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(54) Title: COMPOUNDS FOR USE AS ANTIFIBRINOLYTIC AGENTS

(57) Abstract: It relates to matrix metalloprotease (MMP) inhibitors for their pharmaceutically or veterinary acceptable salts for use as antifibrinolytic agents, in particular, to prevent and control bleeding.

Compounds for use as antifibrinolytic agents

The present invention relates to a second medical indication of known therapeutic agents. Particularly, this invention relates to known compounds for use as antifibrinolytic agents, in particular, to prevent and control bleeding.

BACKGROUND ART

The hemostatic system is responsible for maintaining circulatory fluidity and for preventing hemorrhage in response to vascular injury. Physiological hemostasis is controlled by mechanisms of coagulation and the formation of fibrin and by those favouring the degradation of fibrin (fibrinolysis).

Hyperfibrinolysis refers to a congenital or acquired condition due to pathological activation of natural defense mechanisms, the fibrinolytic system. It is characterized by the generation of large amounts of plasmin, which degrades fibrin leading to massive clot lysis and clinical bleeding. Hyperfibrinolytic states predispose to important hemorrhagic complications, often requiring transfusions and the need for re-exploration having a detrimental effect on patient outcome. Hemorhage is responsible for almost 50% of deaths occurring within 24 hours of traumatic injury and for up to 80% of intraoperative trauma mortality. In western countries about one third of in-hospital deaths due to trauma is caused by abnormal blood loss which is an important contributory factor for other causes of death, particularly multi-organ failure, requiring massive blood transfusion. Failure to start appropriate early management in bleeding trauma patients is a leading cause of preventable death from trauma. Post-partum hemorrhage (PPH) is another leading cause of death in the developing world, accounting for 25% of maternal deaths, and rose in the the developed world from 1.5% in 1999 to 4.1% in 2009. The risk of hemorrhage can also be important in cardiovascular patients on anti-coagulant therapy. Pharmacological approaches are an important part of multimodal therapy aiming to reducing bleeding and transfusion in order to reverse specific defects associated with such states; among them, the role of fibrinolysis inhibitors is growing.

It is well known that subjects who bleed excessively in association with surgery or major trauma and need blood transfusions develop more

complications than those who do not experience any bleeding. However, moderate bleeding requiring the administration of human blood products may lead to complications associated with the risk of transferring human viruses. Extensive bleeding requiring massive blood transfusions may lead to the development of multiple organ failure including lung or kidney function. Therefore, a major goal in surgery as well as in the treatment of major tissue damage is to avoid or minimise bleeding in order to ensure the formation of stable and solid hemostatic plugs that are not easily dissolved by fibrinolytic enzymes. Furthermore, it is of importance to ensure quick and effective formation of such plugs or clots.

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce blood loss. Currently two synthetic lysine analogs, epsilon-aminocaproic acid (EACA) and tranexamic acid (TXA), are the only antifibrinolytics commercially avaliable to control bleeding. These agents competitively inhibit activation of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen and other plasma proteins.
However, there are some concerns with these currently available antifibrinolytic agents due to the potential risk of thrombotic complications.

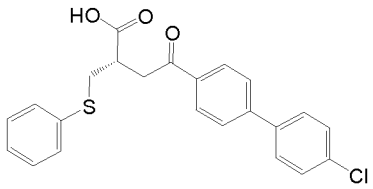
There is still a need for improved treatment of subjects experiencing bleeding episodes, including those due to surgery, trauma, or other forms of tissue damage, as well as in clinical scenarios characterized by excessive fibrinolysis.

SUMMARY OF THE INVENTION

Inventors have identified a series of known therapeutic agents which show good antifibrinolytic properties. In particular, these compounds, which have in common that are capable of inhibiting matrix metalloprotease (MMP) activity, show a significant delay in the lysis time in a thromboelastometry assay. In addition, they also show an important reduction of the bleeding time in vivo animal model as it will be shown in detail in the examples. These characteristics of the compounds of the invention allow a rapid cessation of hemorrhage; favor an effective formation of plugs or clots; have a sustained action (persistence of the clot and prevention of hemorrhage) and aid in

minimizing the adverse effects related to other antifibrinolytic/antihemorrhagic treatments having risk of thrombotic complications.

Accordingly, the present invention relates to a compound selected from the group consisting of:



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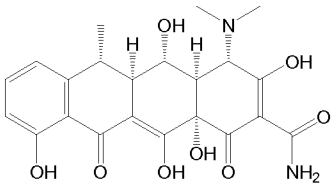

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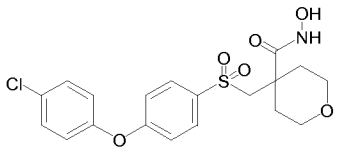

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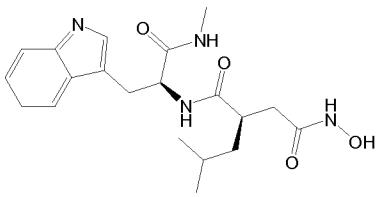

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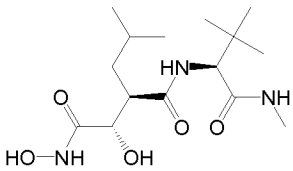

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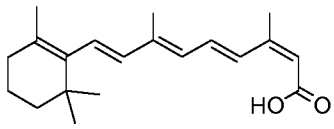

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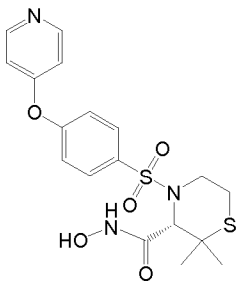

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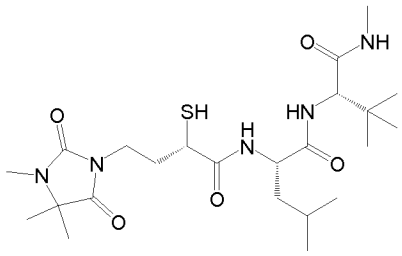

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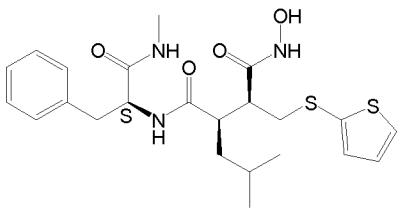

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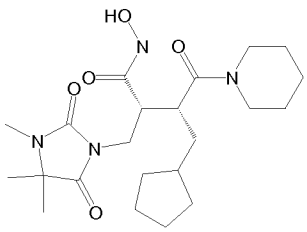

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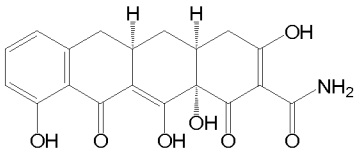

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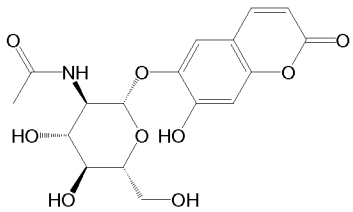

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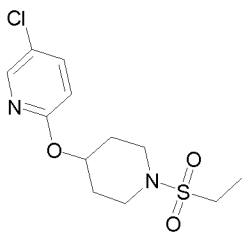

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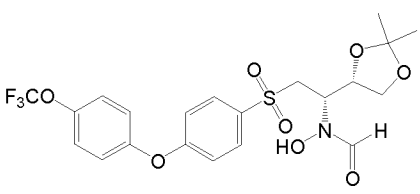

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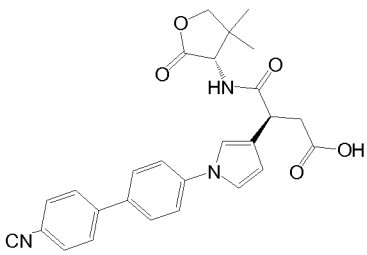

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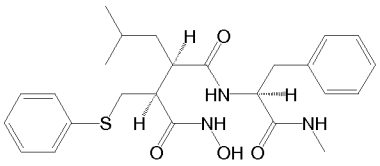

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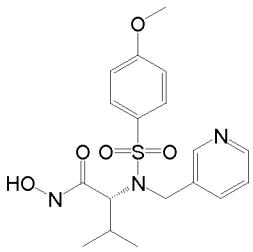

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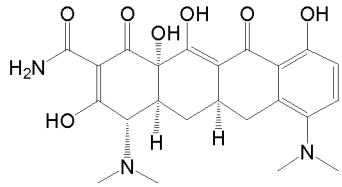

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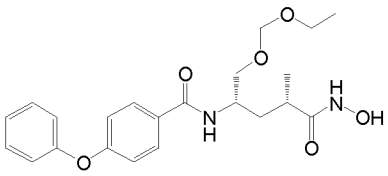

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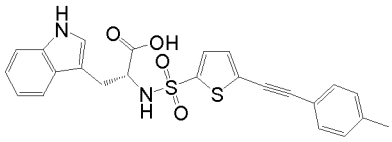

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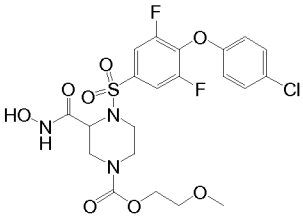
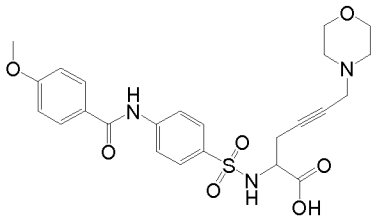


(XXI)



(XXII)

or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of any of the compounds of formula (I) to formula (XXII) or of any of their pharmaceutically or veterinary acceptable salts, for use as an antifibrinolytic agent.

As mentioned above, the compounds of formula (I) to formula (XXII) have in common that they are capable of inhibiting matrix metalloprotease (MMP) activity. Further, there are also some structural similarities between some of them.

As far as the inventors know, a link between the ability of a small molecule of inhibiting matrix metalloprotease (MMP) activity and an antifibrinolytic effect has not been established in the prior art.

Thus, this aspect can also be formulated as the use of a compound which is selected from the group consisting of formula (I) to formula (XXII) as defined

above, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of any of the compounds of formula (I) to formula (XXII) or of any of their pharmaceutically or veterinary acceptable salts, for the manufacture of a medicament for use as antifibrinolytic agent.

This aspect may also be formulated as a method for the treatment and/or prevention of hyperfibrinolysis comprising administering an effective amount of compound which is selected from the group consisting of formula (I) to formula (XXII) as defined above, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of any of the compounds of formula (I) to formula (XXII) or of any of their pharmaceutically or veterinary acceptable salts, and one or more pharmaceutically or veterinary acceptable excipients or carriers, in a mammal in need thereof, including a human.

DETAILED DESCRIPTION OF THE INVENTION

All terms as used herein in this application, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. Other more specific definitions for certain terms as used in the present application are as set forth below and are intended to apply uniformly through-out the specification and claims unless an otherwise expressly set out definition provides a broader definition.

In all embodiments of the invention referring to some of the compounds of formula (I) to formula (XXII), the pharmaceutically or veterinary acceptable salts thereof and the stereoisomers either of any of the compounds of formula (I) to formula (XXII) or of any of their pharmaceutically or veterinary acceptable salts are always contemplated even if they are not specifically mentioned.

There is no limitation on the type of salt that can be used, provided that these are pharmaceutically or veterinary acceptable when they are used for therapeutic purposes. The term "pharmaceutically or veterinary acceptable salts", embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases.

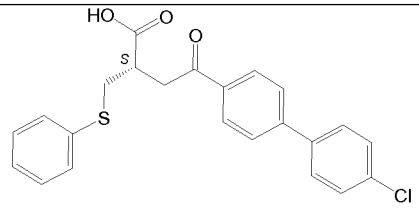
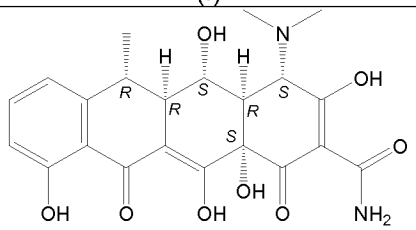
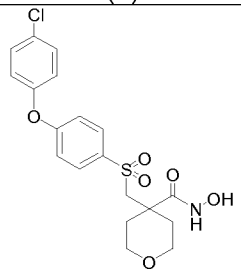
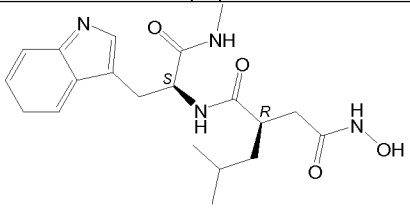
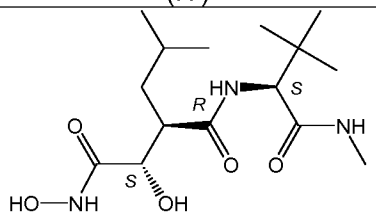
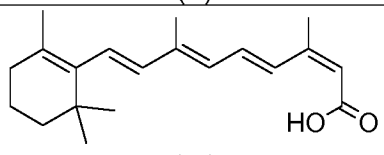
The preparation of pharmaceutically or veterinary acceptable salts of the compounds of formula (I) to formula (XXII) can be carried out by methods known in the art. For instance, they can be prepared from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate pharmaceutically or veterinary acceptable base or acid in water or in an organic solvent or in a mixture of them. The compounds of formula (I) to formula (XXII) and their salts may differ in some physical properties but they are equivalent for the purposes of the present invention.

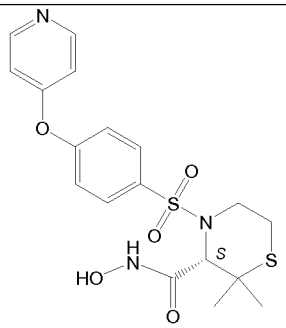
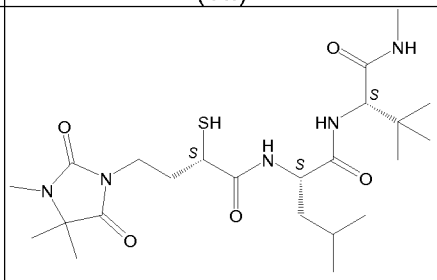
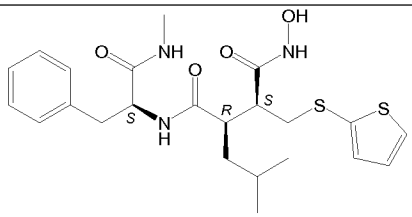
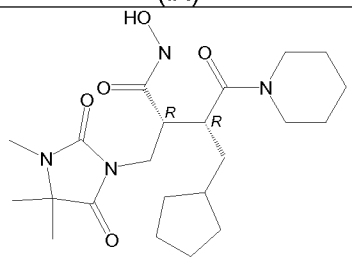
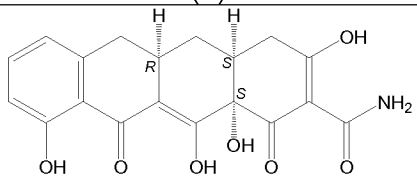
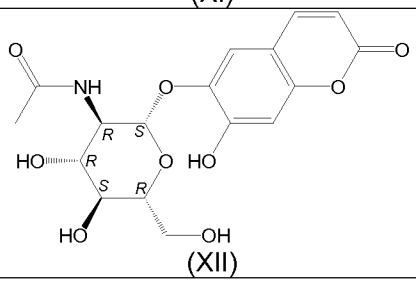
Some compounds of formula (I) to formula (XXII) may be in crystalline form either as free solvation compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art. In general, the solvated forms with pharmaceutically or veterinary acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated form for the purposes of the invention.

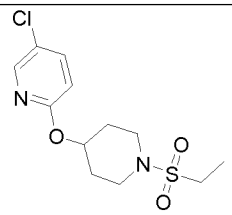
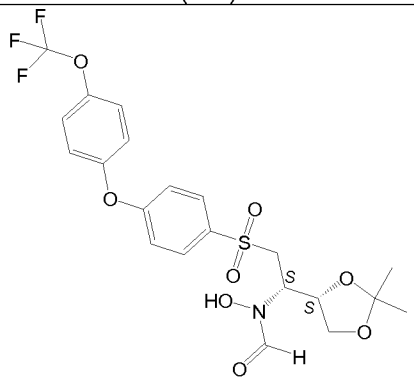
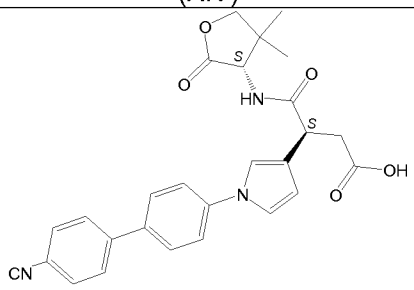
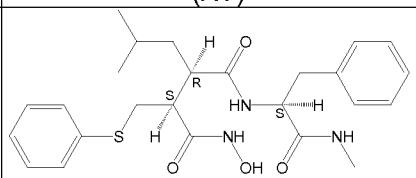
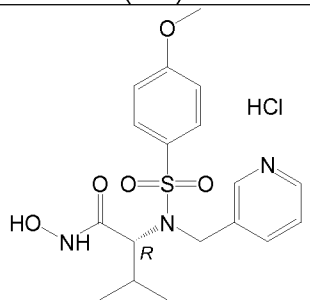
Some compounds of the invention can have chiral centres that can give rise to various stereoisomers. The present invention relates to each of these stereoisomers and also mixtures thereof. Moreover, some of the compounds of the present invention can show cis/trans isomers. The present invention relates to each of the geometric isomers and mixtures thereof.

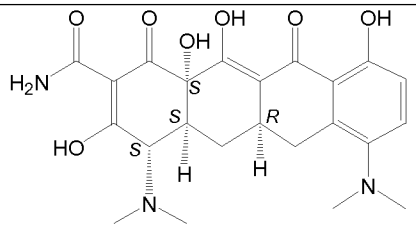
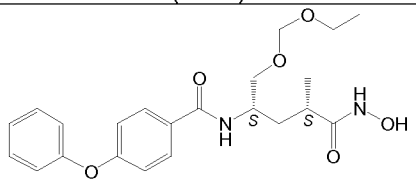
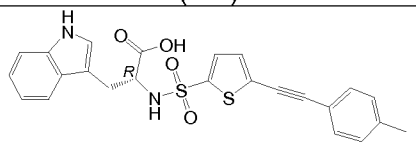
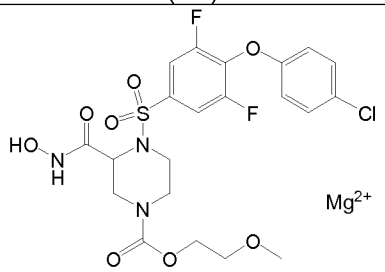
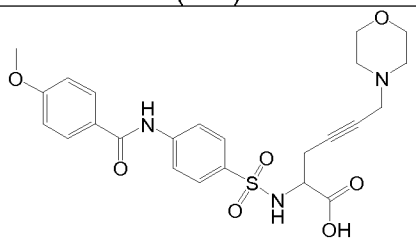
Diastereoisomers can be separated by conventional techniques such as chromatography or fractional crystallization. Optical isomers can be resolved by conventional techniques of optical resolution to give optically pure isomers. This resolution can be carried out on any chiral synthetic intermediate or on products of general formula (I) to formula (XXII). Optically pure isomers can also be individually obtained using enantiospecific synthesis.

In the table below, the common names, synonyms, chemical structures, chemical names and CAS Registry numbers for some of the compounds of the invention are summarized.

Name and synonyms	Chemical formula	Chemical name	CAS registry number
Tanomastat (BAY 12-9566)	 (I)	(2S)-4-[4-(4-chloro-phenyl)phenyl]-4-oxo-2-(phenylsulfanylmethyl)-butanoic acid	179545-77-8
Doxycycline	 (II)	(4S,4aR,5S,5aR,6R,12aS)-4-(dimethylamino)-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide	564-25-0
CTS-1027	 (III)	4-[[4-(4-chlorophenoxy)-phenyl]sulfonylmethyl]tetrahydropyran-4-carbo-hydroxamic acid	193022-04-7
Ilomastat (GM6001)	 (IV)	(2R)-2-[2-(hydroxyamino)-2-oxo-ethyl]-N-[(1S)-1-(5H-indol-3-ylmethyl)-2-(methylamino)-2-oxo-ethyl]-4-methyl-pentanamide	142880-36-2
Marimastat (BB2516)	 (V)	(2R)-N-[(1S)-2,2-dimethyl-1-(methylcarbamoyl)propyl]-2-[(1S)-1-hydroxy-2-(hydroxyamino)-2-oxo-ethyl]-4-methyl-pentanamide	154039-60-8
Isotretinoin	 (VI)	(2Z,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclo-hexen-1-yl)nona-2,4,6,8-tetraenoic acid	4759-48-2

Name and synonyms	Chemical formula	Chemical name	CAS registry number
Prinomastat (AG-3340)	 (VII)	(3S)-2,2-dimethyl-4-[4-(4-pyridyloxy)phenyl]sulfonyl-thiomorpholine-3-carbohydroxamic acid	192329-42-3
Rebimastat (BMS-275291)	 (VIII)	(2S)-N-[(1S)-2,2-dimethyl-1-(methylcarbamoyl)propyl]-4-methyl-2-[[(2S)-2-sulfanyl-4-(3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)butanoyl]-amino]pentanamide	259188-38-0
Batimastat (BB-94)	 (IX)	(2R)-N-[(1S)-1-benzyl-2-(methylamino)-2-oxo-ethyl]-2-[(1S)-2-(hydroxyamino)-2-oxo-1-(2-thienylsulfanyl-methyl)ethyl]-4-methyl-pentanamide	130370-60-4
Cipemastat (Ro 32-3555)	 (X)	(2*R*,3*R*)-3-(cyclopentylmethyl)-*N*-hydroxy-4-oxo-4-(piperidin-1-yl)-2-[(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)methyl]butanamide	190648-49-8
Incyclinide (CMT-3, COL-3)	 (XI)	(4aS,5aR,12aS)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide	15866-90-7
CPA-926	 (XII)	N-[(2S,3R,4R,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl)-2-(7-hydroxy-2-oxo-chromen-6-yl)oxy-tetrahydropyran-3-yl]acetamide	169673-60-3

Name and synonyms	Chemical formula	Chemical name	CAS registry number
AZD-1236	 (XIII)	5-chloro-2-[(1-ethylsulfonyl-4-piperidyl)oxy]pyridine	1414809-96-3
ABT-518	 (XIV)	N-[(1S)-1-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[4-[4-(trifluoromethoxy)phenoxy]phenyl]sulfonyl-ethyl]-N-hydroxy-formamide	286845-00-9
AG-3433	 (XV)	(3S)-3-[1-[4-(4-cyanophenyl)phenyl]pyrrol-3-yl]-4-[[(3S)-4,4-dimethyl-2-oxo-tetrahydrofuran-3-yl]amino]-4-oxo-butanoic acid	207118-71-6
GI 129471 (BB2827)	 (XVI)	(2R)-N-[(1S)-1-benzyl-2-(methylamino)-2-oxo-ethyl]-2-[(1S)-2-(hydroxyamino)-2-oxo-1-(phenylsulfanylmethyl)ethyl]-4-methyl-pentanamide	130370-59-1
MMI270	 (XVII')	(2R)-2-[(4-methoxyphenyl)sulfonyl-(3-pyridylmethyl)amino]-3-methyl-butanehydroxamic acid	169799-04-6

Name and synonyms	Chemical formula	Chemical name	CAS registry number
Minocycline	 (XVIII)	(4S,4aS,5aR,12aS)-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide	10118-90-8
ONO-4817	 (XIX)	N-[(1S,3S)-1-(ethoxymethoxymethyl)-4-(hydroxyamino)-3-methyl-4-oxo-butyl]-4-phenoxy-benzamide	223472-31-9
S3304	 (XX)	(2R)-3-(1H-indol-3-yl)-2-[[5-[2-(p-tolyl)ethynyl]-2-thienyl]sulfonylamino]propanoic acid	203640-27-1
XL-784	 (XXI')	2-methoxyethyl 4-[4-(4-chlorophenoxy)-3,5-difluoro-phenyl]sulfonyl-3-(hydroxycarbamoyl)piperazine-1-carboxylate	1224964-36-6
PG-116800	 (XXII)	2-[[4-[(4-methoxybenzoyl)amino]phenyl]sulfonylamino]-6-morpholino-hex-4-ynoic acid	291533-11-4

The compounds of formula (I)-(XI), (XIV), (XVI), (XVIII)-(XX), and (XXII) are commercially available. The compounds of formula (XII)-(XIII), (XV), (XVII), and (XXI) can be synthetized by methods well-known in the art. For example, the compound of formula (XII) may be synthethized as described in EP719770. The compound of formula (XV) may be synthethized as described in WO9817643. The compound of formula (XVII) may be synthethized as described in WO9600214. The compounds (XIII) and (XXI) may be synthetized by routine methods well-known in the art.

In a particular embodiment, optionally in combination with any of the embodiments above or below, the invention relates to a compound for use as an antifibrinolytic agent, which is selected from the group consisting of formula (I), formula (II), formula (III), formula (IV), formula (V), formula (VI), and formula (VII) as previously defined.

In a more particular embodiment, the compound for use as an antifibrinolytic agent is selected from the group consisting of formula (I), formula (II), formula (III), and formula (IV); more particulary, formula (I) and formula (II); and even more particularly formula (I).

As mentioned above, the compounds of formula (I) to formula (XXII) for use as antifibrinolytic agents have in common that they are capable of inhibiting matrix metalloprotease (MMP) activity.

Matrix metalloproteinases (MMPs) are a large family of calcium-dependent zinc-containing endopeptidases, which are responsible for the tissue remodeling and degradation of the extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycan. In humans at least 26 MMPs are known, which are classified on the basis of their specificity into collagenases (such as MMP1, MMP8, MMP13, and MMP18), gelatinases (such as MMP2 and MMP9), stromelysins (such as MMP3, MMP10, and MMP-11), and matrilysins (such as MMP7 and MMP26).

The term “capable of inhibiting matrix metalloprotease (MMP) activity” as used herein refers to their capacity to inhibit partially or totally, directly or indirectly, MMP by inhibiting the catalytic activity of MMPs, by reducing MMPs at pre- and post-translational levels, or by decreasing the degradation of endogenous tissue inhibitors of metalloproteinases (TIMPs) indirectly. The inhibition of MMP activity can be total if the MMP activity measure is equal to or below than 10% compared to basal values. If the MMP activity measure is higher than 10% and lower than 100%, more particularly higher than 10% and equal or lower than 90%, the MMP activity is considered partially inhibited.

The ability of the compounds of formula (I) to formula (XXII) of inhibiting matrix metalloprotease (MMP) activity is, in particular, referred to one or more MMPs selected from the group consisting of MMP1, MMP2, MMP3, MMP8,

MMP9, MMP10, MMP13 and MMP14, more particularly selected from the group consisting of MMP2, MMP3, MMP9, and MMP13. The ability of the compounds of formula (I) to formula (XXII) of inhibiting matrix metalloprotease (MMP) activity is disclosed for example in the bibliographic references summarized in the table below.

Compound of formula	Bibliographic reference
(I), (IV), (V), (VII), (VIII), (IX), (X), (XI), (XII), (XVI), (XX)	Fingleton, B., Current Pharmaceutical Design 2007,vol. 13, pp. 333-346
(II)	Fingleton, B., Current Pharmaceutical Design 2007,vol. 13, pp. 333-346 Liu, J. et al., Journal of Vascular Surgery 2003, vol 38, pp. 1376-1383 Pasternak, B et al, Acta Orthop. Belg. 2006, vol. 72, pp. 756-760
(III)	EP780386
(VI)	Papakonstantinou, E. et al., Journal of Investigative Dermatology 2005, vol. 125, pp. 673-684.
(XIII)	Dahl, Ronald et al., Pulmonary Pharmacology & Therapeutics 2012, vol. 25, pp. 169-177
(XIV)	WO2000044739
(XV)	WO9817643
(XVII)	WO9600214
(XVIII)	Koistinaho, M. et al., Journal of Cerebral Blood Flow & Metabolism 2005, vol. 25, pp. 460-467
(XIX)	EP1024134
(XXI)	Williams, J. M. et al., Am. J. Physiol. Renal Physiol. 2011, vol. 300, F983 – F998.
(XXII)	WO2000051975

In another embodiment, optionally in combination with any of the embodiments above or below, the compound for use as antifibrinolytic agent is a diaryl ether hydroxamate selected from the group consisting of formula (III), formula (XIX), and formula (XXI).

In another embodiment, optionally in combination with any of the embodiments above or below, the compound for use as antifibrinolytic agent is a tetracycline-based compound selected from the group consisting of formula (II), formula (XI), and formula (XVIII).

In another embodiment, optionally in combination with any of the embodiments above or below, the compound is a thiol-based compound selected from the group consisting of formula (I), and formula (VIII).

The compounds of the present invention are useful as antifibrinolytic agents inhibiting the degradation of fibrin, and can be used in a broad range of therapeutic applications.

In a particular embodiment, optionally in combination with any of the embodiments above or below, the invention relates to a compound for use as antifibrinolytic agent in the treatment and/or prevention of hemorrhage associated to hyperfibrinolysis in a mammal, including a human.

In some cases, hyperfibrinolytic states can be associated to congenital abnormalities or acquired complications, e.g. those related to treatment with fibrinolytic or anticoagulant agents, others related to some surgery or tumours of tissues or organs rich in fibrinolysis activators, in mammals with disseminated intravascular coagulation (DIC), or in situations of failure to clear plasminogen activators.

Thus, in a more particular embodiment, optionally in combination with any of the embodiments above or below, the hyperfibrinolysis is associated to congenital abnormalities, more particularly, in a mammal suffering from Hemophilia A, von Willebrand disease, deficiency of Plasminogen Activator Inhibitor 1 (PAI-1), or deficiency of Alpha2-Antiplasmin.

In another more particular embodiment, optionally in combination with any of the embodiments above or below, the invention relates to a compound for use antifibrinolytic agent in the treatment and/or prevention of hemorrhage associated to hyperfibrinolysis in a mammal receiving fibrinolytic or anticoagulant treatment.

In another more particular embodiment, optionally in combination with any of the embodiments above or below, the invention relates to a compound for use as antifibrinolytic agent in the treatment and/or prevention of hemorrhage associated to hyperfibrinolysis in a mammal with disseminated intravascular coagulation (DIC).

In another more particular embodiment, optionally in combination with any of the embodiments above or below, the hyperfibrinolysis is caused by surgery or tumours of tissues or organs rich in fibrinolysis activators.

In another more particular embodiment, optionally in combination with any of the embodiments above or below, the hyperfibrinolysis is caused by failure to clear plasminogen activators, more particularly, caused by severe liver disease or acute promyelocytic leukaemia associated with DIC.

In another more particular embodiment, optionally in combination with any of the embodiments above or below, the hyperfibrinolysis is caused by trauma, by thrombolytics administered to patients suffering acute heart attack, ischemic stroke or acute peripheral artery disease.

In another more particular embodiment, optionally in combination with any of the embodiments above or below, the hyperfibrinolysis is caused by thrombolytics administered to patients suffering vascular graft occlusion.

In a more particular embodiment, optionally in combination with any of the embodiments above or below, the hemorrhage is selected from the group consisting of: major hemorrhage, intracraneal hemorrhage, menstrual hemorrhage (menorrhage), post-partum hemorrhage, gastrointestinal hemorrhage, subarachnoid haemorrhage, urinary hemorrhage (including prostatectomy), tooth hemorrhage, and hemorrhage caused by surgery.

In one embodiment, the hemorrhage caused by surgery comprises hemorrhage prior, during and/or post surgery and includes transplants and biopsies. More particularly, the surgery is selected from surgery on organs rich in plasminogen activators (prostate, lung, uterus); cardiac surgery, orthopaedic surgery, liver surgery, spinal and cranial surgery, and other surgical procedures such as ocular and dental surgery.

In one embodiment of the invention, optionally in combination with any of the embodiments above or below, the compound of formula (I) to formula (XXII) for use as antifibrinolytic agent is an active pharmaceutical or veterinary ingredient of a pharmaceutical or veterinary composition, which comprises an effective amount of the compound slected from the group consisting of formula (I) to formula (XXII), or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of any of the compounds of formula (I) to formula (XXII) or of any of their pharmaceutically or veterinary acceptable

salts, together with one or more pharmaceutically or veterinary acceptable excipients or carriers.

The expression "effective amount" as used herein, refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease which is addressed. The specific dose of the compound of the invention to obtain a therapeutic benefit may vary depending on the particular circumstances of the individual patient including, among others, the size, weight, age and sex of the patient, the nature and stage of the disease, the aggressiveness of the disease, and the route of administration. For example, a dose of from about 0.01 to about 300 mg/kg may be used.

The expression "pharmaceutically or veterinary acceptable excipients or carriers" refers to pharmaceutically or veterinary acceptable materials, compositions or vehicles. Each component must be pharmaceutically or veterinary acceptable in the sense of being compatible with the other ingredients of the pharmaceutical or veterinary composition. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problems or complications commensurate with a reasonable benefit/risk ratio.

The election of the pharmaceutical or veterinary formulation will depend upon the nature of the active compound and its route of administration. Any route of administration may be used. In one embodiment of the invention, optionally in combination with any of the embodiments above or below, the pharmaceutical or veterinary composition is administered orally, topically or parenterally.

For example, the pharmaceutical or veterinary composition may be formulated for oral administration and may contain one or more physiologically compatible carriers or excipients, in solid or liquid form. These preparations may contain conventional ingredients such as binding agents, fillers, lubricants, and acceptable wetting agents.

The pharmaceutical or veterinary composition may be formulated for parenteral administration in combination with conventional injectable liquid

carriers, such as water or suitable alcohols. Conventional pharmaceutical or veterinary excipients for injection, such as stabilizing agents, solubilizing agents, and buffers, may be included in such compositions. These pharmaceutical or veterinary compositions may be injected subcutaneously, intramuscularly, intraperitoneally, or intravenously.

The pharmaceutical or veterinary composition may be formulated for topical administration. Formulations include creams, lotions, gels, powders, solutions and patches wherein the compound is dispersed or dissolved in suitable excipients. The topical compositions of the invention may be administered by means of a carrier material, which can be a solid support. Thus, it also forms part of the invention a topical composition comprising a carrier material, which can be a solid support. Illustrative, non-limiting examples of solid supports include intelligent textiles, dressings, coatings, sponges, band-aids, sanitary pads, compresses, plasters, etc. The manufacture of such compositions can be obtained by conventional methods, for example, by mixing the combinations of the invention and the material carrier.

The pharmaceutical or veterinary compositions may be in any form, including, among others, tablets, pellets, capsules, aqueous or oily solutions, suspensions, emulsions, or dry powdered forms suitable for reconstitution with water or other suitable liquid medium before use, for immediate or retarded release.

The appropriate excipients and/or carriers, and their amounts, can readily be determined by those skilled in the art according to the type of formulation being prepared.

Throughout the description and claims the word "comprise" and variations of thereof, are not intended to exclude other technical features, additives, components, or steps. Furthermore, the word “comprise” encompasses the case of “consisting of”. Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description or may be learned by practice of the invention. The following examples are provided by way of illustration, and they are not intended to be limiting of the present invention. Furthermore, the present invention covers all possible combinations of particular and preferred embodiments described

herein.

EXAMPLES

Antifibrinolytic effect on whole blood clot formation and lysis

Thromboelastometry is a viscoelastometric method for hemostasis testing in whole blood. TEM® measures the interactions of coagulation factors, inhibitors and cellular components during the phases of clotting and subsequent lysis over time. The rheological conditions of this method mimic the sluggish flow of blood in veins.

Detection method:
Blood samples were obtained between 8-9 a.m. from healthy volunteers and mice in tubes containing citrate solution (0.129 M sodium citrate, Vacutainer BD) and ROTEM tests were performed following the technical details of the ROTEM® analyser (Pentapharm GmbH, Munich, Germany). A modification of in-tem test as described below was used for the examination of antifibrinolytic effects of tested compounds and its interaction with platelets in citrated blood. Kits: START-TEM assay as a recalcification reagent (ref#503-01) and IN-TEM assay for activation of intrinsic coagulation pathway (ref#503-02).

Procedure:
In a pre-warmed cuvette and holder 1 µL of tPA (150,000 U/mL, Actylise), 20 µL of start-tem reagent ($CaCl_2$), 20 µL of in-tem reagent (activators of coagulation system), 3 µL of DMSO (control) or tested compounds (CMs) in DMSO and 300 µL of citrated blood pre-warmed were pipetted. The cup holder containing the sample mixture was placed immediately on the appropriate channel. The measurement was recorded for 60 min to allow clot formation and lysis.

Table 1 shows the results in human blood as effective concentration to delay lysis time by 50% (EC_{50LT}); where, $EC_{50LT} \geq 25$ µM (+),10 µM $\leq EC_{50LT} < 25$ µM (++), 1 µM $\leq EC_{50LT} < 10$ µM (+++), $EC_{50LT} < 1$ µM (++++) at all the assayed concentrations (1000-0.2 µM).

Example	EC_{50LT}
TXA	+++

Example	EC_{50LT}
Ilomastat	++++
Isotretionine	+++
Marimastat	+++
Doxycycline	++++
Tanomastat	+++
CTS-1027	++++

Table 1

Table 2 shows the results in mice blood as effective concentration to delay lysis time by 50% (EC_{50LT}); where, EC_{50LT} ≥10μM (+),1 μM ≤ EC_{50LT} < 10μM (++),1 nM ≤ EC_{50LT} < 1 μM (+++) and EC_{50LT} < 1 nM (++++) for all the assayed concentrations (1000-0.2 μM).

Example	EC_{50LT}
TXA	+++
Ilomastat	+++

Table 2

As observed in the tables above (Tables 1 and 2), compounds of the invention show significant delay in the lysis time, in many cases higher than TXA.

Antifibrinolytic effect *in vivo* (tail bleeding assay)

Bleeding time was evaluated in 2 months old wild-type C57Bl6 (n=10) mice by removing the tail tip. Mice (20-25 g) were anaesthetized with 2.5% isoflurane and maintained at 37 ºC on heating pads. The hemostatic efficacy was evaluated in a hyperfibrinolytic bleeding model.

Hyperfibrinolytic bleeding model, consisted in injection of 0.5 mg/kg tPA into the ocular plexus to prolong bleeding time due to excessive fibrinolysis. First, the femoral vein was exposed and cannulated with a saline-filled polyurethane catheter (Microcannula 72-9030, Harvard Apparatus) for agents administration. The catheter was connected to a syringe pump (AL-1000, WPI) for the infusion of 200 μL (10% bolus, 90% perfusion during 40 minutes) of tested agents. Then, tPA (0.5 mg/kg) was injected into the ocular plexus and five minutes after tPA administration, saline or the different compounds

was infused through the femoral catheter to ensure systemic distribution of all the agents. Reference compounds, TXA and Aprotinin, were administered at 300 and 10 mg/Kg respectively; however, all compounds of the invention were administered at 1 mg/Kg. Five minutes later, 5 mm of tail tip were removed using a scalpel blade and the tail tip bathed in 1 mL of sterile saline at 37 ºC. The time of bleeding was defined as the interval between initial transections and the visual cessation of bleeding, that was measured up to 30 minutes. A value of 30 min was assigned to those animals bleeding longer than the observation period. Table 3 shows the results reporting bleeding time (BT); where BT ≥ 20 minutes (+),10 minutes ≤ BT < 20 minutes (++), 5 minutes ≤ BT < 10 minutes (+++) and BT < 5 minutes (++++). Bleeding time was determined in wild type mice (C57/Bl6), where n ≥ 10 per assayed compound; therefore, BT is reported as a mean value - in the case of saline, BT is reported as mean±ESM.

Example	BT
Saline	28.9±0.7
TXA	++**
Aprotinin	++**
Ilomastat	++**
Doxycycline	+++**
Tanomastat	+++**†
CTS-1027	++**

*p<0.05;**p<0.01 vs saline; †p<0.05 vs TXA

Table 3

As shown table 3, tested compounds of the invention show a significant reduction of the bleeding time when compared to the control or TXA.

REFERENCES CITED IN THE APPLICATION

- EP719770.
- WO9817643.
- WO9600214.
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- Liu, J. et al., “Mechanism of inhibition of matrix metalloproteinase-2 expression by doxycycline in human aortic smooth muscle cells”, Journal of

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- EP780386.
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- Dahl, Ronald et al., "Effects of an oral MMP-9 and -12 inhibitor, AZD1236, on biomarkers in moderate/severe COPD: A randomized controlled trial", Pulmonary Pharmacology & Therapeutics 2012, vol. 25, pp. 169-177.
- WO2000044739.
- WO9817643.
- WO9600214.
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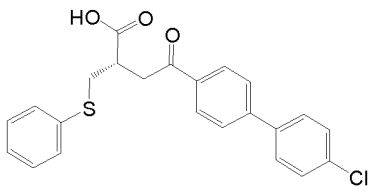
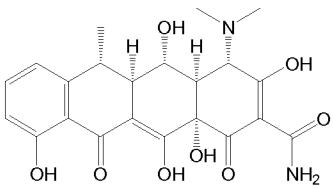
- EP1024134
- Williams, J. M. et al, "Evaluation of metalloprotease inhibitors on hypertension and diabetic Nephropathy", Am. J. Physiol. Renal Physiol. 2011, vol. 300, F983 – F998.
- WO2000051975.

CLAIMS

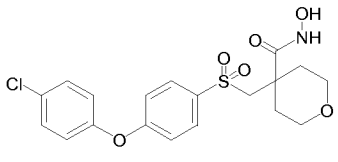
1. A compound capable of inhibiting matrix metalloprotease (MMP) activity which is selected from the group consisting of:



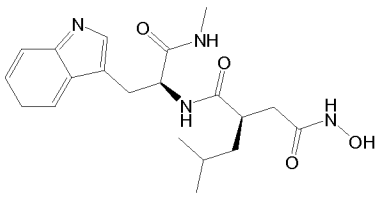
(I)



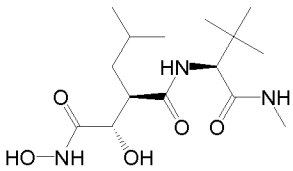
(II)



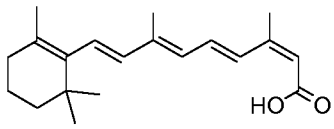
(III)



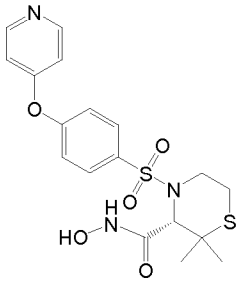
(IV)



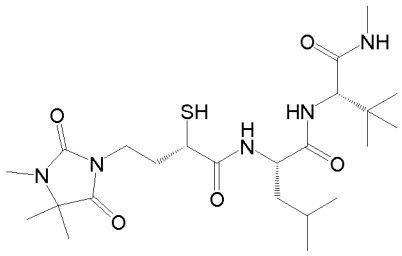
(V)



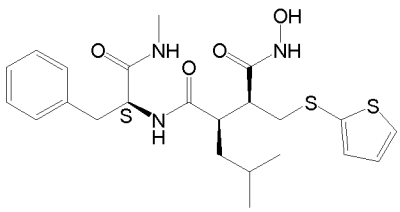
(VI)



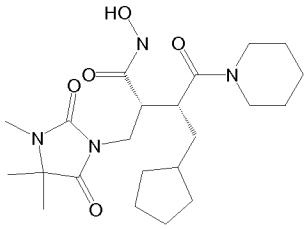
(VII)



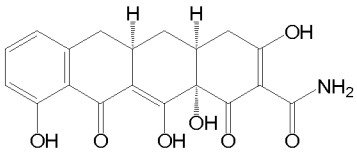
(VIII)



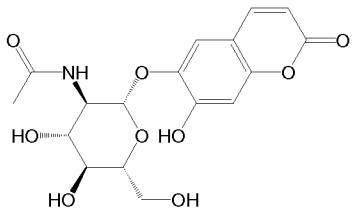
(IX)



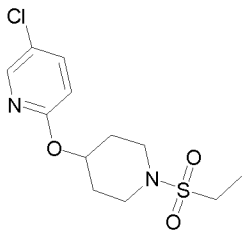
(X)



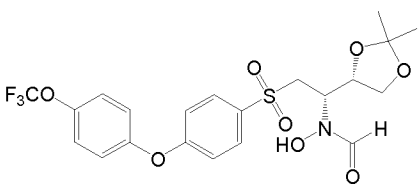
(XI)



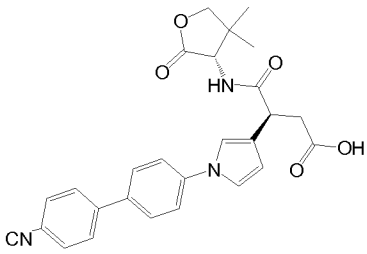
(XII)



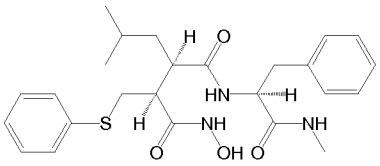
(XIII)



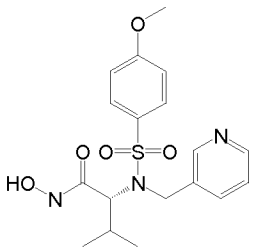
(XIV)



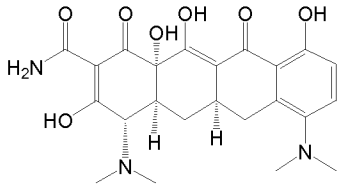
(XV)



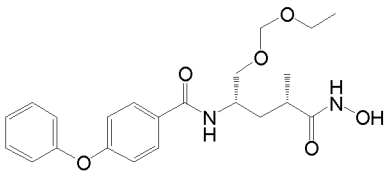
(XVI)



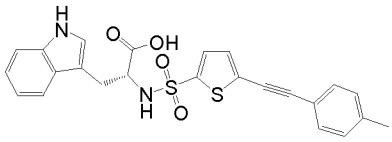
(XVII)



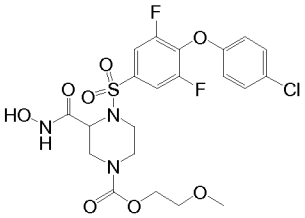
(XVIII)



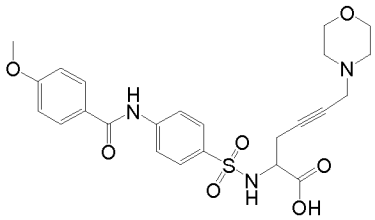
(XIX)



(XX)



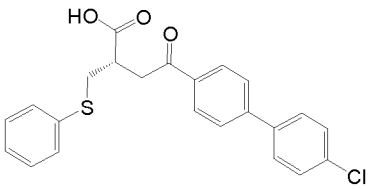
(XXI)



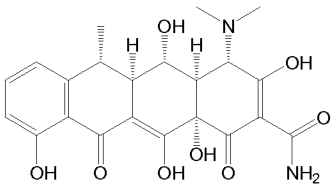
(XXII)

or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of any of the compounds of formula (I) to formula (XXII) or of any of their pharmaceutically or veterinary acceptable salts, for use as an antifibrinolytic agent.

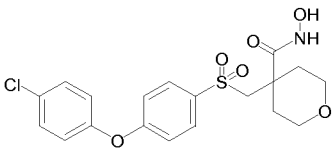
2. The compound for use according to claim 1, wherein the compound is selected from the group consisting of:



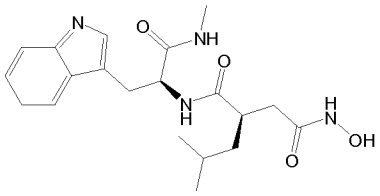
(I)



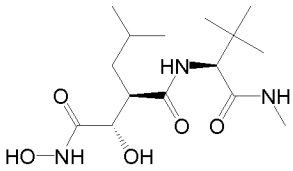
(II)



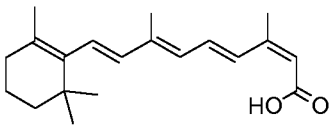
(III)



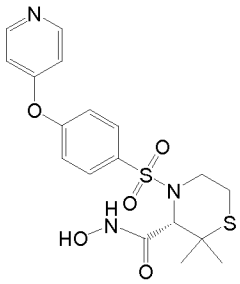
(IV)



(V)

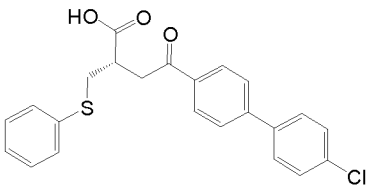


(VI)

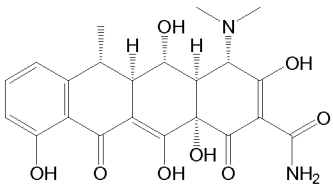


(VII) .

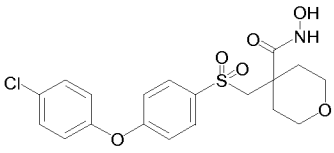
3. The compound for use according to claim 2, wherein the compound is selected from the group consisting of:



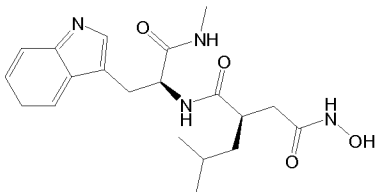
(I)



(II)

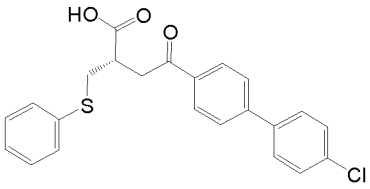


(III)

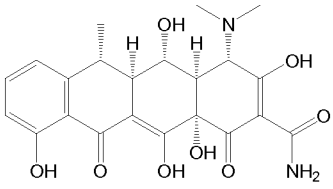


(IV) .

4. The compound for use according to claim 3, wherein the compound is selected from the group consisting of:



(I)



(II) .

5. The compound for use according to any of the claims 1-4, in the treatment and/or prevention of hemorrhage associated to hyperfibrinolysis in a mammal.

6. The compound for use according to claim 5, wherein the hyperfibrinolsis is associated to congenital abnormalities.

7. The compound for use according to claim 5, wherein the mammal is a mammal receiving receiving fibrinolytic or anticoagulant treatment.

8. The compound for use according to claim 5, wherein the mammal is a mammal with disseminated intravascular coagulation.

9. The compound for use according to claim 5, wherein the hyperfibrinolysis is caused by surgery or tumours of tissues or organs rich in fibrinolysis activators.

10. The compound for use according to claim 5, wherein the hyperfibrinolysis is caused by failure to clear plasminogen activators.

11. The compound for use according to claim 5, wherein the hyperfibrinolysis is caused by trauma, or by thrombolytics administered to patients suffering acute heart attack, ischemic stroke or acute peripheral artery disease.

12. The compound for use according to claim 5, wherein the hyperfibrinolysis is caused by thrombolytics administered to patients suffering vascular graft occlusion.

13. The compound for use according to claim 5, wherein the hemorrhage associated to hyperfibrinolysis is selected from the group consisting of: major hemorrhage, intracraneal hemorrhage, menstrual hemorrhage (menorrhage), post-partum hemorrhage, gastrointestinal hemorrhage, subarachnoid haemorrhage, urinary hemorrhage, tooth hemorrhage, and hemorrhage caused by surgery.

14. The compound for use according to any of the claims 1-13, as an active pharmaceutical or veterinary ingredient of a pharmaceutical or veterinary composition comprising an effective amount of the compound as defined in

any of the claims 1-4, or a pharmaceutically or veterinary acceptable salt thereof, or any stereoisomer either of any of the compounds of formula (I) to formula (XXII) or of any of their pharmaceutically or veterinary acceptable salts, together with one or more pharmaceutically or veterinary acceptable excipients or carriers.

15. The compound for use according to claim 14, wherein the pharmaceutical or veterinary composition is administered orally, topically or parenterally.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/050746

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/10 A61K31/203 A61K31/381 A61K31/4166
A61K31/4402 A61K31/541 A61P7/04
ADD.
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)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAUL A LAPCHAK AND DALIA M ARAUJO: "Reducing bleeding complications after thrombolytic therapy for stroke: Clinical potential of metallproteinase inhibitors and spin trap agents", CNS DRUGS, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 15, no. 11, 1 January 2001 (2001-01-01), pages 819-829, XP008128614, ISSN: 1172-7047	1,5,7, 10,11, 13-15
Y	pages 823-825, paragraph 4.2. page 824; figure 3 page 825; figure 4	1-15
	----- -/--	

[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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	Date of mailing of the international search report
18 March 2015	05/06/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lemarchand, Aude

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 2 174 956 A1 (PROYECTO BIOMEDICINA CIMA SL [ES]) 14 April 2010 (2010-04-14) claims page 4, paragraph 27	1-15
X	HANY ABDEL-ALEEM ET AL: "Doxycycline in the treatment of bleeding with DMPA: a double-blinded randomized controlled trial", CONTRACEPTION, vol. 86, no. 3, 1 September 2012 (2012-09-01), pages 224-230, XP055176867, ISSN: 0010-7824, DOI: 10.1016/j.contraception.2012.01.003 abstract page 225, left-hand column, paragraphs 2,3	1-5, 13-15
X	WO 2010/118435 A2 (TUFTS MEDICAL CT INC [US]; KULIOPULOS ATHAN [US]; KOUKOS GEORGIOS [US]) 14 October 2010 (2010-10-14) claims 19-21, 39, 43-45	1-4,14, 15
X	HOWES ET AL: "Neutralization of the haemorrhagic activities of viperine snake venoms and venom metalloproteinases using synthetic peptide inhibitors and chelators", TOXICON, ELMSFORD, NY, US, vol. 49, no. 5, 23 March 2007 (2007-03-23), pages 734-739, XP005935285, ISSN: 0041-0101 abstract page 736; figure 1; table 1	1-4, 13-15
X	MCCARTHY D J ET AL: "Retinoid-induced hemorrhaging and bone toxicity in rats fed diets deficient in vitamin K", TOXICOLOGY AND APPLIED PHARMACOLOGY, ACADEMIC PRESS, AMSTERDAM, NL, vol. 97, no. 2, 1 February 1989 (1989-02-01), pages 300-310, XP024885699, ISSN: 0041-008X, DOI: 10.1016/0041-008X(89)90335-9 [retrieved on 1989-02-01] abstract	1,2,5-15

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FERNIE PENNING-VAN BEEST ET AL: "Main comedications associated with major bleeding during anticoagulant therapy with coumarins", EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 61, no. 5-6, 1 July 2005 (2005-07-01) , pages 439-444, XP019330071, ISSN: 1432-1041, DOI: 10.1007/S00228-005-0947-0 page 442, left-hand column, last sentence	1-7, 13-15
X	BO XU ET AL: "Ulinastatin Reduces Cancer Recurrence after Resection of Hepatic Metastases from Colon Cancer by Inhibiting MMP-9 Activation via the Antifibrinolytic Pathway", BIOMED RESEARCH INTERNATIONAL, vol. 18, no. 6, 1 January 2013 (2013-01-01), pages 893-10, XP055177327, ISSN: 2314-6133, DOI: 10.1111/j.1478-3231.2009.01990.x page 4, paragraph 3.1. page 5; figures 1(g)-(h) page 7, right-hand column	1-3, 13-15
X	MISHIRO K ET AL: "A broad-spectrum matrix metalloproteinase inhibitor prevents hemorrhagic complications induced by tissue plasminogen activator in mice", NEUROSCIENCE, NEW YORK, NY, US, vol. 205, 25 December 2011 (2011-12-25), pages 39-48, XP028466436, ISSN: 0306-4522, DOI: 10.1016/J.NEUROSCIENCE.2011.12.042 [retrieved on 2012-01-05] abstract page 41; figure 1 page 42, right-hand column, paragraph 3	1-3,5,7, 9-11, 13-15
X	US 5 700 838 A (DICKENS JONATHAN PHILIP [GB] ET AL) 23 December 1997 (1997-12-23) column 16; example 10 column 7, line 57 - column 8, line 10; claims 38,39	1,2,5,9, 11,13-15
X	EP 0 780 386 A1 (HOFFMANN LA ROCHE [CH]; AGOURON PHARMA [US]) 25 June 1997 (1997-06-25) cited in the application page 5, line 50; claims 26, 31,33- 34	1-3,5, 13-15

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4

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FINGLETON B: "Matrix metalloproteinases as valid clinical targets", CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS LTD, NL , vol. 13, no. 3 1 January 2007 (2007-01-01), pages 333-346, XP008109550, ISSN: 1873-4286, DOI: 10.2174/138161207779313551 Retrieved from the Internet: URL:http://www.ingentaconnect.com/content/ben/cpd pages 337-338; tables 1-2 -----	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2015/050746

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
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:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

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 fees, this Authority did not invite payment of additional fees.

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.:

3, 4(completely); 1, 2, 5-15(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3, 4(completely); 1, 2, 5-15(partially)

A MMP inhibitor of formulae (I)-(VI) or of any of its pharmaceutically or veterinary acceptable salt, for use as an antifibrinolytic agent preferably in the treatment and/or prevention of hemorrhage associated to hyperfibrinolysis in a mammal.

1.1. claims: 1-15(partially)

A MMP inhibitor or any salt thereof for use as defined above which is a compound of formula (I).

1.2. claims: 1-15(partially)

A MMP inhibitor or any salt thereof for use as defined above which is a compound of formula (II).

1.3. claims: 1-3, 5-15(all partially)

A MMP inhibitor or any salt thereof for use as defined above which is a compound of formula (III).

1.4. claims: 1-3, 5-15(all partially)

A MMP inhibitor or any salt thereof for use as defined above which is a compound of formula (IV).

1.5. claims: 1, 2, 5-15(all partially)

A MMP inhibitor or any salt thereof for use as defined above which is a compound of formula (V).

1.6. claims: 1, 2, 5-15(all partially)

A MMP inhibitor or any salt thereof for use as defined above which is a compound of formula (VI).

2-17. claims: 1, 2, 5-15(all partially)

A MMP inhibitor of formulae (VII)-(XXII) or of any of its pharmaceutically or veterinary acceptable salt, for use as an antifibrinolytic agent preferably in the treatment and/or prevention of hemorrhage associated to hyperfibrinolysis in a mammal.

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