aminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-acetaminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-acetaminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-methylsulfonylaminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methylsulfonylaminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-propoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-allyloxypyrrolidine-1,2-dicarboxamide,

(3R,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl isobutyrate,

(3R,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl propionate,

(3R,5R)-1-(4-chlorophenylcarbamoyl)-5-[4-(3-oxomorpholin-4-yl)phenylcarbamoyl]pyrrolidin-3-yl acetate,

N-4-[(4-chlorophenyl)]-N'-5-{[4-(3-oxomorpholin-4-yl)phenyl]}-1,3-dioxolane-4,5-dicarboxamide,

N-4-[(4-chlorophenyl)]-N'-5-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-1,3-dioxolane-4,5-dicarboxamide,

N-4-[(4-chlorophenyl)]-N'-5-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-1,3-dioxolane-4,5-dicarboxamide,

N-4-[(4-chlorophenyl)]-N'-5-{[4-(3-oxomorpholin-4-yl)phenyl]}-1,3-dioxolane-2,2-dimethyl-4,5-dicarboxamide,

N-4-[(4-chlorophenyl)]-N'-5-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-1,3-dioxolane-2,2-dimethyl-4,5-dicarboxamide,

N-4-[(4-chlorophenyl)]-N'-5-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-1,3-dioxolane-2,2-dimethyl-4,5-dicarboxamide,

1-N-[4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-1-BOC-piperazine-1,2-dicarboxamide,

1-N-[4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-piperazine-1,2-dicarboxamide,

1-N-[4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-1,3-oxazinane-3,4-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-ethynyl-4-hydroxypyrrolidine-1,2-dicarboxamide,

N-6-[(4-chlorophenyl)]-N'-7-{[4-(3-oxomorpholin-4-yl)phenyl]}-4-oxa-6-azaspiro[2.4]heptane-6,7-dicarboxamide,

1-N-[(6-chloropyridin-3-yl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(6-chloropyridin-3-yl)]-2-N-{[4-(2-oxo-2H-pyrazin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-acetaminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-butylsulfonylaminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-4-oxopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-aminopyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(S)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[2-(4-chloro-phenyl)acetyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-(4-chlorobenzoyl)-4-hydroxypyrrolidine-2-carboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-(2-methylpropanoylamino)pyrrolidine-1,2-dicarboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-(1-1*H*-indol-3-yl-methanoyl)-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-(1-1*H*-indol-6-yl-methanoyl)-4-hydroxypyrrolidine-2-carboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-(2R,4S)-4-ethynyl-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(2R,4S)-4-ethynyl-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyridin-1-yl)phenyl]}-4,4-difluoro-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(2-oxo-2*H*-pyridin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

2-N-[(4-chlorophenyl)]-1-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

2-N-[(4-chlorophenyl)]-1-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(S)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-3-methoxy-2*H*-pyridin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-3-methoxy-2*H*-pyridin-1-yl)phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

N-(4-chlorophenyl)-(R)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]-acetyl}pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(S)-1-{2-[4-(3-oxomorpholin-4-yl)phenyl]-acetyl}pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-1-{2-[4-(3-oxomorpholin-4-yl)-phenyl]acetyl}-4-methoxypyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(2R,4S)-1-{2-[4-(3-oxomorpholin-4-yl)-phenyl]acetyl}-4-methoxypyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(2S,4R)-1-{2-[4-(3-oxomorpholin-4-yl)-phenyl]acetyl}-4-methoxypyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(S)-1-{2-[4-(2-oxo-1H-pyridin-1-yl)phenyl]-acetyl}pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(S)-1-{2-[4-(2-oxopyrrolidin-1-yl)phenyl]-acetyl}pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(R)-1-{2-[4-(2-oxopyrrolidin-1-yl)phenyl]-acetyl}pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(R)-1-[4-(2-oxopiperidin-1-yl)benzoyl]pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(R)-1-[4-(2-oxopiperidin-1-yl)phenyloxycarbonyl]pyrrolidine-2-carboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-2*H*-pyrazin-1-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(prop-2-ynyloxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(but-2-ynyloxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,3-dihydroxypropoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2-hydroxy-3-pyrrolidin-1-ylpropoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2-oxooxazolidin-5-ylmethoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(3-amino-2-hydroxypropoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyrazin-1-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-oxo-1*H*-pyridin-1-yl)phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(R)-2,5-dihydropyrrole-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,3S)-3-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-methoxycarbonyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-3-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-carboxy-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-3-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,3S,4R)-3,4-dihydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-allyloxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-(prop-2-ynyloxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4S)-4-(prop-2-ynyloxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(methoxycarbonylmethoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(carboxymethoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-bromophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-(2,3-dihydroxypropoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{N-methoxycarbonylmethyl-N'-[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)cyclohexan-1-yl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-iminopyrrolidin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[3-methyl-4-(2-iminopyrrolidin-1-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[4-{2-[(E)-cyanimino]imidazolidin-1-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methylthiazol-3-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-aminocarbonyl-4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxy-2-methylpyrrolidine-1,2-dicarboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-thiophen-3-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(2E,4E)-5-phenylpenta-2,4-dienyloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-methylfuran-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-thiophen-2-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-chlorophenyl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(3,4-dichlorophenyl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorofuran-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-chlorothiophen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[2-fluoro-4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-3-ylacryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-4-ylacryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-pyridin-4-ylacryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-1*H*-imidazol-4-ylacryloyl]-4-methoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-bromothiophen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(4-bromothiophen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-bromothiophen-2-yl)acryloyl]-4-hydroxypyrrolidine-2-carboxamide,

N-[4-(3-oxomorpholin-4-yl)phenyl]-(2R,4R)-1-[(E)-3-(5-bromothiophen-2-yl)acryloyl]-4-ethoxypyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(R)-1-[4-(2-oxopiperidin-1-yl)benzoyl]pyrrolidine-2-carboxamide,

N-(4-chlorophenyl)-(S)-1-[4-(2-oxopiperidin-1-yl)benzoyl]pyrrolidine-2-carboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(5-oxo-1,4-oxazepan-4-yl)-phenyl]}-(R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(5-oxo-1,4-oxazepan-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-((S)-2-methyl-3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-((S)-2-methyl-3-oxomorpholin-4-yl)phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-((R)-2-methyl-3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-((R)-2-methyl-3-oxomorpholin-4-yl)phenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)-2-phenoxyphenyl]}-(2R)-pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-fluoro-4-((R)-2-methyl-3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-N'-3-{[4-(3-oxomorpholin-4-yl)phenyl]}-piperidine-1,3-dicarboxamide,

1-N-[(4-chlorophenyl)]-N'-3-{[3-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}piperidine-1,3-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2-methoxyethoxy)pyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxo-1,4-oxazepan-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-methyl-4-(3-oxomorpholin-4-yl)-phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

25. Use according to Claim 1 or 2 of pyrrolidinecarboxylic acid derivatives according to Claim 1 selected from the group

1-N-[(4-chlorophenyl)]-2-N-[(1'-methyl-[1,4']bipiperidinyl-4-yl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(3,4,5,6-tetrahydro-2*H*-1,4'-bipyridinyl-4-yl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(3,4,5,6-tetrahydro-2H-1,4'-bipyridinyl-4-yl)-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-(4-pyridin-4-ylpiperazine-1-carbonyl)pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-(2-methoxyphenyl)-piperazine-1-carbonyl]pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4-fluorophenyl)piperazine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carbonyl]pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-(4-pyridin-2-ylpiperazine-1-carbonyl)pyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4-ethylpiperazin-1-yl)piperidine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-2-[4-(4,6-dimethylpyrimidin-2-yl)-piperazine-1-carbonyl]-4-hydroxypyrrolidine-1-carboxamide,

N-(4-chlorophenyl)-(2R,4R)-4-hydroxy-2-[4-(1-methylpiperidin-4-yl)piperazine-1-carbonyl]pyrrolidine-1-carboxamide,

1-N-[(4-chlorophenyl)]-2-N-{[2-(2-dimethylaminoethoxy)-4-morpholin-4-ylphenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(2-ethoxy-4-morpholin-4-ylphenyl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

1-N-[(4-chlorophenyl)]-2-N-[(4-morpholin-4-yl-2-propoxyphenyl)]-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

26. Use according to Claim 1 or 2 of cyclopentanecarboxylic acid derivatives according to Claim 1 selected from the group

N-[4-(3-oxomorpholin-4-yl)phenyl]-(rac)-2-[3-(4-chlorophenyl)-ureido]cyclopentanecarboxamide,

N-[3-methyl-4-(3-oxomorpholin-4-yl)phenyl]-(rac)-2-[3-(4-chlorophenyl)ureido]cyclopentanecarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

27. Use according to Claim 1 or 2 of 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide,
and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

28. Use of compounds according to one or more of Claims 1-27, in combination with at least one further medicament active ingredient.

29. Use according to Claim 28, where the further medicament active ingredients are selected from the group the
antithrombotics,
antiarrhythmics,
contraceptives,
phosphodiesterase V inhibitors.

30. Use according to Claim 29, in which the antithrombotic is selected from the group of the vitamin K antagonists, heparin compounds, thrombocyte aggregation inhibitors, enzymes, other antithrombotic agents, blood platelet glycoprotein receptor (IIb/IIIa) antagonists, thromboxane antagonists, thrombocyte adhesion inhibitors.

31. Use according to Claim 30, where the vitamin K antagonists are selected from the group dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione, tioclomarol.

32. Use according to Claim 30, where the heparin compounds are selected from the group heparin, antithrombin III, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, danaparoid, tinzaparin, sulodexide.

33. Use according to Claim 30, where the thrombocyte aggregation inhibitors are selected from the group ditazole, cloricromen, picotamide, clopidogrel, ticlopidine, acetylsalicylic acid, dipyridamole, calcium carbassalate, epoprostenol, indobufen, iloprost, abciximab, tirofiban, aloxiprin, intrifiban.

34. Use according to Claim 30, where the enzymes are selected from the group streptokinase, alteplase, anistreplase, urokinase, fibrinolysin, brinase, reteplase, saruplase.

35. Use according to Claim 30, where other antithrombotic agents are selected from the group defibrotide, desirudin, lepirudin.

36. Use according to Claim 30, where the thromboxane antagonists are selected from the group ramatroban, equalen sodium, seratrodast.

37. Use according to Claim 29, where the antiarrhythmics are selected from the group

a) chinidin, disopyramide, ajmaline, detajmium,

b) lidocaine, mexiletine, phenytoin, tocainide,

c) propafenone, flecainide,

d) metoprolol, esmolol, propranolol, atenolol, oxprenolol,

e) amiodarone, sotalol,

f) diltiazem, verapamil, gallopamil,

g) adenosine, orciprenaline, ipratropium,

h) cardiac glycosides.

38. Use according to Claim 29, where the contraceptives are selected from the group
desogestrel, medroxyprogesterone acetate, levonorgestrel, etonogestrel, norethisterone enantate.

39. Use according to Claim 29, where the PDE V inhibitors are selected from the group

a) sildenafil, tadalafil, vardenafil,

b) the compounds of the formula I described in WO 99/55708,

c) the compounds of the formula I described in WO 99/28325.

40. Medicament comprising 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-hydroxypyrrolidine-1,2-dicarboxamide and/or pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and a further medicament active ingredient selected from the group the antithrombotics,
antiarrhythmics,

contraceptives,
phosphodiesterase V inhibitors.

41. Medicament according to Claim 40, in which the antithrombotic is selected from the group of the vitamin K antagonists, heparin compounds, thrombocyte aggregation inhibitors, enzymes, other antithrombotic agents, blood platelet glycoprotein receptor (IIb/IIIa) antagonists, thromboxane antagonists, thrombocyte adhesion inhibitors.

42. Medicament according to Claim 41, where the vitamin K antagonists are selected from the group dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione, tioclomarol.

43. Medicament according to Claim 41, where the heparin compounds are selected from the group heparin, antithrombin III, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, danaparoid, tinzaparin, sulodexide.

44. Medicament according to Claim 41, where the thrombocyte aggregation inhibitors are selected from the group ditazole, cloricromen, picotamide, clopidogrel, ticlopidine, acetylsalicylic acid, dipyridamole, calcium carbassalate, epoprostenol, indobufen, iloprost, abciximab, tirofiban, aloxiprin, intrifiban.

45. Medicament according to Claim 41, where the enzymes are selected from the group streptokinase, alteplase, anistreplase, urokinase, fibrinolysin, brinase, reteplase, saruplase.

46. Medicament according to Claim 41, where other antithrombotic agents are selected from the group defibrotide, desirudin, lepirudin.

47. Medicament according to Claim 40, where the antiarrhythmics are selected from the group
    a) chinidin, disopyramide, ajmaline, detajmium,
    b) lidocaine, mexiletine, phenytoin, tocainide,
    c) propafenone, flecainide,
    d) metoprolol, esmolol, propranolol, atenolol, oxprenolol,
    e) amiodarone, sotalol,
    f) diltiazem, verapamil, gallopamil,
    g) adenosine, orciprenaline, ipratropium,
    h) cardiac glycosides.

48. Medicament according to Claim 40, where the contraceptives are selected from the group
desogestrel, medroxyprogesterone acetate, levonorgestrel, etonogestrel, norethisterone enantate.

49. Medicament according to Claim 40, where the PDE V inhibitors are selected from the group
    a) sildenafil, tadalafil, vardenafil,
    b) the compounds of the formula I described in WO 99/55708,
    c) the compounds of the formula I described in WO 99/28325.

50. Compounds selected from the group
    a) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-(4-aminophenoxy)pyrrolidine-1,2-dicarboxamide,

b) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-methoxypyrrolidine-1,2-dicarboxamide,

c) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

d) 1-N-[(4-chlorophenyl)]-2-N-{[4-(2-imino-5-methyl-1,3,4-thiadiazol-3-yl)phenyl]}-(2R,4R)-4-isopropoxypyrrolidine-1,2-dicarboxamide,

e) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4R)-4-(2,2,2-trifluoroethoxy)pyrrolidine-1,2-dicarboxamide,

f) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2R,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

g) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4R)-4-ethoxypyrrolidine-1,2-dicarboxamide,

h) 1-N-[(4-chlorophenyl)]-2-N-{[4-(3-oxomorpholin-4-yl)phenyl]}-(2S,4S)-4-ethoxypyrrolidine-1,2-dicarboxamide,

and pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios.

51. Medicament comprising at least one compound according to Claim 50 and/or pharmaceutically usable derivatives, solvates, salts and stereoisomers thereof, including mixtures thereof in all ratios, and, if desired, excipients and/or adjuvants.

52. Use of compounds according to Claim 50 and/or physiologically acceptable salts and solvates thereof for the preparation of a medicament for the treatment of thromboses, myocardial infarction, arteriosclerosis, inflammation, apoplexy, angina pectoris, restenosis after angioplasty, claudicatio intermittens, migraine, tumours, tumour diseases and/or tumour metastases,

for the prevention and treatment of thromboembolic diseases and/or

thromboses as a consequence of surgery, genetically caused diseases with increased thrombophilia, diseases of the arterial and venous vascular system, cardiac insufficiency, atrial fibrillation, thrombophilia, tinnitus and/or sepsis.