HETEROCYCLIC COMPOUNDS REGULATING CLOTTING

The invention relates to the use of heterocyclic compounds with formulas (I) and (II), and pharmaceutical acceptable salts thereof, for the manufacture of a pharmaceutical preparation for treatment of coagulation-related diseases. The compounds are inhibitors of TF–FVIIa activity and thus show anticoagulant activity. The invention also relates to methods of treatment. The invention furthermore relates to novel compounds with the formula (I) or (II).
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HETEROCYCLIC COMPOUNDS REGULATING CLOTTING

FIELD OF INVENTION

5 The present invention relates to reagents useful as anticoagulants. More specifically, the invention relates to the use of compounds having formulas I and II, and pharmaceutical salts thereof, as anticoagulants. The invention further relates to methods for inhibiting clotting activity, tissue factor activity, and FVIIa activity as well as methods for treatment of coagulation related disease states.
10 The invention also relates to novel compounds with anticoagulative activity and pharmaceutical compositions comprising such compounds.

BACKGROUND OF INVENTION

15 Blood coagulation is a process consisting of a complex interaction of various blood components, or factors, which eventually gives rise to a fibrin clot. Generally, the blood components which participate in what has been referred to as the coagulation "cascade" are proenzymes or zymogens, enzymatically inactive proteins, which are converted to proteolytic enzymes by the action of an activator, itself an activated clotting factor. Coagulation factors that have undergone such a conversion and generally referred to as "active factors", and are designated by the addition of the letter "a" to the name of the coagulation factor (e.g. FVIIa).

20 Activated factor X (FXa) is required to convert prothrombin to thrombin, which then converts fibrinogen to fibrin as a final stage in forming a fibrin clot. There are two systems, or pathways that promote the activation of factor X. The "intrinsic pathway" refers to those reactions that lead to thrombin formation through utilisation of factors present only in plasma. A series of protease-mediated activations ultimately generates factor IXa, which, in conjunction with factor VIIIa, cleaves factor X into Xa. FVIIa and its cofactor TF in the "extrinsic pathway" of blood coagulation effect an identical proteolysis. TF is a membrane bound protein and does not normally circulate in plasma. Upon vessel disruption, however, it is exposed and forms a complex with FVIIa to catalyse factor X activation or factor IX activation in the presence of Ca²⁺ and phospholipid (Nemerson and Gentry, Biochemistry 25:4020-4033 (1986)). While the relative importance of the two coagulation pathways in
hemostasis is unclear, in recent years FVIIa and TF have been found to play a pivotal role in
the initiation and regulation of blood coagulation.

FVII is a trace plasma glycoprotein that circulates in blood as a single-chain zymogen. The
zymogen is catalytically inactive (Williams et al., J. Biol. Chem. 264:7536-7543 (1989); Rao
converted to two-chain FVIIa by factor Xa, factor XIIa, factor IXa, FVIIa or thrombin in vitro.
Factor Xa is believed to be the major physiological activator of FVII. Like several other
plasma proteins involved in haemostasis, FVII is dependent on vitamin K for its activity,
which is required for the gamma-carboxylation of multiple glutamic acid residues that are
clustered in the amino terminus of the protein. These gamma-carboxylated glutamic acids
are required for the metal-associated interaction of FVII with phospholipids.

The conversion of zymogen FVII into the activated two-chain molecule occurs by cleavage of
an internal Arg152-Ile153 peptide bond (Hagen et al., Proc. Natl. Acad. Sci. USA 83: 2412-
2416 (1986); Thim et al., Biochemistry 27:7785-7793 (1988)). In the presence of TF,
phospholipids and calcium ions, the two-chain FVIIa rapidly activates factor X or factor IX by
limited proteolysis.

It is often desirable to selectively block or inhibit the coagulation cascade in a patient.
Anticoagulants such as heparin, coumarin, derivatives of coumarin, indandione derivatives,
thrombin inhibitors, factor Xa inhibitors, modified FVII or other agents may be used.

Inhibition of coagulation is beneficial in a number of diseased states, for example during
kidney dialysis, or to treat deep vein thrombosis, disseminated intravascular coagulation
(DIC), atherosclerosis and a host of other medical disorders. For example, heparin treatment
or extracorporeal treatment with citrate ions (U.S. Patent 4, 500, 309) may be used in
dialysis to prevent coagulation during the course of treatment. Heparin is also used in
preventing deep vein thrombosis in patients undergoing surgery. Treatment with heparin and
other anticoagulants may, however, have undesirable side effects. Available anticoagulants
generally act throughout the body, rather than acting specifically at the site of injury, i.e. the
site at which the coagulation cascade is active. Heparin, for example, may cause severe
bleedings. Furthermore, with a half-life of approximately 80 minutes, heparin is rapidly
cleared from the blood, necessitating frequent administrating. Because heparin acts as a
cofactor for antithrombin III (AT III), and AT III is rapidly depleted in DIC treatment, it is often difficult to maintain the proper heparin dosage, necessitating continuous monitoring of AT III and heparin levels. Heparin is also ineffective if AT III depletion is extreme. Further, prolonged use of heparin may also increase platelet aggregation and reduce platelet count, and has been implicated in the development of osteoporosis. Indandione derivatives may also have toxic side effects.

Other known anticoagulants comprise thrombin and factor Xa inhibitors derived from bloodsucking organisms. Antithrombins, hirudin, hirulog and hirugen are recombinant proteins or peptides derived from the leach Hirudo medicinalis, whereas the factor Xa inhibitor antistatin and the recombinant derivative rTAP are tick-derived proteins. Inhibitors of platelet aggregation such as monoclonal antibodies or synthetic peptides, which interfere with the platelet receptor GPIIb/IIIa are also effective as anticoagulants.

Bleeding complications are observed as an undesired major disadvantage of anti-thrombin, anti-factor Xa, as well as anti-platelet reagents. This side effect is strongly decreased or absent with inhibitors of the FVIIa/TF activity. Such anticoagulants comprise the physiological inhibitor TFPI (tissue factor pathway inhibitor) and modified FVII (FVIIa), which is FVIIa modified in such a way that it is catalytically inactive but still binds to TF and competes with active FVIIa.

In addition to the anticoagulants briefly described above, several naturally occurring proteins have been found to have anticoagulant activity. For example, Reuteblingsperger (U.S. Patent No. 4,736, 018) isolated anticoagulant proteins from bovine aorta and human umbilical vein arteries. Maki et al. (U.S. Patent No. 4, 732, 891) discloses human placenta-derived anticoagulant proteins. In addition, AT III has been proposed as a therapeutic anticoagulant (Schipper et al., Lancet 1 (8069): 854-856 (1978); Jordan, U.S. Patent No. 4, 386, 025; Bock et al., U.S. Patent No. 4, 517, 294).

Proliferation of smooth muscle cells (SMCs) in the vessel wall is an important event in the formation of vascular lesions in atherosclerosis, after vascular reconstruction or in response to other vascular injury. For example, treatment of atherosclerosis frequently includes the clearing of blocked vessels by angioplasty, endarterectomy or reduction atherectomy, or by bypass grafting. These are surgical procedures in which atherosclerotic plaques are
compressed or removed through catheterization (angioplasty), stripped away from the arterial wall through an incision (endarterectomy) or bypassed with natural or synthetic grafts. These procedures remove the vascular endothelium, disturb the underlying intimal layer, and result in the death of medial SMCs. Medial SMC proliferation and migration follow this injury into the intima, which typically occurs within the first few weeks and up to six months after injury and stops when the overlying endothelial cell layer is re-established. In humans, these lesions are composed of about 20% cells and 80% extracellular matrix. In about 30% or more of patients treated by angioplasty, endarterectomy or bypass grafts, thrombosis and/or SMC proliferation in the intima causes re-occlusion of the vessel and consequent failure of the reconstructive surgery. This closure of the vessel subsequent to surgery is known as restenosis.

Modified FVIIa (FVIIai) has been shown to effectively suppress the restenosis process possibly as a result of a decreased procoagulant activity and thrombin generation initially after treatment of the constricted vessel.

For long term prophylactic treatment and increased compliance it would be desirable to have access to low-molecular-weight compounds which may be administered via a route other than intravenously and which have an inhibitory effect on FVIIa-TF activity similar to that of FVIIai.

Related patent applications covering low-molecular-weight compounds which down-regulate FVIIa-TF activity include:

- JP 07242538 describes naphthalene derivatives with tissue factor antagonist activity.
- US 5639739 describes FVII-inhibiting peptide analogues derived from imidazolyl-boronic acid.
- JP 6157591 describes compounds based on peptides from TFPI.

Further related references include:

Japanese Patent Application No. 55022634 (Hisamitsu Pharmaceutical Co., Inc.) describes 2-(3,4,5-trimethoxyphenyl)-pyrido[2,3-d][1,3]oxazin-4-one and 2-(4-butoxyphenyl)-pyrido[2,3-d][1,3]oxazin-4-one. The compounds have antiallergic activity.


There is still a need in the art for improved compositions having anticoagulant activity which can be administered orally or otherwise non-intravenously at relatively low doses and which does not produce any undesirable side effects. The present invention fulfils this need by providing anticoagulants that act specifically on FVIIa-TF at sites of injury, and further provides other related advantages such as its effect on the restenosis process. As compared to most other anticoagulants with an effect on the FVIIa-TF activity, the present invention has the advantage that it provides small synthetic molecules suitable for oral administration.

**SUMMARY OF THE INVENTION**

It has now been found that the activity of FVIIa in complex with TF can be inhibited by compounds with formulas I and II. By this action the initiation of blood coagulation by FVIIa-TF is prevented, avoiding the formation of undesired thrombi.

The present invention thus provides the use of a compound of the general formula I or formula II for the preparation of a pharmaceutical composition for the treatment and/or prevention of coagulation-related diseased states.

The present invention also provides novel compounds with the formula I and II. The compounds are useful for the treatment of coagulation-related diseased states.

It is an object of the present invention to provide compounds having pharmacological activity as inhibitors of FVIIa-TF activity.
It is an object of the present invention to provide compounds with formulas I and II which are potent modulators of the TF-FVIIa pathway of the coagulation process through an inhibitory action on the TF-FVIIa complex.

It is an object of the present invention to provide the use of compounds with the general formulas I or II for the manufacture of a medicament for treatment of coagulation-related diseases. The coagulation-related diseases include, but are not limited to, diseases such as deep vein thrombosis, pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition, myocardial infarction, or the prophylactic treatment of mammals with atherosclerotic vessels at risk for thrombosis.

It is an object of the present invention to provide the use of compounds with the general formulas I and II for the manufacture of a medicament for modulating and normalizing an impaired haemostatic balance in a mammal.

It is an object of the present invention to provide the use of compounds with the general formulas I and II for the manufacture of a medicament for use as an inhibitor of blood coagulation in a mammal, or for use as an inhibitor of clotting activity in a mammal, or for use as an inhibitor of deposition of fibrin in a mammal, or for use as an inhibitor of fibrin in a mammal.

It is an object of the present invention to provide methods for:
treatment of coagulation-related diseases;
treatment of mammals suffering from deep vein thrombosis, pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition and associated disorders, and myocardial infarction;
prophylactic treatment of mammals with atherosclerotic vessels at risk for thrombosis;
modulating and normalizing an impaired haemostatic balance in a mammal;
inhibiting blood coagulation in a mammal, or inhibiting clotting activity in a mammal, or inhibiting deposition of fibrin in a mammal, or inhibiting fibrin in a mammal.

The mammal is preferably a human.

Further objects will become apparent from the following description.
DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein: The term "C₁₈⁺-alkyl", "C₂₃⁺-alkenyl", "C₂₄⁺-alkynyl" as used herein, alone or in combination, refers to a straight or branched, saturated or unsaturated hydrocarbon chain. The C₁₈⁺-alkyl residues include aliphatic hydrocarbon residues, unsaturated aliphatic hydrocarbon residues, alicyclic hydrocarbon residues. Examples of the aliphatic hydrocarbon residues include saturated aliphatic hydrocarbon residues having 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, isopentyl, neopentyl, tert.pentyl, n-hexyl, iso-hexyl. Examples of the unsaturated aliphatic hydrocarbon residues include those having 2 to 6 carbon atoms, such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, ethynyl, 1-propionyl, 2-propionyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, and 5-hexynyl.

The term C₃₃⁺-cycloalkyl means alicyclic hydrocarbon residues including saturated alicyclic hydrocarbon residues having 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl; and C₆⁺ unsaturated alicyclic hydrocarbon residues having 5 to 6 carbon atoms such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl.

The term "C₁₄⁺-alkoxy" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C₁₄⁺-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen and having 1 to 6 carbon atoms e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy.

The term "C₁₄⁺-alkylthio" as used herein, alone or in combination, refers to a straight or branched monovalent substituent comprising a C₁₄⁺-alkyl group linked through an thioether sulfur atom having its free valence bond from the thioether sulfur and having 1 to 6 carbon atoms.

The terms "aryl" and "heteroaryl" as used herein refers to an aryl which can be optionally substituted or a heteroaryl which can be optionally substituted and includes phenyl, biphenyl,
indene, fluorene, naphthyl (1-naphthyl, 2-naphthyl), anthracene (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophene (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl), indolyl, oxadiazolyl, isoxazolyl, quinazolin, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydrobenzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoazolyl (1-benzoazolyl, 2-benzoazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepin-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, and 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl).

The invention also relates to partly or fully saturated analogues of the ring systems mentioned above.
The term “leaving group” includes, but is not limited to, halogen, sulfonate or an acyl group. A person skilled in the art will know suitable leaving groups.

The term “protection group” (PG) refers to a chemical group that exhibits the following characteristics: 1) reacts selectively with the desired functionality in good yield to give a protected substrate that is stable to the projected reactions for which protection is desired; 2) is selectively removable from the protected substrate to yield the desired functionality; and 3) is removable in good yield by reagent compatible with the other functional group(s) generated in such protected reactions. Protection groups include but are not limited to CH₃, benzyl (Bn), butyloxy carbonyl (BOC), benzyloxy carbonyl (CBz), 9-fluorenyl methoxycarbonyl (Fmoc), or tosyl (Ts) groups. A person skilled in the art will know other nitrogen protection groups. Examples of protecting groups can be found in, for example, Greene et al. (1991) Protective Groups in Organic Chemistry, 2nd Ed. (John Wiley & Sons, Inc., New York).

“Coupling agent” means an agent suitable for formation of acid derivatives from acids or activated acids and amines, phenols, alcohols, or acids including, but not limited to hydroxybenzotriazole (HOBt) and derivatives thereof and carbodiimides like dicyclohexylcarbodiimide and ethyldimethylaminopropyl carbodiimide (DCC, EDAC). The skilled person will know suitable coupling agents. Activated acids include, but are not limited to acid chlorides, acid anhydrides, esters, and similar derivatives.

“Agent capable of introducing ring closure” means an agent capable of introducing combined hydrolysis and ring closure under absorption of water. This include, but are not limited to, organic and inorganic acid anhydrides, e.g. acetic anhydride and P₂O₅, mineral acids, e.g. concentrated sulfuric acid, phosphoric acid and the like, acid chlorides, e.g. SOCl₂, PCl₅, and POCl₃.

“Halogen” refers to fluorine, chlorine, bromine, and iodine. “Halo” refers to fluoro, chloro, bromo and iodo.

“Halo-alkyl” means the group -R-halo in which R is alkyl, and both alkyl and halo are as defined herein. The alkyl group may bear one, two or three halo substituents; examples include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, chloroethyl, dichloroethyl, bromoethyl, iodoethyl, and the like.
"Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occur and instances in which is does not. For example, "aryl ... optionally substituted" means that the aryl may or may not be substituted and that the description includes both unsubstituted aryls and aryls wherein there is substitution.

"Treatment" means the administration of an effective amount of a therapeutically active compound of the invention with the purpose of preventing any symptoms or disease state to develop or with the purpose of curing or easing such symptoms or disease states already developed. The term "treatment" is thus meant to include prophylactic treatment.

"Coagulation-related disease states": Diseases or symptoms which are caused by unwanted blood coagulation, clotting activity, deposition of fibrin and/or platelets or TF-FVIIa activity. Such diseases include, but are not limited to, deep vein thrombosis, pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition, or myocardial infarction, or the prophylactic treatment of mammals with atherosclerotic vessels at risk for thrombosis.

"Inhibitors of FVIIa-TF activity": It has now been found that compounds with the general formulas I or II inhibit FVIIa-TF in in vitro assays of amidolytic and proteolytic activity and thus are able to prolong the TF-induced coagulation in human plasma. They may do so by inhibiting FVIIa activity, by inhibiting FVIIa-TF activity, by preventing the formation of a FVIIa-TF complex or by preventing the activation of factor X by FVIIa-TF. Compounds which solely inhibit the proteolytic activity of FVIIa-TF and/or prolong the coagulation time may do so by preventing the association of factor X with the FVIIa-TF complex or by preventing the activation of factor X bound to the complex.

"Modulators of the TF-FVIIa pathway": Compounds that modulate the coagulation process through an inhibitory action on the TF-FVIIa complex or on TF activity. The activity of FVIIa in complex with TF, in particular its activation of factor X, can be inhibited by a low-molecular weight compound. By this action, the initiation and acceleration of the blood coagulation cascade upon exposure of TF to flowing blood is prevented.
"Modulating and normalizing an impaired haemostatic balance" means achieving an effect on the coagulation system measurable in vitro assays and/or animal models which effect diminishes the risk for thrombosis or bleedings.

5 **Abreviations**

- TF: Tissue factor
- FVII or fVII: factor VII
- FVIIa or fVIIa: activated factor VII
- FVIIa-TF: complex between activated factor VII and tissue factor initiating blood coagulation

The present invention relates to the use of compounds of formulas I and II

![Chemical Structures](image)

wherein

- X, Y, Z and W independently are CH, CH2, O, S, N, NH or N-PG, where PG is CH3, benzyl (Bn), butyloxy carbonyl (BOC), benzyloxy carbonyl (CBz), 9-fluorenylmethoxycarbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

- at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.

R1 and R2 independently are

- C1-6-alkyl, C2-8 alkenyl, C2-8 alkynyl, or C3-6 cycloalkyl, each optionally substituted with halogen, OH, NH2, NHR4, N(R4)2, NHCOR4, C1-4 alkoxy, trifluoromethoxy, carbamoyl, CONHR4, or CON(R4)2;

- H, Halogen, CF3, C1-6 alkoxy, C1-6 alkylthio, OCF3, COOH, CN, CONH2, CONHR4, OH, NH2,
NHR₄, N(Rᵢ)₂, NHCOR₄, CON(Rᵢ)₂, CONHSO₂R₄, SO₂NH₂, SO₂NHR₄, C₁₋₄ alkoxy carbonyl, phenyl, alkyphenyl, or tetrazole

Rᵡ is aryl or heteroaryl, each optionally substituted with one or more
C₁₋₄ alkyl, C₂₋₃ alkenyl, C₂₋₄ alkynyl, or C₃₋₆ cycloalkyl, each optionally substituted with halogen, OH, NO₂, NH₂, N(Rᵢ)₄, NHR₄, NHCOR₄, C₁₋₄ alkoxy, trifluoromethoxy, carbamoyl, CONHR₄, or CON(Rᵢ)₂;
Halogen, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR₄, OH, NO₂,
NH₂, NHR₄, N(Rᵢ)₂, NHCOR₄, CON(Rᵢ)₂, CONHSO₂R₄, SO₂NH₂, SO₂NHR₄, C₁₋₄ alkoxy car-

Rᵣ is C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, or phenyl;
or a pharmaceutical acceptable salt thereof, for the manufacture of a medicament for treat-
ment of coagulation-related diseased states.

Certain of the above defined terms may occur more than once in the above formulas I and II, and upon such occurrence each term shall be defined independently of the other.

The compounds of the present invention may have one or more asymmetric centres and it is intended that stereoisomers (optical isomers), as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention.

Preferred Rᵢ and Rᵣ are: hydrogen, 4-fluoro, 1-methyl, 5-methyl, 6-methyl, 6-fluoro, 5,8-
dichloro, 6-chloro, 6-iodo, 7-chloro, 5-nitro, 5-amo, 5-acetylamino, 6-nitro, 6-acetylamino, 6-
carboxy, 5-hydroxy, 6-hydroxy, 7-ethylthio;

Preferred Rᵡ are: 2,6-difluorophenyl, 2-fluorophenyl, 2-chlorophenyl, 2-fluorophenyl, 2,3-
dichlorophenyl, 2-bromophenyl, 2-bromo-5-methoxyphenyl, 2-trifluoromethoxyphenyl, 7-
benzofuranyl, 2-thienyl, 2-furanyl, 5-chloro-2-methoxyphenyl, 5-nitrofurany1, 2-piperidyl, 3-
chloro-5-trifluoromethyl-2-pyridyl, 2-tolyl, 3-tolyl, 4-tolyl, 2-nitrophenyl.

Preferred Rᵣ are: Methyl, ethyl, isopropyl, propyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl.
Preferably, \( R^3 \) is an ortho-substituted aryl (mono-or dissubstituted) or a heteroaryl ring.

The formulas I and II include, but are not limited to, ring systems of the following types (all having substituents \( R^1, R^2 \) and \( R^3 \) placed as shown in formulas I and II and defined as above and in claim 1):

- pyrido [3,4-d] [1,3] oxazin-4-one
- pyrido [2,3-d] [1,3] oxazin-4-one
- pyrazino [2,3-d] [1,3] oxazin-4-one
- pyrimido [4,5-d] [1,3] oxazin-4-one
- pyrazolo [3,4-d] [1,3] oxazin-4-one
- thieno [3,2-d] [1,3] oxazin-4-one
- thieno [2,3-d] [1,3] oxazin-4-one
- piperidino[1,3]oxazin-4-one,
- piperazino[1,3]oxazin-4-one
- morpholin[1,3]oxazin-4-one
- pyrrolidino[1,3]oxazin-4-one
- pyrrolino[1,3]oxazin-4-one
- imidazolino[1,3]oxazin-4-one
- pyrazolidino[1,3]oxazin-4-one
- pyrano[1,3]oxazin-4-one
- pyridino[1,3]oxazin-4-one
- pyridazino[1,3]oxazin-4-one
- pyrimidino[1,3]oxazin-4-one
- pyrazino[1,3]oxazin-4-one
- furano[1,3]oxazin-4-one
- pyrrolo[1,3]oxazin-4-one
- imidazolo[1,3]oxazin-4-one
- pyrazolo[1,3]oxazin-4-one
- isoxazolo[1,3]oxazin-4-one
- isothiazolo[1,3]oxazin-4-one
- furazano[1,3]oxazin-4-one
- 5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
- 5,6,7,8-tetrahydro-3-oxa-9-aza-1-aza-fluoren-4-one
- 5,6,7,8-tetrahydro-3-oxa-9-aza-1-aza-fluoren-4-one
tetrahydrofurano[1,3]oxazin-4-one
tetrahydrothiopheno[1,3]oxazin-4-one
imidazolidino [1,3]oxazin-4-one
pyrazolino[1,3]oxazin-4-one
oxidathiolano[1,3]oxazin-4-one
oxazolo[1,3]oxazin-4-one
isothiazolidino[1,3]oxazin-4-one
thiazolidino[1,3]oxazin-4-one
thiazolo[1,3]oxazin-4-one
oxadiazolo[1,3]oxazin-4-one
thiadiazolo[1,3]oxazin-4-one

Preferred formulas I and II are \((R^1, R^2, R^3)\) as defined above and in claim 1):

- pyrido [3,4-d] [1,3] oxazin-4-ones with the formula:

```
\[\begin{array}{c}
  \text{R}^1 \\
  \text{N} \\
  \text{R}^2 \\
  \text{O} \\
  \text{R}^3 \\
\end{array}\]
```

- pyrido [2,3-d] [1,3] oxazin-4-ones with the formula:

```
\[\begin{array}{c}
  \text{R}^1 \\
  \text{N} \\
  \text{R}^2 \\
  \text{O} \\
  \text{R}^3 \\
\end{array}\]
```

pyrazino [2,3-d] [1,3] oxazin-4-ones with the formula:
pyrimido \([4,5-d] \[1,3\]\) oxazin-4-ones with the formula:

\[
\begin{array}{c}
\text{R1} \\
\text{N} \\
\text{N} \\
\text{R2} \\
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R2} \\
\text{R3} \\
\end{array}
\]

pyrazolo \([3,4-d] \[1,3\]\) oxazin-4-ones with the formula:

\[
\begin{array}{c}
\text{R1} \\
\text{N} \\
\text{N} \\
\text{R2} \\
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{R2} \\
\text{R3} \\
\end{array}
\]

thieno \([3,2-d] \[1,3\]\) oxazin-4-ones with the formula:

\[
\begin{array}{c}
\text{R1} \\
\text{S} \\
\text{N} \\
\text{R2} \\
\end{array}
\]

\[
\begin{array}{c}
\text{R3} \\
\end{array}
\]

thieno \([2,3-d] \[1,3\]\) oxazin-4-ones with the formula:
5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluorene with the formula:

Preferred Compounds with formula I are:

2-(2-Fluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (1)
2-(2,6-Difluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (2)
2-Thiophen-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (3)
2-Furan-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (4)
2-(2-Fluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (5)
2-(2,6-Difluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (6)
2-Furan-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (8)
2-(2-Fluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (9)
2-(2,6-Difluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (10)
2-o-Tolyl-pyrazino[2,3-d][1,3]oxazin-4-one (11)
7-Ethylthio-2-(2-fluoro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (12)
7-Ethylthio-(2-nitro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (13)
7-Ethylthio-2-o-tolyl-pyrimido[4,5-d][1,3]oxazin-4-one (14)
2-(2-Chloro-phenyl)-7-ethylthio-pyrimido[4,5-d][1,3]oxazin-4-one (15)

Preferred Compounds with formula II are:

6-(2-Fluoro-phenyl)-1-methyl-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (16)
1-Methyl-6-(2-nitro-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (17)
1-Methyl-6-(2-methyl-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (18)
2-[(2,6-Difluoro-phenyl)-7-methyl-thieno[3,2-d][1,3]oxazin-4-one (19)
5-Methyl-2-(2-nitro-phenyl)-thieno[2,3-d][1,3]oxazin-4-one (20)

Preparation of compounds

The compounds with general formula I and II may be prepared from compounds having formulas III or IV or V, VI or VII or VIII by the following methods:

Method A):

1) Reacting a compound of formula III

\[
\begin{align*}
\text{R}_1 & \quad \text{O} \\
\text{X} & \quad \text{Y} \\
\text{Z} & \quad \text{W} \\
\text{R}_2 & \quad \text{N} \\
\text{H} & \quad \text{O} \\
\end{align*}
\]

(III)

with a compound of the formula R3COL; R1, R2, R3, X, Y, Z and W having the meanings as defined above, L being a leaving group such as halogen, sulphate or acyl group, under formation of a structure IV;

2) reacting a compound of formula IV

\[
\begin{align*}
\text{R}_1 & \quad \text{O} \\
\text{X} & \quad \text{Y} \\
\text{Z} & \quad \text{W} \\
\text{R}_2 & \quad \text{N} \quad \text{R}_3 \\
\text{H} & \quad \text{O} \\
\end{align*}
\]

(IV)

where R1, R2, R3, X, Y, Z and W are as defined above, with an agent capable of introducing ring closure to form a structure of the formula I. Such agents can be carboxylic acid anhydrides such as acetic anhydride, concentrated sulphuric acid, POC13, P2O5, CF3COOH, or similar agents.
Method B):

1) Reacting a compound of formula III

\[
\begin{align*}
\text{III} & \quad \begin{array}{c}
\text{R1} \\
\text{Y} \\
\text{X} \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{Z} \\
\text{W} \\
\text{N} \\
\text{H} \\
\text{R2}
\end{array}
\end{align*}
\]

with a compound of the formula R3COOH; R1, R2, R3, X, Y, Z and W having the meanings as defined above; using a standard coupling agent such as HOBT or a carbodiimide such as DCC or EDAC, or similar agents suitable for formation of amide bonds from acids or activated acids and amines,

under formation of a structure IV;

2) Reacting a compound of formula IV

\[
\begin{align*}
\text{IV} & \quad \begin{array}{c}
\text{R1} \\
\text{Y} \\
\text{X} \\
\text{O} \\
\text{O} \\
\text{H} \\
\text{Z} \\
\text{W} \\
\text{N} \\
\text{R3} \\
\text{R2}
\end{array}
\end{align*}
\]

where R1, R2, R3, X, Y, Z and W are as defined above, with an agent capable of introducing ring closure to form a structure of the formula I. Such agents can be carboxylic acid anhydrides such as acetic anhydride, concentrated sulphuric acid, POCl3, P2O5, CF3COOH, or similar agents.
Method C): Reacting a compound of formula IV

\[
\begin{array}{c}
\text{R1} \\
\text{X} \\
\text{Y} \\
\text{Z} \\
\text{R2} \\
\text{W} \\
\text{N} \\
\text{R3} \\
\text{O} \\
\text{O} \\
\text{H}
\end{array}
\]

(IV)

where R1, R2, R3, X, Y, Z and W are as defined above, with an agent capable of introducing ring closure to form a structure of the formula I. Such agents can be carboxylic acid anhydrides such as acetic anhydride, concentrated sulphuric acid, POCl₃, P₂O₅, CF₃COOH, or similar agents.

Method D): Reacting a compound of formula V

\[
\begin{array}{c}
\text{R1} \\
\text{X} \\
\text{Y} \\
\text{Z} \\
\text{R2} \\
\text{W} \\
\text{N} \\
\text{R3} \\
\text{R5} \\
\text{O} \\
\text{O}
\end{array}
\]

(V)

where R1, R2, R3, X, Y, Z and W are as defined above and R5 is an C1-8 alkyl group, with an agent capable of introducing ring closure such as concentrated H₂SO₄ or PPh₃/Et₃N/C₂Cl₄Br₂, or similar agents which can introduce combined hydrolysis and ring closure under absorption of water, under formation of a compound of structure I.
Method E):
1) Reacting a compound of formula VI

\[
\begin{align*}
\text{O} & \\
\text{R}2, & \text{X} & \text{O-H} \\
\text{Y} & \text{N-H} \\
\text{R}1, & \text{z} & \\
\text{H} & \\
\end{align*}
\]

(VI)

with a compound of the formula R3COL; R1, R2, R3, X, Y, and Z having the meanings as defined above, L being a leaving group such as halogen, sulphate or acyl group, under formation of a structure VII;
2) Reacting a compound of formula VII

\[
\begin{align*}
\text{O} & \\
\text{R}2, & \text{X} & \text{O-H} \\
\text{Y} & \text{N-R}3 \\
\text{R}1, & \text{z} & \text{O} \\
\text{H} & \\
\end{align*}
\]

(VII)

where R1, R2, R3, X, Y, and Z are as defined above, with an agent capable of introducing ring closure to form a structure of the formula II. Such agents can be carboxylic acid anhydrides such as acetic anhydride, concentrated sulphuric acid, POCI3, P2O5, CF3COOH, or similar agents.

Method F):
1) Reacting a compound of formula VI

\[
\begin{align*}
\text{O} & \\
\text{R}2, & \text{X} & \text{O-H} \\
\text{Y} & \text{N-H} \\
\text{R}1, & \text{z} & \\
\text{H} & \\
\end{align*}
\]

(VI)
with a compound of the formula R₃COOH; R₁, R₂, R₃, X, Y, and Z having the meanings as defined above; using a standard coupling agent such as HOBr or a carbodiimide such as DCC or EDAC, or similar agents suitable for formation of amide bonds from acids or activated acids and amines,

under formation of a structure VII;

2) reacting a compound of formula VII

\[
\begin{align*}
\text{O} & \\
\text{R₂} & \text{X} \\
\text{Y} & \\
\text{R₁} & \text{z} \\
\text{N} & \text{O} \\
\text{R₃} & \text{O-H}
\end{align*}
\]

(VII)

where R₁, R₂, R₃, X, Y, and Z are as defined above, with an agent capable of introducing ring closure to form a structure of the formula II. Such agents can be carboxylic acid anhydrides such as acetic anhydride, concentrated sulphuric acid, POCl₃, P₂O₅, CF₃COOH, or similar agents.

Method G):

Reacting a compound of formula VII

\[
\begin{align*}
\text{O} & \\
\text{R₂} & \text{X} \\
\text{Y} & \\
\text{R₁} & \text{z} \\
\text{N} & \text{O} \\
\text{R₃} & \text{O-H}
\end{align*}
\]

(VII)

where R₁, R₂, R₃, X, Y, and Z are as defined above, with an agent capable of introducing ring closure to form a structure of the formula II. Such agents can be carboxylic acid anhydrides such as acetic anhydride, concentrated sulphuric acid, POCl₃, P₂O₅, CF₃COOH, or similar agents.
Method H):

Reacting a compound of formula VIII

\[
\begin{align*}
&\text{O} \\
&\text{R}_2, \text{X} \\
&\text{R}_1, \text{Z} \\
&\text{Y} \\
&\text{R}_3, \text{O} \\
&\text{R}_5
\end{align*}
\]

where \( R_1, R_2, R_3, X, Y, \) and \( Z \) are as defined above and \( R_5 \) is an C1-8 alkyl group, with an agent capable of introducing ring closure such as concentrated \( \text{H}_2\text{SO}_4 \) or \( \text{PPh}_3/\text{Et}_3\text{N}/\text{C}_2\text{Cl}_4\text{Br}_2/2 \), or similar agents which can introduce combined hydrolysis and ring closure under absorption of water, under formation of a compound of structure II.

Examples of the synthetic methods described above are known to a person skilled in the art and described several places in the literature; see for example


J.L. Gilmore et al.: Bioorganic and Medicinal Chemistry Letters 6 (6), 679-682, 1996;

M. Davies, R.J. Hook, Wen Yang Wu: J. Heterocyclic. Chem. 21 369-373, 1984;


Some of the structures described in the present invention are commercially available from companies selling special chemicals. Examples are companies like Maybridge, Specs, Merlin, CSC and Salor.

Examples of compounds of formula I are the following:
2-(2-Fluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (1)
2-(2,6-Difluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (2)
2-Thiophen-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (3)
2-Furan-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (4)
2-(2-Fluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (5)
2-(2,6-Difluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (6)
2-Furan-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (8)
2-(2-Fluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (9)
2-(2,6-Difluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (10)
2-o-Tolyl-pyrazino[2,3-d][1,3]oxazin-4-one (11)
7-Ethylthio-2-(2-fluoro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (12)
7-Ethylthio-(2-nitro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (13)
7-Ethylthio-2-o-tolyl-pyrimido[4,5-d][1,3]oxazin-4-one (14)
2-(2-Chloro-phenyl)-7-ethylthio-pyrimido[4,5-d][1,3]oxazin-4-one (15)

Examples of compounds of formula II are the following:

6-(2-Fluoro-phenyl)-1-methyl-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (16)
1-Methyl-6-(2-nitro-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (17)
1-Methyl-6-(2-methyl-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (18)
2-(2,6-Difluoro-phenyl)-7-methyl-thieno[3,2-d][1,3]oxazin-4-one (19)
5-Methyl-2-(2-nitro-phenyl)-thieno[2,3-d][1,3]oxazin-4-one (20)

Within the present invention, the compounds of formulas I and II may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid, ascorbic acid, embonic acid, methanesulphonic acid, malonic acid, and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.
The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

The compounds of formulas I and II may be administered in pharmaceutically acceptable acid addition salt form or, where appropriate, as a alkali metal or alkaline earth metal or lower alkylammonium salt. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

Apart from the pharmaceutical use of the compounds of formulas I and II, they may be useful in vitro tools for investigating the inhibition of FVIIa or FVIIa/TF activity.

**Pharmaceutical compositions**

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds as described in claim 13 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I or II combined with one or more other compounds exhibiting anticoagulant activity, e.g., platelet aggregation inhibitor.

The compounds with general formulas I and II may be formulated into pharmaceutical composition comprising the compounds and a pharmaceutically acceptable carrier or diluent. Such carriers include water, physiological saline, ethanol, polyols, e.g., glycerol or propylene glycol, or vegetable oils. As used herein, "pharmaceutically acceptable carriers" also encompasses any and all solvents, dispersion media, coatings, antifungal agents, preservatives, isotonic agents and the like. Except insofar as any conventional medium is incompatible with the active ingredient and its intended use, its use in the compositions of the present invention is contemplated.

The pharmaceutical composition may also comprise one or more one or more other compounds exhibiting anticoagulant activity, e.g., platelet aggregation inhibitor.
The compositions containing the compounds with general formulas I and II may be prepared by conventional techniques and appear in conventional forms, for example, capsules, tablets, solutions or suspensions. The pharmaceutical carrier employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatine, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water. Similarly, the carrier or diluent may include any time delay material known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral, e.g., rectal, transdermal, subcutaneous, intranasal, intramuscular, topical, intravenous, intraurethral, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier for oral administration is used, the preparation can be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier may vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabens.
For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

5 Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

10 A typical tablet, which may be prepared by conventional tabletting techniques, contains

Core:

- Active compound (as free compound or salt thereof) 100 mg
- Colloidal silicon dioxide (Areosil®) 1.5 mg
- Cellulose, microcryst. (Avicel®) 70 mg
- Modified cellulose gum (Ac-Di-Sol®) 7.5 mg
- Magnesium stearate

Coating:

- HPMC approx. 9 mg
- ‘Mywacett® 9-40 T approx. 0.9 mg
- ‘Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of various coagulation-related diseases as mentioned above. Such mammals also include animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients, it may frequently be necessary to begin with a dosage of from about 20 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The
exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

The compounds may be administered concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, whether by oral, rectal, or parenteral (including subcutaneous) route. The compounds are often, and preferably, in the form of an alkali metal or earth alkali metal salt thereof.

Suitable dosage ranges varies as indicated above depending upon the exact mode of administration, form in which administered, the indication towards which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

Methods for identifying inhibitory compounds
The general strategy for identifying compounds is depicted below:

\[
\text{FVIIa/TF-CATALYZED FX ACTIVATION ASSAY} \\
\downarrow \\
\text{FVIIa/TF-INDUCED PLASMA CLOTTING ASSAY}
\]

Inhibitory compounds are identified in a FX activation assay:
The compounds are dissolved in DMSO and mixed with a solution of FVIIa in Ca\(^{2+}\)-containing buffer (1+5). 30 μl of this mixture was then mixed with 45 μl TF (relipidated in
PC/PS vesicles) and 25 μl of a solution containing FX, all in Ca^{2+}-containing buffer. This gives final concentrations of 100 pM FVIIa, 5 pM TF, 175 nM FX and various concentrations of the compounds. After a 5-min incubation, the FVIIa/TF-catalyzed activation of FX is terminated by the addition of 50 μl buffer containing enough EDTA to give an excess over the Ca^{2+} ions present. 50 μl of a 2-mM solution of S-2765 (FXa substrate) is then added and the FXa formed is allowed to hydrolyze the substrate for 10 minutes during which the absorbance at 405 nm is continuously monitored in a SPECTRAmax™ 340 plate reader. The slope of the absorption curve is compared to that of a control where DMSO alone was added to FVIIa/TF/FX.

Test of anticoagulant potency in a FVIIa/TF-initiated clotting assay:
The test compounds, 20 mM in DMSO, are diluted in citrated normal human plasma just before the analysis (1+19) and placed in the sample carousel. 55 μl sample (compound in plasma) is mixed with 55 μl of thromboplastin (Innovin, Dade) and incubated for 5 min. The clotting reaction is started by adding 55 μl of a 25-mM CaCl_2 solution, yielding a final compound concentration of 0.33 mM. The clotting time is measured using an ACL 300 R coagulometer. The ratio between the clotting time in the presence and absence of test compound is used to quantify the anticoagulant efficiency.

The compounds with general formula I or II have interesting pharmacological properties. For example, the compounds of this invention can be used to modulate and normalize an impaired haemostatic balance in mammals caused by deficiency or malfunction of blood clotting factors or their inhibitors. The FVIIa and in particular the FVIIa/TF activity plays an important role in the control of the coagulation cascade, and modulators of this key regulatory activity such as the present invention can be used in the treatment of coagulation-related diseased states.

The pharmaceutical composition comprising compounds with formulas I and II may be useful for modulating and normalizing an impaired haemostatic balance in a mammal. In particular, the pharmaceutical composition may be useful for the treatment of coagulation-related diseased states.

More particularly, the pharmaceutical composition may be useful as an inhibitor of blood coagulation in a mammal, as an inhibitor of clotting activity in a mammal, as an inhibitor of deposition of fibrin in a mammal, as an inhibitor of platelet deposition in a mammal, in the
treatment of mammals suffering from deep vein thrombosis, pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition and associated disorders, myocardial infarction, and in the prophylactic treatment of mammals with atherosclerotic vessels at risk for developing thrombosis.

Furthermore the invention relates to a method for inhibiting TF activity in a mammal which method comprises administering an effective amount of at least one compound with formula I or II, in combination with a pharmaceutical acceptable excipient and/or carrier to the mammal in need of such a treatment.

The invention also relates to a method for inhibiting FVIIa activity by substantially reducing the ability of activated FVIIa to catalyse TF-enhanced activation of factors X and IX, the method comprising administering at least one compound with formula I or II, in combination with a pharmaceutical acceptable excipient and/or carrier to a mammal in need of such a treatment.

The invention also relates to a method for substantially inhibiting the binding of FVII/FVIIa to TF which method comprises administering an effective amount of at least one compound with formula I or II, in combination with a pharmaceutical acceptable excipient and/or carrier, to the mammal in need of such a treatment.

The present invention is further illustrated by the following examples.

EXAMPLES

The following examples 1-7, 9-10, 12-16, and 18-22 describe synthesis of new compounds according to the invention.

Example 1

2-(2-Fluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (1)

3-Aminopyridine-4-carboxylic acid (0.28 g, 2.0 mmol) was dissolved in dry pyridine (10 mL), cooled in an ice bath, and 2-fluorobenzoyl chloride (0.53 mL, 4.5 mmol) was added drop-wise. The solution was stirred at room temperature for 16h, and the solvent was evaporated in vacuo. The solid was purified by flash chromatography on silicagel using EtOAc:heptane
1:1 as the eluent, to give 1 as colourless crystals, 0.44 g (91%). Mp. 130 - 135°C. Rf 0.50 (EtOAc:heptane 1:1). \(^1\)H-NMR (CDCl\(_3\)), \(^{13}\)C-NMR (CDCl\(_3\)).

**Example 2**

2-(2,6-Difluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (2)

3-Aminopyridine-4-carboxylic acid (0.28g, 2.0 mmol) was dissolved in dry pyridine (8 mL), and 2,6-difluorobenzoyl chloride (0.56 mL, 4.5 mmol) was added dropwise under stirring and cooling. The reaction was stirred at room temperature for 24 h after which it was concentrated *in vacuo*. The crude product was purified by flash chromatography on silicagel using EtOAc:heptane 1:4 - EtOAc:MeOH 10:1 as the eluent. Two compounds were isolated: impure 2, 0.39g, Rf 0.50 EtOAc:heptane 1:1, and a yellow crystalline compound, 0.11g, Rf 0.50 EtOAc:MeOH 10:1. Impure 2 was dissolved in CH\(_2\)Cl\(_2\), washed with aq. NaHCO\(_3\) (5 x 10 mL), dried (Na\(_2\)SO\(_4\)) and concentrated to give 2 as colourless crystals, 0.22g (44%). Mp. 137 - 140°C. El/ SP MS: M+ 260. \(^1\)H NMR (CDCl\(_3\)), \(^{13}\)C NMR (CDCl\(_3\)).

**Example 3**

2-Thiophen-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (3)

3-Aminopyridine-4-carboxylic acid (0.28 g, 2.0 mmol) was dissolved in dry pyridine (8 mL), and 2-thiophenecarbonyl chloride (0.47 mL, 4.5 mmol) was added dropwise under cooling and stirring. The solution was stirred at room temperature for 30 h and subsequently concentrated *in vacuo*. Purification by flash chromatography on silicagel using CH\(_2\)Cl\(_2\):acetone 50:1 as the eluent gave crude 3, 0.50 g. The crude product was dissolved in CH\(_2\)Cl\(_2\) (40 mL) and washed with aqueous NaHCO\(_3\) (5 x 20 mL), dried (Na\(_2\)SO\(_4\)) and concentrated to give 3, 0.35 g (76%). The compound was recrystallized from EtOAc, mp. 167-168 °C. El/ SP MS: M+ 230. \(^1\)H NMR (CDCl\(_3\)). \(^{13}\)C NMR (CDCl\(_3\)). Analysis calcd for: C: 57.38%; H, 2.63%; N, 12.17%. Found: C, 57.38%; H, 2.59%; N, 12.00%.

**Example 4**

2-Furan-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (4)

3-Aminopyridine-4-carboxylic acid (0.28g, 2.0 mmol) was dissolved in dry pyridine (8 mL), and 2-furan-carbonyl chloride (0.45 mL, 4.5 mmol) was added under stirring and cooling. The solution was stirred at room temperature for 30h, the solvent was evaporated and the residue was dissolved in CH\(_2\)Cl\(_2\) (40mL) and and the organic phase was washed with saturated NaHCO\(_3\) (5 x 20 mL) and concentrated *in vacuo* to give 4, 0.32 g (76%). The com-
pound was dissolved in EtOAc and filtered through activated charcoal, followed by recrystal-
isation from EtOAc to give 4 as a colourless crystals, mp. 173-174 °C. El/ SP MS: M* 214.
\(^1\)H NMR (CDCl\(_3\)). Analysis calcd. for: C, 61.69%; H, 2.28%; N, 13.08%. Found: C, 61.67%;
H, 2.78%; N, 12.81%.

Example 5
2-(2-Fluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (5)
2-Aminopyridine-3-carboxylic acid (0.28g, 2.0 mmol) was dissolved in dry pyridine (8 mL)
and 2-fluorobenzoyl chloride (0.53 mL, 4.5 mmol) was added under stirring and cooling. Stir-
ring was maintained for 18 h at room temperature after which the solvent was evaporated.
The residue was dissolved in CH\(_2\)Cl\(_2\) (40mL), the organic phase was washed with saturated
NaHCO\(_3\) (5 x 20 mL) and concentrated. The crude product was purified by flash chromato-
graphy on silicagel using EtOAc:heptane 1:1 as the eluent. This gave 5 as a colourless solid,
0.40 g (83%), R\(_f\) 0.20 (EtOAc:heptane 1:1). Mp. 146-147 °C. El/ SP MS: M* 242. \(^1\)H NMR
(CDCl\(_3\)). \(^13\)C NMR (CDCl\(_3\)). Analysis calcd. for: C, 64.47%; H, 2.91%; N, 11.57%. Found: C,
64.33%; H, 2.91%, N, 11.44%.

Example 6
2-(2,6-Difluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (6)
2-Aminopyridine-3-carboxylic acid (0.28g, 2.0 mmol) was dissolved in dry pyridine (8 mL)
and 2,6-difluorobenzoyl chloride (0.52 mL, 4.5 mmol) was added under stirring and cooling.
Stirring was maintained for 18 h at room temperature after which the solvent was evapo-
rated. The residue was dissolved in CH\(_2\)Cl\(_2\) (40mL), the organic phase was washed with
saturated NaHCO\(_3\) (5 x 20 mL) and concentrated. The solid was purified by flash chromatog-
raphy on silicagel using EtOAc:heptane 1:1 - EtOAc:MeOH 10:1 as the eluent. This gave two
products. Compound 6 was isolated as a colourless crystalline compound, 0.18g (35%), R\(_f\)
0.30 (EtOAc:heptane 1:1). Furthermore a yellow crystalline compound was isolated, 0.11g,
R\(_f\) 0.25 (EtOAc:MeOH 10:1), this compound was not fully characterized.
Compound 6 had: mp. 209-210 °C. El/ SP MS: M* 260. \(^1\)H NMR (CDCl\(_3\)). \(^13\)C NMR (CDCl\(_3\)).

Example 7
2-Thiophen-2-y1-pyrido[2,3-d][1,3]oxazin-4-one (7)
2-Aminopyridine-3-carboxylic acid (0.28g, 2.0 mmol) was dissolved in dry pyridine (8 mL)
and 2-thiophenecarbonyl chloride (0.47 mL, 4.5 mmol) was added under stirring and cooling.
Stirring was maintained for 20 h at room temperature after which the solvent was evaporated. The residue was dissolved in CH₂Cl₂ (40 mL), the organic phase was washed with saturated NaHCO₃ (5 x 20 mL) and concentrated. The solid was purified by flash chromatography on silicagel using EtOAc:heptane 1:1 as the eluent. This gave compound 7 as colourless crystals, 0.28 g (61%), Rf 0.25 (EtOAc:Heptane 1:1). Mp. 199-200 °C. EI/SP MS: M⁺ 230. ¹H NMR (CDCl₃). ¹³C NMR (CDCl₃). Analysis calcd. for: C, 57.38%; H, 2.63%; N, 12.17%. Found: C, 57.50%; H, 2.60%, N, 11.92%.

Example 8

2-Furan-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (8)

2-Aminopyridine-3-carboxylic acid (0.28 g, 2.0 mmol) was dissolved in dry pyridine (8 mL) and 2-furancarbonyl chloride (0.45 mL, 4.5 mmol) was added under stirring and cooling. Stirring was maintained for 20 h at room temperature after which the solvent was evaporated. The residue was dissolved in CH₂Cl₂ (40 mL), the organic phase was washed with saturated NaHCO₃ (10 x 20 mL) and concentrated. The solid was purified by flash chromatography on silicagel using EtOAc:heptane 3:2 as the eluent. Compound 8 was isolated as colourless crystals, 0.28 g (65%), Rf 0.28 (EtOAc:heptane 3:2). Mp. 147-148 °C. EI/SP MS: M⁺ 214. ¹H NMR (CDCl₃). ¹³C NMR (CDCl₃).

Example 9

2-(2-Fluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (9)

2-Aminopyrazine-3-carboxylic acid (0.14 g, 1.0 mmol) was dissolved in dry DMF (5 mL), Et₃N (0.28 mL, 2.0 mmol) was added, followed by addition of 2-fluorobenzoyl chloride (0.25 mL, 2.1 mmol). The suspension was stirred at room temperature for 17 h after which the solvent was evaporated. The residue was suspended and stirred with 0.2 M HCl (5 mL). Saturated NaHCO₃ (10 mL) was added, and the aqueous phase was extracted with CH₂Cl₂ (3 x 10 mL). The organic phase was washed with saturated NaHCO₃ (2 x 10 mL) followed by concentration. The solid was purified by flash chromatography on silicagel using EtOAc:heptane 1:3 - 1:0 as the eluent. Impure 9 was isolated, 50 mg (21%). The product was dissolved in CH₂Cl₂ (10 mL), washed with saturated NaHCO₃ (5 x 5 mL), and the solvent was evaporated to give a solid (45 mg) which was recrystallized from EtOAc to give compound 9 as colourless crystals. Mp. 218-220 °C (decomposition). EI/SP MS: M⁺ 243. ¹H NMR (CDCl₃). ¹³C NMR (CDCl₃). Analysis calcd. for: C, 59.27%; H, 2.48%; N, 17.28%. Found: C, 59.32%; H, 2.46%, N, 16.94%.
Example 10

2-(2,6-Difluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (10)

2-Aminopyrazine-3-carboxylic acid (0.14g, 1.0 mmol) was dissolved in dry DMF (5 mL), Et$_3$N (0.27 mL, 2.0 mmol) was added, followed by addition of 2,6-difluorobenzoyl chloride (0.25 mL, 2.0 mmol). The suspension was stirred at room temperature for 16 h after which the solvent was evaporated. The residue was suspended and stirred with 0.2 M HCl (5 mL). Saturated NaHCO$_3$ (10 mL) was added, and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organic phase was washed with saturated NaHCO$_3$ (10 x 10 mL) followed by concentration. The solid was purified by flash chromatography on silicagel using EtOAc:heptane 1:2 - 1:0 as the eluent. Impure 10 was isolated, 70 mg (21%). The product was dissolved in CH$_2$Cl$_2$ (10 mL), washed with saturated NaHCO$_3$ (5 x 5 mL), and the solvent was evaporated to give 10, 50 mg (19%), as a solid. The compound was recrystallized from EtOAc to give compound 10 as colourless crystals. $^1$H NMR (CDCl$_3$). EI/ SP MS: M$^+$ 261.

Example 11

2-o-Tolyl-pyrazino[2,3-d][1,3]oxazin-4-one (11)

Compound 11 was prepared in three steps starting from 3-aminopyrazine-2-carboxylic acid methyl ester as described in: Wamhoff, H.; Kroth, E., Synthesis (1994) 405.

$^1$H NMR (CDCl$_3$). $^{13}$C NMR (CDCl$_3$). R$_f$ 0.70 (EtOAc). Mp. 174-175 °C. [Lit. 166 °C] EI/ SP MS: M$^+$ 271. Analysis calcd. for: C, 65.27%; H, 3.79%; N, 17.56%. Found: C, 65.26%; H, 3.77%; N, 17.39%.

Example 12

7-Ethylthio-2-(2-fluoro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (12)

4-Amino-5-carboxy-2-ethyl mercaptopyrimidine (100 mg, 0.50 mmol) was dissolved in dry DMF (5 mL), and Et$_3$N (0.14 mL, 1.0 mmol) and subsequently 2-fluorobenzoyl chloride (0.12 mL, 1.0 mmol) were added dropwise. The solution was stirred at room temperature for 17 h and the solvent was evaporated. The solid was stirred with 0.2 M HCl (5 mL) followed by addition of saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the organic phase was washed with saturated NaHCO$_3$ (10 mL) and concentrated. Purification by flash chromatography on silicagel using EtOAc:heptane 1:1 as the eluent.
gave 12 as a crystalline compound, 80 mg (53%). The compound was recrystallized from EtOAc.

$^1$H NMR (CDCl$_3$) showed traces of impurities. $^{13}$C NMR (CDCl$_3$)

Mp. 155-156 °C. El/ SP MS: M$^+$ 303.

Example 13

7-Ethylthio-(2-nitro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (13)

4-Amino-5-carboxy-2-ethyl mercaptopyrimidine (120 mg, 0.60 mmol) was dissolved in dry DMF (5 mL), and Et$_3$N (0.17 mL, 1.2 mmol) and subsequently 2-nitrobenzoyl chloride (0.16 mL, 1.2 mmol) were added dropwise. The solution was stirred at room temperature for 18 h and the solvent was evaporated. The solid was stirred with 0.2 M HCl (5 mL) followed by addition of saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the organic phase was washed with saturated NaHCO$_3$ (3 x 10 mL) and concentrated. Purification by flash chromatography on silicagel using EtOAc:heptane 1:2 as the eluent gave 13 as a crystalline compound, 120 mg (60%). The compound was recrystallized from EtOAc:heptane. $^1$H NMR (CDCl$_3$). $^{13}$C NMR (CDCl$_3$). R, 0.45 (EtOAc:heptane 1:1). Mp. 113-114 °C. El/ SP MS: M$^+$ 330.

Example 14

7-Ethylthio-2-o-tolyl-pyrimido[4,5-d][1,3]oxazin-4-one (14)

4-Amino-5-carboxy-2-ethyl mercaptopyrimidine (120 mg, 0.60 mmol) was dissolved in dry DMF (5 mL), and Et$_3$N (0.17 mL, 1.2 mmol) and subsequently 2-methylbenzoyl chloride (0.16 mL, 1.2 mmol) were added dropwise. The solution was stirred at room temperature for 24 h and the solvent was evaporated. The solid was stirred with 0.2 M HCl (5 mL) followed by addition of saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the organic phase was washed with saturated NaHCO$_3$ (3 x 10 mL) and concentrated. Purification by flash chromatography on silicagel using EtOAc:heptane 1.6 - 1:4 as the eluent gave 14 as a crystalline compound, 60 mg (33%). The compound was recrystallized from EtOAc:heptane.

$^1$H NMR (CDCl$_3$). $^{13}$C NMR (CDCl$_3$). R, 0.45 (EtOAc:heptane 1:3). Mp. 127-128 °C. El/ SP MS: M$^+$ 299. Analysis calcd. for: C, 60.19%; H, 4.38%; N, 14.04%. Found: C, 60.44%; H, 4.33%; N, 13.90%.
Example 15

2-(2-Chloro-phenyl)-7-ethylthio-pyrimido[4,5-d][1,3]oxazin-4-one (15)

4-Amino-5-carboxy-2-ethyl mercaptopryrimidine (120 mg, 0.60 mmol) was dissolved in dry DMF (5 mL), and Et$_3$N (0.17 mL, 1.2 mmol) and subsequently 2-chlorobenzoyl chloride (0.15 mL, 1.2 mmol) were added dropwise. The solution was stirred at room temperature for 24 h and the solvent was evaporated. The solid was stirred with 0.2 M HCl (5 mL) followed by addition of saturated NaHCO$_3$ (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the organic phase was washed with saturated NaHCO$_3$ (3 x 10 mL) and concentrated. Purification by flash chromatography on silicagel using EtOAc:heptane 1:3 as the eluent gave impure 15 (100 mg). The solid was dissolved in CH$_2$Cl$_2$ (10 mL), washed with saturated NaHCO$_3$ (3 x 5 mL), dried (Na$_2$SO$_4$) and concentrated to give compound 15 as colourless crystals, 80 mg (42%). The compound was recrystallized from EtOAc:heptane.

$^1$H NMR (CDCl$_3$). $^{13}$C NMR (CDCl$_3$). R$_f$ 0.20 (EtOAc:heptane 1:3). Mp. 154 - 155°C. El/SP MS: M* 319. Analysis calcd. for: C, 52.59%; H, 3.15%; N, 13.14%. Found: C, 52.71%; H, 3.14%; N, 12.97%.

Example 16

6-(2-Fluoro-phenyl)-1-methyl-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (16)

Ethyl 5-amino-1-methylpyrazol-4-carboxylate (0.51g, 3.0 mmol) was dissolved in dry pyridine (15 mL) and 2-fluorobenzoyl chloride (0.44 mL, 3.6 mmol) was added dropwise. The solution was stirred at 50°C for 5 h, and the solvent was evaporated. The residue was dissolved in CH$_2$Cl$_2$ (20 mL) and washed with saturated NaHCO$_3$ (3 x 10 mL). The organic phase was dried (Na$_2$SO$_4$) and concentrated, and the crude product was purified by flash chromatography on silicagel using EtOAc:heptane 1:3 as the eluent. This gave two products: the bis-acylated compound, 0.3 g, R$_f$ 0.52 (EtOAc:heptane 1:1), and 5-(2-Fluoro-benzoylamino)-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester, 0.22g (25%) as colourless crystals, R$_f$ 0.38 (EtOAc:heptane 1:1), mp. 106-108°C. $^1$H NMR (CDCl$_3$). $^{13}$C NMR (CDCl$_3$). El/SP MS: M* 291. Analysis calcd. For: C, 57.73%; H, 4.84%; N, 14.43%. Found: C, 58.16%; H, 4.87%; N, 14.07%.

5-(2-Fluoro-benzoylamino)-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (0.16g, 0.55 mmol) was dissolved in dry toluene (6 mL). Triphenylphosphine (0.16g, 0.60 mmol) was added, followed by addition of Et$_3$N (0.23 mL, 1.65 mmol). Br$_2$C$_2$Cl$_4$ (0.20 g, 0.60 mmol) was
dissolved in dry toluene (1 mL) and added dropwise. The reaction was stirred at 80 °C for 24 h after which the solvent was evaporated. Purification by flash chromatography on silicagel using EtOAc:heptane 1:3 as the eluent gave 16 as colourless crystals, 95 mg (73%). Rf 0.30 (EtOAc:heptane 1:2). 1H NMR (CDCl₃). 13C NMR (CDCl₃). The compound was recrystallized from EtOAc:heptane, mp. 134-135 °C. EI/SP MS: M⁺ 245. Analysis calcd. For: C, 58.78%; H, 3.29%; N, 17.14%. Found: C, 58.85%; H, 3.22%; N, 16.89%.

Example 17
1-Methyl-6-(2-nitro-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (17)

Ethyl 5-amino-1-methylpyrazol-4-carboxylate (0.85g, 5.0 mmol) was dissolved in dry pyridine (25 mL), and 2-nitrobenzoyl chloride (2.0 mL, 15.0 mmol) was added dropwise. The suspension was stirred at 40 °C for 17 h. The suspension was subsequently stirred with NaHCO₃ (1.26 g, 15.0 mmol), and the solvent was evaporated. The solid was suspended in CH₂Cl₂ (40 mL) and washed with H₂O (20 mL) and aq. NaHCO₃ (3 x 15 mL). The organic phase was dried (Na₂SO₄), filtered and concentrated, and the crude product was crystallized from EtOAc:heptane to give 5-[bis-(2-nitro-benzoyl)-amino]-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester as slightly coloured crystals, 1.83 g (78%). 1H NMR (CDCl₃). Mp. 167-168 °C. Rf 0.32 (EtOAc:heptane 1:1). EI/SP MS: M⁺ 467.

5-[bis-(2-nitro-benzoyl)-amino]-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (1.71 g, 3.7 mmol) was dissolved in dioxane (10 mL) and i-propanol (6 mL), and hydrazine hydrate (0.18 mL, 3.7 mmol) was added dropwise. The solution was refluxed for 1.5 h and the solvent was evaporated. Purification by flash chromatography on silicagel using EtOAc:heptane 1:1 as the eluent gave 1-methyl-5-(2-nitro-benzoylamino)-1H-pyrazole-4-carboxylic acid ethyl ester as colourless crystals, 0.95 g (81%). Rf 0.20 (EtOAc:heptane 1:1). 1H NMR (CDCl₃). Mp. 204-205 °C. EI/SP MS: M⁺ 318. Analysis calcd. For: C, 52.83%; H, 4.43%; N, 17.60%. Found: C, 52.89%; H, 4.44%; N, 17.54%.

1-Methyl-5-(2-nitro-benzoylamino)-1H-pyrazole-4-carboxylic acid ethyl ester (0.37g, 1.16 mmol) was dissolved in dry toluene (75 mL) at 80°C. Triphenylphosphine (0.34g, 1.28 mmol) was added, followed by addition of Et₃N (0.48 mL, 3.49 mmol). Br₂C₂Cl₄ (0.42 g, 1.28 mmol) was dissolved in dry toluene (2 mL) and added dropwise. The reaction was stirred at 80 °C for 18 h, after which the suspension was filtered and the filtrate was concentrated. Purification by flash chromatography on silicagel using EtOAc:heptane 2:3 as the eluent gave 17 as
colourless crystals, 0.24 g (75%). Rf 0.37 (EtOAc:heptane 1:1). 1H NMR (CDCl₃). 13C NMR (CDCl₃). The compound was recrystallized from EtOAc:heptane, mp. 175-176 °C. EI/SP MS: M⁺ 272. Analysis calcd. For: C, 52.95%; H, 2.96%; N, 20.58%. Found: C, 52.94%; H, 2.95%; N, 20.48%.

Example 18

1-Methyl-6-(2-methyl-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (18)

Ethyl 5-amino-1-methylpyrazol-4-carboxylate (0.85g, 5.0 mmol) was dissolved in dry pyridine (25 mL), and 2-methylbenzoyl chloride (1.96 mL, 15.0 mmol) was added dropwise. The suspension was stirred at 40 °C for 17 h. The suspension was subsequently stirred with NaHCO₃ (1.26 g, 15.0 mmol), and the solvent was evaporated. The solid was suspended in CH₂Cl₂ (40 mL) and washed with H₂O (20 mL) and aq. NaHCO₃ (3 x 15 mL). The organic phase was dried (Na₂SO₄), filtered and concentrated, and the crude product was crystallized from EtOAc:heptane to give 5-[bis-(2-methyl-benzoyl)-amino]-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester as slightly colored crystals, 1.60 g (79%). 1H NMR (CDCl₃). Mp. 170-171 °C. Rf 0.51 (EtOAc:heptane 1:1). EI/SP MS: M⁺ 405.

5-[Bis-(2-methyl-benzoyl)-amino]-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (1.49 g, 3.7 mmol) was dissolved in dioxane (10 mL) and i-propanol (6 mL), and hydrazine hydrate (0.18 mL, 3.7 mmol) was added dropwise. The solution was refluxed for 1.5 h and the solvent was evaporated. Purification by flash chromatography on silica gel using EtOAc:heptane 2:3 - 1:1 as the eluent gave 1-methyl-5-(2-methyl-benzoylamino)-1H-pyrazole-4-carboxylic acid ethyl ester as colourless crystals, 1.0 g (94%). Rf 0.40 (EtOAc:heptane 1:1). 1H NMR (CDCl₃). Mp. 119-120 °C. EI/SP MS: M⁺ 287. Analysis calcd. For: C, 62.71%; H, 5.96%; N, 14.62%. Found: C, 62.84%; H, 6.00%; N, 14.58%.

1-Methyl-5-(2-methyl-benzoylamino)-1H-pyrazole-4-carboxylic acid ethyl ester (0.52g, 1.88 mmol) was dissolved in dry toluene (15 mL) at 80°C. Triphenylphosphine (0.54g, 2.07 mmol) was added, followed by addition of Et₃N (0.78 mL, 5.64 mmol). Br₂C₂Cl₄ (0.67g, 2.07 mmol) was dissolved in dry toluene (3 mL) and added dropwise. The reaction was stirred at 80 °C for 18 h, after which the suspension was filtered and the filtrate was concentrated. Purification by flash chromatography on silica gel using EtOAc:heptane 1:3 as the eluent gave 18 as colourless crystals, 0.40 g (89%). Rf 0.25 (EtOAc:heptane 1:3). 1H NMR (CDCl₃). 13C NMR (CDCl₃). The compound was recrystallized from EtOAc:heptane, mp. 130-131 °C. EI/SP
MS: M⁺ 241. Analysis calcd. For: C, 64.72%; H, 4.60%; N, 17.42%. Found: C, 64.60%; H, 4.63%; N, 17.38%.

Example 19

5-(2,6-Difluoro-phenyl)-7-methyl-thieno[3,2-d][1,3]oxazin-4-one (19)

Methyl 3-amino-4-methylthiophene-2-carboxylate (0.68g, 4.0 mmol) was dissolved in dry pyridine (10 mL) and 2,6-difluorobenzoyl chloride (0.53 mL, 4.2 mmol) was added. The suspension was stirred at room temperature for 7 d after which the solvent was evaporated. The solid was dissolved in CH₂Cl₂ (50 mL) and the organic phase was washed with saturated NaHCO₃ (3 x 30 mL), dried (Na₂SO₄), filtered and concentrated. This gave 3-(2,6-difluorobenzoylamino)-4-methylthiophene-2-carboxylic acid methyl ester as a colourless crystalline compound (1.17g, 94%). Rₑ 0.33 (EtOAc:heptane 1:2). ¹H NMR (CDCl₃). The compound was recrystallized from EtOAc, mp. 159-160°C. El/ SP MS: M⁺ 311. Analysis calcd for: C, 54.02%; H, 3.56%; N, 4.50%. Found: C, 53.97%; H, 3.53%; N, 4.45%.

3-(2,6-Difluoro-benzoylamino)-4-methyl-thiophene-2-carboxylic acid methyl ester (0.45g, 1.45 mmol) was dissolved in dry toluene (25 mL) at 80°C. Then PPh₃ (0.42g, 1.59 mmol) was added followed by addition of Et₃N (0.60 mL, 4.34 mmol). C₂Br₂Cl₂ (0.52g, 1.59 mmol) was dissolved in dry toluene (2 mL) and added to the reaction mixture. The suspension was stirred at 80°C for 7 h and at 50°C for 90 h, after which it was filtered, and the filtrate was concentrated. The crude product was purified by flash chromatography on silicagel using EtOAc:heptane 1:4 as the eluent. This gave 19 as a colourless crystalline compound (0.32g, 80%). Rₑ 0.50 (EtOAc:heptane 1:2). ¹H NMR (CDCl₃). ¹³C NMR (CDCl₃). The compound was recrystallized from EtOAc, mp. 149-151°C. El/ SP MS: M⁺ 279. Analysis calcd. For: C, 55.91; H, 2.53%; N, 5.02%. Found: C, 55.95%; H, 2.49%; N, 4.98%.

Example 20

5-Methyl-2-(2-nitro-phenyl)-thieno[2,3-d][1,3]oxazin-4-one (20)

Ethyl 2-amino-4-methylthiophene-3-carboxylate (0.74g, 4.0 mmol) was dissolved in dry CH₂Cl₂ (10 mL). 2-Nitrobenzoyl chloride (0.58 mL, 4.4 mmol) was added followed by the addition of Et₃N (0.61 mL, 4.4 mmol). The suspension was stirred at room temperature for 72 h after which the organic phase was washed with saturated NaHCO₃ (3 x 30 mL), dried (Na₂SO₄), filtered and concentrated. This gave 4-methyl-2-(2-nitro-benzoylamino)-thiophene-3-carboxylic acid ethyl ester as slightly coloured crystals (1.23g, 92%). Rₑ 0.25
(EtOAc:heptane 1:2). $^1$H NMR (CDCl$_3$). The compound was recrystallized from EtOAc, mp. 135-137 °C. EI/SP MS: M$^+$ 334.

4-Methyl-2-(2-nitro-benzoylamino)-thiophene-3-carboxylic acid ethyl ester (0.38g, 1.1 mmol) was dissolved in dry toluene (25 mL) at 80°C. PPh$_3$ (0.33g, 1.3 mmol) was added followed by the addition of Et$_3$N (0.47 mL, 3.4 mmol). C$_2$Br$_2$Cl$_4$ (0.41g, 1.3 mmol) was dissolved in dry toluene (2 mL) and added to the reaction mixture. The suspension was stirred at 80°C for 24h after which it was filtered, and the filtrate was concentrated. The crude product was purified by flash chromatography on silicagel using EtOAc:heptane 1:4 as the eluent. This gave 20 as a slightly yellow crystalline compound (0.29g, 91%). R$_f$ 0.31 (EtOAc:heptane 1:2). $^1$H NMR (CDCl$_3$). $^{13}$C NMR (CDCl$_3$). The compound was recrystallized from EtOAc to give slightly coloured crystals, mp. 155-165 °C. EI/SP MS: M$^+$ 288. Analysis calcd. For: C, 54.16%; H, 2.80%; N, 9.72%. Found: C, 54.11%; H, 2.75%; N, 9.66%.

Example 21

2-Furan-2-yl-thieno[2,3-d][1,3]oxazin-4-one (21)

2-[(Furan-2-carbonyl)-amino]-thiophene-3-carboxylic acid methyl ester (0.1g) was dissolved in LiOH in methanol (5%, 1.6 ml) and methylenchloride (2 ml). The mixture was refluxed for 24 h and evaporated to dryness. After drying over P2O$_5$ overnight the residue was refluxed with acetic anhydride (8 ml) for 24 h. The reaction mixture was subsequently evaporated to dryness, and the residue purified on silicagel using dichloromethane as eluent. The fraction containing the title compound was collected. Yield 0.035 g, (38%). Mp 144.5 °C, the product identified by NMR and MS.

Example 22

2-Thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one (22)

2-[(Thiophene-2-carbonyl)-amino]-thiophene-3-carboxylic acid methyl ester (0.1g) was refluxed in KOH (10% in Methanol, 0.36 ml) and methanol (2 ml) for 24 h. Acetic anhydride (3 ml) was added and the mixture further refluxed for 18 h. The mixture was evaporated to dryness extracted between sat. NaCl solution and toluene, the organic layer separated and washed with water (x4), dried with MgSO$_4$, filtered and evaporated to dryness. The residue was purified on silicagel using dichloromethane as eluent.

30 mg (35%) of the title compound was isolated. Mp 162 C MS: M+ 235.
Examples 23-33

The following examples (23 - 33) of compounds useful according to the present invention are commercially available from commercial sources like Specs, Maybridge, Bionet, and Salor.

<table>
<thead>
<tr>
<th>Example</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>2-tert-Butyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one</td>
</tr>
<tr>
<td>24</td>
<td>2-(4-Bromo-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one</td>
</tr>
<tr>
<td>25</td>
<td>2-(4-Methoxy-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one</td>
</tr>
<tr>
<td>26</td>
<td>2-(2-Methoxy-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one</td>
</tr>
<tr>
<td>27</td>
<td>2-Methyl-5-thiopen-2-yl-thieno[2,3-d][1,3]oxazin-4-one</td>
</tr>
<tr>
<td>28</td>
<td>2-Furan-2-yl-5-thiopen-2-yl-thieno[2,3-d][1,3]oxazin-4-one</td>
</tr>
<tr>
<td>29</td>
<td>2-(2-Bromo-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one</td>
</tr>
<tr>
<td>30</td>
<td>2-Methyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one</td>
</tr>
<tr>
<td>31</td>
<td>2-(4-Chloro-phenyl)-5,6-dimethyl-thieno[2,3-d][1,3]oxazin-4-one</td>
</tr>
<tr>
<td>32</td>
<td>2-Phenyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one</td>
</tr>
<tr>
<td>33</td>
<td>2-(3-Trifluoromethyl-phenyl)-thieno[3,2-d][1,3]oxazin-4-one</td>
</tr>
</tbody>
</table>
Example 34
The inhibitory effect of representative compounds are tested in a FVIIa/TF-catalysed FX activation assay. The anticoagulant potency is tested in a FVIIa/TF-induced plasma clotting assay.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ex. No.</th>
<th>IC50 TF/FVII/FX</th>
<th>Clot Ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Furan-2-yl-5-thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one</td>
<td>28</td>
<td>21</td>
<td>1.07</td>
</tr>
<tr>
<td>5-Methyl-2-(2-nitro-phenyl)-thieno[2,3-d][1,3]oxazin-4-one (20)</td>
<td>20</td>
<td>3.5</td>
<td>2.18</td>
</tr>
<tr>
<td>2-(2,6-Difluoro-phenyl)-7-methyl-thieno[3,2-d][1,3]oxazin-4-one (19)</td>
<td>19</td>
<td>5.3</td>
<td>1.8</td>
</tr>
<tr>
<td>1-Methyl-6-(2-methyl-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (18)</td>
<td>18</td>
<td>18</td>
<td>1.8</td>
</tr>
<tr>
<td>7-Ethylthio-2-o-tolyl-pyrimido[4,5-d][1,3]oxazin-4-one (14)</td>
<td>14</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>2-(2,6-Difluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (6)</td>
<td>6</td>
<td>0.6</td>
<td>1.4</td>
</tr>
<tr>
<td>2-(2-Fluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (5)</td>
<td>5</td>
<td>2.8</td>
<td>1.3</td>
</tr>
<tr>
<td>2-(2,6-Difluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (2)</td>
<td>2</td>
<td>1.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>
CLAIMS

1. Use of a compound with the formula I or the formula II

\[
\begin{align*}
\text{I} & : R_1 \quad X \quad Y \quad A \quad R_2 \quad \text{O} \\
\text{II} & : R_1 \quad Z \quad R_2 \quad X \quad B \quad \text{O} \\
\end{align*}
\]

wherein

X, Y, Z and W independently are CH, CH₂, O, S, N, NH or N-PG, where PG is CH₃, benzyl (Bn), butyloxy carbonyl (BOC), benzyloxy carbonyl (CBz), 9-fluorenylmethoxycarbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

5 at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.

R¹ and R² independently are

15 C₁₋₈-alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, or C₃₋₆ cycloalkyl, each optionally substituted with halogen, OH, NH₂, NHR⁴, N(R⁴)², NHCOR⁴, C₁₋₄ alkoxy, trifluoromethoxy, carbamoyl, CONHR⁴, or CON(R⁴)²;

H, Halogen, CF₃, C₁₋₈ alkoxy, C₁₋₈ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR⁴, OH, NH₂, NHR⁴, N(R⁴)², NHCOR⁴, CON(R⁴)², CONHSO₂R⁴, SO₂NH₂, SO₂NHR⁴, C₁₋₄ alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R³ is aryl or heteroaryl, each optionally substituted with one or more

C₁₋₈-alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, or C₃₋₆ cycloalkyl, each optionally substituted with halogen, OH, NO₂, NH₂, NHR⁴, N(R⁴)², NHCOR⁴, C₁₋₄ alkoxy, trifluoromethoxy, carbamoyl, CONHR⁴, or CON(R⁴)²;

Halogen, CF₃, C₁₋₈ alkoxy, C₁₋₈ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR⁴, OH, NO₂, NH₂, NHR⁴, N(R⁴)², NHCOR⁴, CON(R⁴)², CONHSO₂R⁴, SO₂NH₂, SO₂NHR⁴, C₁₋₄ alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

30 R⁴ is C₁₋₄-alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, or phenyl;
or a pharmaceutical acceptable salt thereof,
for the manufacture of a medicament for the treatment of coagulation-related diseased states.

2. Use of a compound with the formula I or the formula II

![Chemical structures](image)

wherein

X, Y, Z and W independently are CH, CH2, O, S, N, NH or N-PG, where PG is CH3, benzyl (Bn), butyloxycarbonyl (BOC), benzyloxycarbonyl (Cbz), 9-fluorenlymethoxycarbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.

R1 and R2 independently are
C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or C3-8 cycloalkyl, each optionally substituted with halogen, OH, NH2, NHR4, N(R4)2, NHCOR4, C1-4 alkoxy, trifluoromethoxy, carbamoyl, CONHR4, or CON(R4)2;

H, Halogen, CF3, C1-6 alkoxy, C1-6 alkylthio, OCF3, COOH, CN, CONH2, CONHR4, OH, NH2, NHR4, N(R4)2, NHCOR4, CON(R4)2, CONHSO2R4, SO2NH2, SO2NHR4, C1-4 alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R3 is aryl or heteroaryl, each optionally substituted with one or more
C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or C3-8 cycloalkyl, each optionally substituted with halogen, OH, NO2, NH2, NHR4, N(R4)2, NHCOR4, C1-4 alkoxy, trifluoromethoxy, carbamoyl, CONHR4, or CON(R4)2;

Halogen, CF3, C1-6 alkoxy, C1-6 alkylthio, OCF3, COOH, CN, CONH2, CONHR4, OH, NO2,
NH₂, NHR⁻, N(R⁻)₂, NHCOR⁻, CON(R⁻)₂, CONHSO₂R⁻, SO₂NH₂, SO₂NHR⁻, C₁₋₄ alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R⁻ is C₁₋₄-alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₄ cycloalkyl, or phenyl;

or a pharmaceutical acceptable salt thereof,

for the manufacture of a medicament for the inhibition of TF-FVIIa activity in a mammal.

3. Use according to claim 1 or claim 2, wherein the compounds are selected from compounds having one of the below listed formulas:
or a pharmaceutically acceptable salt thereof.

4. Use, according to any of claims 1-3, wherein R3 is an ortho-monosubstituted aryl, an orto-disubstituted aryl or a heteroaryl ring.

5. Use, according to claim 4, in which the compound with formula I or II are selected from a list consisting of

2-(2-Fluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (1)
2-(2,6-Difluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (2)
2-Thiophen-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (3)
2-Furan-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (4)
2-(2-Fluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (5)
2-(2,6-Difluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (6)
2-Thiophen-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (7)
2-Furan-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (8)
2-(2-Fluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (9)
2-(2,6-Difluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (10)
2-o-Tolyl-pyrazino[2,3-d][1,3]oxazin-4-one (11)
7-Ethylthio-(2-fluoro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (12)
7-Ethylthio-(2-nitro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (13)
7-Ethylthio-2-o-tolyl-pyrimido[4,5-d][1,3]oxazin-4-one (14)
2-(2-Chloro-phenyl)-7-etethylthio-pyrimido[4,5-d][1,3]oxazin-4-one (15)
6-(2-Fluoro-phenyl)-1-methyl-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (16)
1-Methyl-6-(2-nitro-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (17)
1-Methyl-6-(2-methyl-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (18)
2-(2,6-Difluoro-phenyl)-7-methyl-thieno[3,2-d][1,3]oxazin-4-one (19)
5-Methyl-2-(2-nitro-phenyl)-thieno[2,3-d][1,3]oxazin-4-one (20)
2-Furan-2-yl-thieno[2,3-d][1,3]oxazin-4-one (21)
2-Thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one (22)
2-tert-Butyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(4-Bromo-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(4-Methoxy-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(2-Methoxy-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-Methyl-5-thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one
2-Furan-2-yl-5-thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one
2-(2-Bromo-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-Methyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(4-Chloro-phenyl)-5,6-dimethyl-thieno[2,3-d][1,3]oxazin-4-one
2-Phenyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(3-Trifluoromethyl-phenyl)-thieno[3,2-d][1,3]oxazin-4-one

and pharmaceutical acceptable salts thereof.

6. Use according to any of claims 1-5, wherein the medicament is for use as an inhibitor of blood coagulation in a mammal, or for use as an inhibitor of clotting activity in a mammal, or for use as an inhibitor of deposition of fibrin in a mammal, or for use as an inhibitor of platelet deposition in a mammal.

7. Use according to any of claims 1-6, wherein the medicament is for the treatment of mammals suffering from deep vein thrombosis, pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition, or myocardial infarction, or for prophylactic treatment of mammals with atherosclerotic vessels at risk for thrombosis.

8. A method of modulating and normalizing an impaired haemostatic balance in a mammal, which method comprises administering an effective amount of at least one compound with
formula I or II

wherein

X, Y, Z and W independently are CH, CH2, O, S, N, NH or N-PG, where PG is CH3, benzyl (Bn), butyloxy carbonyl (BOC), benzyl oxycarbonyl (CBz), 9-fluorenylmethoxy carbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.

R1 and R2 independently are

C1-8-alkyl, C2-8 alkenyl, C2-8 alkynyl, or C3-6 cycloalkyl, each optionally substituted with halogen, OH, NH2, NHR4, N(R4)2, NHCOR4, C1-4 alkoxy, trifluoromethoxy, carbamoyl, CONHR4, or CON(R4)2;

H, Halogen, CF3, C1-6 alkoxy, C1-6 alkylthio, OCF3, COOH, CN, CONH2, CONHR4, OH, NH2, NHR4, N(R4)2, NHCOR4, CON(R4)2, CONHSO2R4, SO2NH2, SO2NHR4, C1-4 alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R3 is aryl or heteroaryl, each optionally substituted with one or more

C1-8-alkyl, C2-8 alkenyl, C2-8 alkynyl, or C3-6 cycloalkyl, each optionally substituted with halogen, OH, NO2, NH2, NHR4, N(R4)2, NHCOR4, C1-4 alkoxy, trifluoromethoxy, carbamoyl, CONHR4, or CON(R4)2;

Halogen, CF3, C1-6 alkoxy, C1-6 alkylthio, OCF3, COOH, CN, CONH2, CONHR4, OH, NO2, NH2, NHR4, N(R4)2, NHCOR4, CON(R4)2, CONHSO2R4, SO2NH2, SO2NHR4, C1-4 alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R4 is C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C3-8 cycloalkyl, or phenyl;
or a pharmaceutical acceptable salt thereof; in combination with a pharmaceutical acceptable excipient and/or carrier, to the mammal in need of such a treatment.

9. A method for treatment of coagulation-related diseased states in a mammal, which method comprises administering an effective amount of at least one compound with formula I or II

![Chemical Structures]

wherein

X, Y, Z and W independently are CH, CH2, O, S, N, NH or N-PG, where PG is CH3, benzyl (Bn), butyloxycarbonyl (BOC), benzoxycarbonyl (CBz), 9-fluorenylmethoxycarbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.

R1 and R2 independently are

C1-8-alkyl, C2-8 alkenyl, C2-8 alkynyl, or C3-6 cycloalkyl, each optionally substituted with halogen, OH, NH2, NHR4, N(R4)2, NHCOR4, C1-4 alkoxy, trifluoromethoxy, carbamoyl, CONHR4, or CON(R4)2;

H, Halogen, CF3, C1-6 alkoxy, C1-6 alkylthio, OCF3, COOH, CN, CONH2, CONHR4, OH, NH2, NHR4, N(R4)2, NHCOHR4, CON(R4)2, CONHSO2R4, SO2NH2, SO2NHR4, C1-4 alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R3 is aryl or heteroaryl, each optionally substituted with one or more

C1-8-alkyl, C2-8 alkenyl, C2-8 alkynyl, or C3-4 cycloalkyl, each optionally substituted with halogen, OH, NO2, NH2, NHR4, N(R4)2, NHCOR4, C1-4 alkoxy, trifluoromethoxy, carbamoyl, CONHR4, or CON(R4)2;

Halogen, CF3, C1-6 alkoxy, C1-6 alkylthio, OCF3, COOH, CN, CONH2, CONHR4, OH, NO2,

NH2, NHR4, N(R4)2, NHCOR4, CON(R4)2, CONHSO2R4, SO2NH2, SO2NHR4, C1-4 alkoxyca-
bonyl, phenyl, alkylphenyl, or tetrazole

R¹ is C₁₋₄-alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, or phenyl;

or a pharmaceutical acceptable salt thereof, in combination with a pharmaceutical acceptable excipient and/or carrier, to the mammal in need of such a treatment.

10. A method for treatment of mammals suffering from deep vein thrombosis, pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition and associated disorders and myocardial infarction, and for the prophylactic treatment of mammals with atherosclerotic vessels at risk for thrombosis, which method comprises administering a therapeutically effective amount of at least one compound with formula I or II

wherein
X, Y, Z and W independently are CH, CH₂, O, S, N, NH or N-PG, where PG is CH₃, benzyl (Bn), butyloxy carbonyl (BOC), benzyl oxycarbonyl (CBz), 9-fluorenylmethoxycarbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.

R¹ and R² independently are
C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, or C₃₋₆ cycloalkyl, each optionally substituted with halogen, OH, NH₂, NHR¹, N(R¹)₂, NHCOR¹, C₁₋₄ alkoxy, trifluoromethoxy, carbamoyl, CONHR¹, or CON(R¹)₂;
H, Halogen, CF₃, C₁₋₄ alkoxy, C₁₋₄ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR¹, OH, NH₂, NHR¹, N(R¹)₂, NHCOR¹, CON(R¹)₂, CONHSO₂R¹, SO₂NH₂, SO₂NHR¹, C₁₋₄ alkoxy carbonyl, phenyl, alkyl phenyl, or tetrazole
R³ is aryl or heteroaryl, each optionally substituted with one or more C₁₅₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, or C₃₋₆ cycloalkyl, each optionally substituted with halogen, OH, NO₂, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, C₁₋₄ alkoxy, trifluoromethoxy, carbamoyl, CONHR⁴, or CON(R⁴)₂; Halogen, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR⁴, OH, NO₂, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, CON(R⁴)₂, CONHSO₂R⁴, SO₂NH₂, SO₂NHR⁴, C₁₋₄ alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R⁴ is C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, or phenyl; or a pharmaceutical acceptable salt thereof, in combination with a pharmaceutical acceptable excipient and/or carrier, to the mammal in need of such a treatment.

11. A method for inhibiting tissue factor activity in a mammal which method comprises administering an effective amount of at least one compound with formula I or II

\[
\begin{align*}
\text{I} & \\
R₁ & \\
R₂ & \\
R₃ & \\
\text{II} & \\
R₂ & \\
R₁ & \\
\end{align*}
\]

wherein
X, Y, Z and W independently are CH, CH₂, O, S, N, NH or N-PG, where PG is CH₃, benzyl (Bn), butyloxy carbonyl (BOC), benzyl oxy carbonyl (CBz), 9-fluorenylmethoxycarbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.

R¹ and R² independently are C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, or C₃₋₆ cycloalkyl, each optionally substituted with halogen, OH, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, C₁₋₄ alkoxy, trifluoromethoxy, carbamoyl, CONHR⁴, or CON(R⁴)₂;
H, Halogen, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR⁴, OH, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, CON(R⁴)₂, CONHSO₃R⁴, SO₂NH₂, SO₂NHR⁴, C₁₋₄ alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R² is aryl or heteroaryl, each optionally substituted with one or more
C₁₋₃ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or C₃₋₆ cycloalkyl, each optionally substituted with halogen, OH, NO₂, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, C₁₋₄ alkoxy, trifluoromethoxy, carbamoyl, CONHR⁴, or CON(R⁴)₂;
Halogen, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR⁴, OH, NO₂, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, CON(R⁴)₂, CONHSO₃R⁴, SO₂NH₂, SO₂NHR⁴, C₁₋₄ alkoxy carbonyl, phenyl, alkylphenyl, or tetrazole

R⁴ is C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, or phenyl;

or a pharmaceutical acceptable salt thereof, in combination with a pharmaceutical acceptable excipient and/or carrier, to the mammal in need of such a treatment.

12. A method for inhibiting factor VII activity by substantially reducing the ability of activated factor VII to catalyze tissue factor-enhanced activation of factors X and IX, which method comprises administering at least one compound with formula I or II

![Diagram](image)

wherein
X, Y, Z and W independently are CH, CH₂, O, S, N, NH or N-PG, where PG is CH₃, benzyl (Bn), butyloxy carbonyl (BOC), benzyl oxycarbonyl (CBz), 9-fluorenylmethoxy carbonyl (Fmoc), or tosyl (Ts), or another nitrogen protection group;

at least one of X, Y, Z and W is O, S, N, NH or N-PG;

A and B may be aromatic, saturated or partly saturated.
R¹ and R² independently are
C₁-₆-alkyl, C₂-₈ alkenyl, C₂-₈ alkynyl, or C₃-₆ cycloalkyl, each optionally substituted with halo-
gen, OH, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, C₁-₄ alkoxy, trifluoromethoxy, carboxamoyl, CONHR⁴, or
CON(R⁴)₂;
H, Halogen, CF₃, C₁-₆ alkoxy, C₁-₆ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR⁴, OH, NH₂,
NHR⁴, N(R⁴)₂, NHCOR⁴, CON(R⁴)₂, CONHSO₂R⁴, SO₂NH₂, SO₂NHR⁴, C₁-₄ alkoxy carbonyl,
phenyl, alkylphenyl, or tetrazole

R³ is aryl or heteroaryl, each optionally substituted with one or more
C₁-₆-alkyl, C₂-₈ alkenyl, C₂-₈ alkynyl, or C₃-₆ cycloalkyl, each optionally substituted with halo-
gen, OH, NO₂, NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, C₁-₄ alkoxy, trifluoromethoxy, carboxamoyl,
CONHR⁴, or CON(R⁴)₂;
Halogen, CF₃, C₁-₆ alkoxy, C₁-₆ alkylthio, OCF₃, COOH, CN, CONH₂, CONHR⁴, OH, NO₂,
NH₂, NHR⁴, N(R⁴)₂, NHCOR⁴, CON(R⁴)₂, CONHSO₂R⁴, SO₂NH₂, SO₂NHR⁴, C₁-₄ alkoxy carb-
onyl, phenyl, alkylphenyl, or tetrazole

R⁴ is C₁-₄-alkyl, C₂-₄ alkenyl, C₂-₄ alkynyl, C₃-₈ cycloalkyl, or phenyl;
or a pharmaceutical acceptable salt thereof, in combination with a pharmaceutical accept-
able excipient and/or carrier, to a mammal in need of such a treatment.

13. Method, according to claims 8-12, wherein the compounds are selected from compounds
having one of the below listed formulas:

![Chemical Structure]
or a pharmaceutically acceptable salt thereof.

14. Method, according to claim 8-13, wherein R3 is an ortho-monosubstituted aryl, an ortho-disubstituted aryl or a heteroaryl ring.

15. Method according to claim 14 in which the compound with formula I or II are selected from a list consisting of
2-(2-Fluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (1)
2-(2,6-Difluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (2)
2-Thiophen-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (3)
2-Furan-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (4)
2-(2-Fluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (5)
2-(2,6-Difluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (6)
2-Thiophen-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (7)
2-Furan-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (8)
2-(2-Fluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (9)
2-(2,6-Difluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (10)
2-O-Tolyl-pyrazino[2,3-d][1,3]oxazin-4-one (11)
2-Ethylthio-2-(2-fluoro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (12)
2-Ethylthio-(2-nitro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (13)
2-Ethylthio-2-o-tolyl-pyrimido[4,5-d][1,3]oxazin-4-one (14)
2-(2-Chloro-phenyl)-7-ethylthio-pyrimido[4,5-d][1,3]oxazin-4-one (15)
6-(2-Fluoro-phenyl)-1-methyl-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (16)
1-Methyl-6-(2-nitro-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (17)
1-Methyl-6-(2-methyl-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (18)
2-(2,6-Difluoro-phenyl)-7-methyl-thieno[3,2-d][1,3]oxazin-4-one (19)
5-Methyl-2-(2-nitro-phenyl)-thieno[2,3-d][1,3]oxazin-4-one (20),
2-Furan-2-yl-thieno[2,3-d][1,3]oxazin-4-one (21)
2-Thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one (22)
2-tert-Butyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(4-Bromo-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(4-Methoxy-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(2-Methoxy-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-Methyl-5-thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one
2-Furan-2-yl-5-thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one
2-(2-Bromo-phenyl)-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-Methyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(4-Chloro-phenyl)-5,6-dimethyl-thieno[2,3-d][1,3]oxazin-4-one
2-Phenyl-5,6,7,8-tetrahydro-3-oxa-9-thia-1-aza-fluoren-4-one
2-(3-Trifluoromethyl-phenyl)-thieno[3,2-d][1,3]oxazin-4-one
and pharmaceutical acceptable salts thereof.

16. A compound with formula I or formula II, selected from a list consisting of the compounds:

5 2-(2-Fluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (1)
2-(2,6-Difluoro-phenyl)-pyrido[3,4-d][1,3]oxazin-4-one (2)
2-Thiophen-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (3)
2-Furan-2-yl-pyrido[3,4-d][1,3]oxazin-4-one (4)
2-(2-Fluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (5)
2-(2,6-Difluoro-phenyl)-pyrido[2,3-d][1,3]oxazin-4-one (6)
2-Thiophen-2-yl-pyrido[2,3-d][1,3]oxazin-4-one (7)
2-(2-Fluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (9)
2-(2,6-Difluoro-phenyl)-pyrazino[2,3-d][1,3]oxazin-4-one (10)
7-Ethylthio-2-(2-fluoro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (12)
15 7-Ethylthio-(2-nitro-phenyl)-pyrimido[4,5-d][1,3]oxazin-4-one (13)
7-Ethylthio-2-o-tolyl-pyrimido[4,5-d][1,3]oxazin-4-one (14)
2-(2-Chloro-phenyl)-7-ethylthio-pyrimido[4,5-d][1,3]oxazin-4-one (15)
6-(2-Fluoro-phenyl)-1-methyl-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (16)
1-Methyl-6-(2-methyl-phenyl)-1H-pyrazolo[3,4-d][1,3]oxazin-4-one (18)
20 2-(2,6-Difluoro-phenyl)-7-methyl-thieno[3,2-d][1,3]oxazin-4-one (19)
5-Methyl-2-(2-nitro-phenyl)-thieno[2,3-d][1,3]oxazin-4-one (20)
2-Furan-2-yl-thieno[2,3-d][1,3]oxazin-4-one (21)
2-Thiophen-2-yl-thieno[2,3-d][1,3]oxazin-4-one (22)
and pharmaceutical acceptable salts thereof.

17. A pharmaceutical composition comprising a therapeutically active amount of a compound according to claim 16, or a pharmaceutical acceptable salt thereof, in combination with a pharmaceutical acceptable excipient and/ or carrier.

18. The pharmaceutical composition according to claims 16-17, for use as an inhibitor of blood coagulation in a mammal, or for use as an inhibitor of clotting activity in a mammal, or for use as an inhibitor of deposition of fibrin in a mammal, or for use as an inhibitor of platelet deposition in a mammal or for modulating and normalizing an impaired haemostatic balance in a mammal, or for treatment of coagulation-related diseased states.
19. The pharmaceutical composition according to claims 16-18, for use in the treatment of mammals suffering from deep vein thrombosis, pulmonary embolism, stroke, disseminated intravascular coagulation (DIC), vascular restenosis, platelet deposition and associated disorders, or myocardial infarction, or in the prophylactic treatment of mammals with atherosclerotic vessels at risk for thrombosis.
### INTERNATIONAL SEARCH REPORT

#### A. CLASSIFICATION OF SUBJECT MATTER

**IPC7:** A61K 31/5365, C07D 498/04, A61P 7/02, A61P 9/10

According to International Patent Classification (IPC) or to both national classification and IPC

#### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC7:** A61K, C07D, A61P

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

**SE, DK, FI, NO classes as above**

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

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>EP 0147211 A2 (SYNTEX INC.), 3 July 1985 (03.07.85), see page 50, lines 9-30</td>
<td>1-19</td>
</tr>
<tr>
<td>X</td>
<td>EP 0206323 A1 (SYNTEX INC.), 30 December 1986 (30.12.86), see page 37, lines 22-35 and page 38, lines 1-7</td>
<td>1-19</td>
</tr>
<tr>
<td>X</td>
<td>WO 9607648 A1 (WARNER-LAMBERT COMPANY), 14 March 1996 (14.03.96), see page 16, lines 1-3</td>
<td>1-19</td>
</tr>
</tbody>
</table>

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

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

Date of the actual completion of the international search: 20 March 2000

Date of mailing of the international search report: 05-04-2000

Name and mailing address of the ISA/SG: Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
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Form PCT/ISA/3(10) second sheet (July 1997)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>A</td>
<td>Il Farmaco, Volume 46, No 7,8, 1991, Giuseppe Daidone et al, &quot;Researches on antiinflammatory agents. Studies on some 1-methyl- or 1-phenyl-6-(2-substitutedphenyl)-pyrazol(3,4-d)-1,3-oxazin-4(1H)-ones&quot; page 945 - page 957</td>
<td>1-19</td>
</tr>
<tr>
<td>A</td>
<td>Synthesis, April 1994, Heinrich Wamhoff et al, &quot;Dihalogentriphenylphosphorane in der Heterocyclensynthese, 29.1 Eine einfache Synthese von Pteridin-4-onen aus 3-Amino-2-pyrazincarbonsäuremethylster und Pyrazino(3,1)oxazin-4-onen&quot; page 405 - page 410</td>
<td>1-19</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK99/00646

Box I  Observations where certain claims were found uns searchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: 8–15 because they relate to subject matter not required to be searched by this Authority, namely:
   see next sheet

2. □ Claims Nos.: 3 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
   The last structure in claim 3 is not considered to be within the scope of protection according to claims 1 and 2.

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 

Remark on Protest □ The additional search fees were accompanied by the applicant’s protest.
□ No protest accompanied the payment of additional search fees.
Claims 8-15 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1 (iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.
## INTERNATIONAL SEARCH REPORT

Information on patent family members

**02/12/99**

**PCT/DK 99/00646**

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