

Description

Title of Invention

NOVEL CRYSTALLINE FORM OF 5-CHLORO-N-({(5S)-2-OXO-3-[4-(5,6-
5 DIHYDRO-4H-[1,2,4]TRIAZIN-1-YL)PHENYL]-1,3-OXAZOLIDIN-5-
YL}METHYL)THIOPHENE-2-CARBOXAMIDE METHANESULFONATE AND
PHARMACEUTICAL COMPOSITION COMPRISING SAME

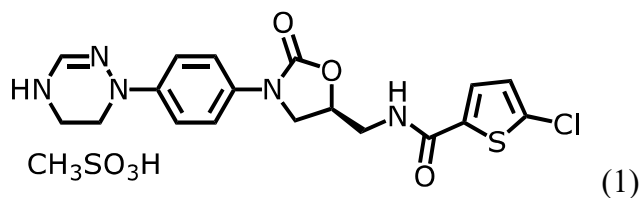
Technical Field

10 The present invention generally relates to a novel crystalline form of 5-chloro-N-
({(5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-
yl}methyl) thiophene-2-carboxamide methanesulfonate and a pharmaceutical
composition comprising the same.

The present invention has been accomplished under the auspices of National
15 Research and Development Project (Detailed Project No.: KDDF-201210-04; Project
Identification No.: 1345193908; Research Project Title: Development of novel
therapeutic agent for the inhibition of blood coagulation factor Xa).

Background Art

20 5-Chloro-N-({(5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-
oxazolidin-5-yl}methyl)thiophene-2-carboxamide methanesulfonate of the following
formula (1) has been known as an inhibitor of blood coagulation factor Xa and used for
treating and preventing thrombosis, myocardial infarction, arteriosclerosis,
inflammation, stroke, angina pectoris, recurrent stricture after angioplasty, and
25 thromboembolism such as intermittent claudication (see US Patent No. 817825).



According to the guidelines and regulations which are promulgated by drug regulatory authorities in various countries, the stability of a drug crystal is required for obtaining the market approval of the drug. Accordingly, there has been a need for developing a novel crystalline form of 5-chloro-N-((5S)-2-oxo-3-[4-(5,6-dihydro-4H-
5 [1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide methanesulfonate which has an excellent dissolution rate and stability even in a high temperature and humid environments.

Summary of Invention

10 A novel crystalline form of 5-chloro-N-((5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide methanesulfonate which is uniform and stable may be provided.

A pharmaceutical composition comprising the novel crystalline form for treating or preventing at least one disease or symptom selected from the group consisting of
15 thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, recurrent stricture after angioplasty, and thromboembolism such as intermittent claudication may be provided.

In accordance with one aspect disclosed herein, there is provided an anhydrous
20 crystalline 5-chloro-N-((5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide methanesulfonate, whose X-ray powder diffraction spectrum using Cu-K α radiation comprises peaks at an angle of diffraction 2 θ of 4.302, 8.621, 9.606, 12.103, 12.879, 15.648, 17.353, 17.949, 19.26, 19.577, 20.252, 21.792, 23.108, 23.356, 25.76 and 27.463.

25 In accordance with another aspect disclosed herein, there is provided an anhydrous crystalline 5-chloro-N-((5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide methanesulfonate, whose X-ray powder diffraction spectrum using Cu-K α radiation comprises peaks at an

angle of diffraction 2θ of 12.022, 15.721, 15.971, 18.125, 18.928, 19.979, 20.311, 20.726, 21.66, 22.805, 23.18, 23.985, 25.857, 27.25, 27.829, 28, 28.189 and 29.753.

A pharmaceutical composition comprising the anhydrous crystalline 5-chloro-N-
({(5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-
5 yl}methyl)thiophene-2-carboxamide methanesulfonate as an active ingredient may be
provided.

The inventive novel crystalline compound has an excellent dissolution rate and
stability even in a high temperature and humid environments, and, thus, can be
10 effectively used for preventing or treating at least one disease or symptom selected from
the group consisting of thrombosis, myocardial infarction, arteriosclerosis,
inflammation, stroke, angina pectoris, recurrent stricture after angioplasty, and
thromboembolism such as intermittent claudication.

15 **Brief Description of Drawings**

The features disclosed herein will become apparent from the following description,
when taken in conjunction with the accompanying drawings, which respectively show:

Fig. 1 shows analysis results of X-ray powder diffraction (PXRD) of Crystalline
Form 1.

20 Fig. 2 shows results of thermogravimetric analysis (TGA) of Crystalline Form 1.

Fig. 3 shows analysis results of X-ray powder diffraction of Crystalline Form 5.

Fig. 4 shows analysis results of differential scanning calorimetry of Crystalline
Form 5.

Fig. 5 shows results of thermogravimetric analysis of Crystalline Form 5.

25 Fig. 6 is photographs of polarized microscope of Crystalline Forms 1 and 5.

Fig. 7 is a graph comparing the dissolution rates of capsules and tablets containing
Crystalline Form 1 or 5 disclosed herein.

Fig. 8 is a graph showing the dissolution rates of tablets containing Crystalline Form 1 or 5 disclosed herein depending on crystalline forms.

Best Mode for Carrying out the Invention

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The novel crystalline form of 5-chloro-N-((5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl)methylthiophene-2-carboxamide methanesulfonate (hereinafter referred to as “GCC-4401C”) disclosed herein has an excellent solubility and stability in a high temperature and humid environments.

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The novel crystalline form of GCC-4401C can be easily obtained by a crystallization method by organic solvent cooling, a vacuum crystallization method or a solvent-antisolvent crystallization method.

GCC-4401C which is used as a reaction material can be prepared by the method disclosed in WO2011/005029. The novel crystalline compound disclosed herein can be prepared by dissolving the reaction material in an organic solvent, adding an anti-solvent thereto and cooling the mixture, followed by filtering and drying the crystals formed therein.

The organic solvents that may be used are selected from the group consisting of methanol, dimethylacetamide (DMA), dimethylsulfoxide (DMSO) and combinations thereof, and methanol is preferred. The anti-solvents that may be used are selected from the group consisting of isopropyl alcohol (IPA), n-butanol, ethyl acetate, toluene and combinations thereof, and n-butanol is preferred.

The anti-solvent can be used in an amount of 1 to 10 folds by volume, preferably 2 to 3 folds by volume, based on the volume of the organic solvent.

The crystals, formed by the addition of an anti-solvent and cooling of the mixture,

can be filtered out by a conventional filtration method, and then dried at the temperature ranging from 55 to 65°C for 3 to 4 hours for removing the residual solvent to obtain the novel crystalline compound disclosed herein.

5 According to one embodiment disclosed herein, the novel crystalline compound referred to as Crystalline Form 1 can be obtained from the process in which GCC-4401C is dissolved in an organic solvent (e.g., methanol), an anti-solvent (e.g., n-butanol) is added thereto and the mixture is cooled, and then the crystals formed in the previous step are filtered and dried at 60±5°C for 3 to 4 hours.

10 According to another embodiment disclosed herein, the novel crystalline compound referred to as Crystalline Form 5 can be obtained from the process in which GCC-4401C is dissolved in an organic solvent (e.g., methanol), the resulting solution is heated to a temperature of 45°C or higher, an anti-solvent (e.g., n-butanol) is added thereto and the mixture is cooled, and then the crystals formed in the previous step are
15 filtered and dried at 60±5°C for 3 to 4 hours.

 In accordance with one aspect disclosed herein, Crystalline Form 1 has a crystalline structure whose X-ray powder diffraction spectrum using Cu-K α radiation comprises characteristic peaks at an angle of diffraction 2 θ of 4.302, 8.621, 9.606, 12.103, 12.879,
20 15.648, 17.353, 17.949, 19.26, 19.577, 20.252, 21.792, 23.108, 23.356, 25.76 and 27.463. Each peak at the angle of diffraction 2 θ has a relative intensity of 10% or higher. In addition, its differential scanning calorimetry (DSC) analysis shows a peak at 178±2°C (see Example 1).

 In accordance with another aspect disclosed herein, Crystalline Form 5 has a
25 crystalline structure whose X-ray powder diffraction spectrum using Cu-K α radiation comprises characteristic peaks at an angle of diffraction 2 θ of 12.022, 15.721, 15.971,

18.125, 18.928, 19.979, 20.311, 20.726, 21.66, 22.805, 23.18, 23.985, 25.857, 27.25, 27.829, 28, 28.189 and 29.753. Each peak at the angle of diffraction 2θ has a relative intensity of 10% or higher. In addition, its differential scanning calorimetry analysis shows a peak at $186\pm 2^\circ\text{C}$ (see Example 2).

5 As confirmed from the results of X-ray powder diffraction spectrum, Crystalline Forms 1 and 5 disclosed herein are anhydrous crystalline forms, and have stability without change of crystalline forms even when being ground or exposed to humid conditions (see Test Example 1). Furthermore, the crystalline forms disclosed herein show an excellent dissolution rate of 80% or higher within 10 minutes regardless of the
10 form of the pharmaceutical formulations such as tablets and capsules containing the crystalline forms (see Test Example 2). Thus, the novel crystalline forms disclosed herein, Crystalline Forms 1 and 5 of GCC-4401C, are effective for treating thrombosis, myocardial infarction, arteriosclerosis, inflammation, stroke, angina pectoris, recurrent stricture after angioplasty, and thromboembolism such as intermittent claudication.

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In accordance with another aspect, a pharmaceutical composition comprising a novel crystalline form of 5-chloro-N-({(5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide methanesulfonate as an active ingredient may be provided.

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The pharmaceutical composition disclosed herein can further comprise a pharmaceutically acceptable carrier or excipient. The pharmaceutically acceptable carrier, excipient, or combinations thereof can be selected depending on the administration method used for treating a specific patient, types of medical conditions,
25 or disease conditions.

Examples of the pharmaceutically acceptable carrier or excipient are as follows: excipients such as starches, sugar, lactose, dextrin, mannitol, sorbitol, crystalline

cellulose, low-substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, Arabic gum, amylopectin, light anhydrous silicic acid, and synthetic aluminum silicate; fillers or extending agents such as calcium phosphate and silica derivatives; binding agents such as starches, sugar, mannitol, trehalose, dextrin, amylopectin, sucrose, gluten, 5 Arabic gum, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, crystalline cellulose, cellulose derivatives (e.g., including hydroxypropyl cellulose and hydroxypropylmethyl cellulose), gelatin, arginic acid salt, and polyvinyl pyrrolidone; lubricating agents such as talc, magnesium or calcium stearate, hydrogenated castor oil, talcum powder, and solid polyethylene glycol; disintegrants 10 such as povidone, sodium croscarmellose, and crospovidone; and surfactants such as polysorbate, cetyl alcohol and glycerol monostearate.

The pharmaceutical composition disclosed herein may be prepared in accordance with any of the conventional procedures. Regarding the conventional formulation procedures, see [*Remington: The Science and Practice of Pharmacy*, 20th Edition, 15 Lippincott Williams & White, Baltimore, Maryland (2000)]; and [H. C. Ansel *et al.*, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th Edition, Lippincott Williams & White, Baltimore, Maryland (1999)].

The pharmaceutical composition disclosed herein may comprise Crystalline Form 1 20 or 5 of 5-chloro-N-({(5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin -1-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide methanesulfonate as an active ingredient in an amount of 0.1 to 95 wt%, preferably 1 to 70 wt%, based on the total weight of the composition.

25 The pharmaceutical composition disclosed herein may be formulated as an oral or parenteral preparation, etc. and administered to a patient via suitable administration routes. Preferably, the inventive composition may be formulated as capsules, tablets, dispersions, suspensions, etc. and then administered orally.

The pharmaceutical composition disclosed herein can be administered in a single dose or in divided doses per one day, and a typical daily dose for human may range from 2.5 to 80 mg based on the amount of the active ingredient, Crystalline Form 1 or 5 of 5-chloro-N-({(5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide methanesulfonate.

Mode for the Invention

Hereinafter, the present invention is explained in detail by Examples. The following Examples are intended to further illustrate the present invention without limiting its scope.

[Example]

The analysis data described in the following Examples were measured under the following conditions.

- 1) X-ray powder diffraction (PXRD) spectrum was obtained by X-ray diffraction spectrometer (Bruker Corporation, Germany) using Cu-K α radiation. The instruments and conditions used for the measurement of PXRD spectrum are listed in Table 1 below.

[Table 1]

Model name and Detector	
Model name	Bruker Axs, D8 Advance
Detector	PSD-Lynx Eye
Instrument Setting	
Goniometer	Theta/Theta Vertical
Mode of collection	Reflection
Measuring circle	435 mm
Radiation	Cu K α (wavelength = 1.5418 Å)
Scan Parameters	
Voltage (kV) and current (mA)	40 / 40

	Dimethyl acetamide : EA	3	20	Crystalline Form 5 (187.05)
	MeOH : IPA	7	20	Crystalline Form 5 (186.80)

As shown in Table 4, Crystalline Form 1 tends to convert into Crystalline Form 5 while it is stirred in the solvent for 24 hours, whereas Crystalline Form 5 maintains the initial form even when it is stirred in various combinations of solvents for 24 hours, which indicates the stability of Crystalline Form 5.

2) Measurement of interconversion at high temperature

In order to determine the interconversion of crystalline forms at a high temperature, each of Crystalline Forms 1 and 5 was dried at $80\pm 5^{\circ}\text{C}$ in non-vacuum state, and then cooled to a temperature of $30\pm 5^{\circ}\text{C}$. DSC analysis was performed for the obtained samples to identify the final crystalline form. Table 5 shows the results.

[Table 5]

Initial form (DSC peak)	Final form (DSC peak)
Crystalline Form 1 (178.0)	Crystalline Form 1 (178.0)
Crystalline Form 5 (186.0)	Crystalline Form 5 (187.0)

As shown in Table 5, it is confirmed that Crystalline Forms 1 and 5 disclosed herein are stable at high temperature.

3) Measurement of stability under physical stimulus

Multi-milling, manual grinding and humidification test were performed for the crystalline forms disclosed herein to confirm their stability under physical stimulus. For multi-milling test, each of Crystalline Forms 1 and 5 was milled at 3,000 rpm by using a prototype multi-mill instrument (Sreenex Machines Pvt. Ltd.). For manual grinding, each of the crystalline forms was gradually ground by using a pestle and mortar. In the humidification test, Crystalline Forms 1 and 5 were stored at 30°C

and 90% RH for 24 hours.

DSC analysis was performed for the crystalline forms obtained from the tests to identify the final crystalline form. Table 6 shows the results.

5 [Table 6]

	Crystalline Form 1		Crystalline Form 5	
	Initial form	Final form	Initial form	Final form
Multi-milling	Crystalline Form 1	Crystalline Form 1	Crystalline Form 5	Crystalline Form 5
Manual grinding	Crystalline Form 1	Crystalline Form 1	Crystalline Form 5	Crystalline Form 5
Humidification	Crystalline Form 1	Crystalline Form 1	Crystalline Form 5	Crystalline Form 5

As shown in Table 6, it is confirmed that both Crystalline Forms 1 and 5 disclosed herein are stable under physical stimulus such as milling, grinding and humidification.

10 4) Solubility

The solubility of each of Crystalline Forms 1 and 5 disclosed herein was measured after being dissolved in the methanol solvent. As a result, the solubility of Crystalline Form 1 was 70 mg/mL, while the solubility of Crystalline Form 5 was 30 mg/mL, which indicates that Crystalline Form 5 is more stable than Crystalline Form 1.

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Test Example 2: Dissolution test of novel crystalline forms

1) Preparation of capsules

20 Capsules containing Crystalline Form 1 disclosed herein were prepared according to a conventional capsulation method. First, 20 mg of Crystalline Form 1 disclosed herein and 279.1 mg of lactose were added into a V-Mixer, which is generally used in the mixing procedure for manufacturing medicines, and then mixed at

20 rpm for 20 minutes. 0.9 mg of magnesium stearate was added thereto, and the mixture was further mixed at 20 rpm for 5 minutes. The mixture was filled into hard gelatin capsules to prepare capsules of Crystalline Form 1.

5 2) Preparation of tablets

Tablets containing Crystalline Form 1 or 5 disclosed herein were prepared according to a conventional tableting method.

Specifically, 20mg of Crystalline Form 1, 175.5 mg of lactose, 7 mg of Primojel, 5 mg of hydroxypropylmethyl cellulose (HPMC) and 1.5 mg of Aerosil 200 were added
10 into a V-Mixer, which is generally used in the mixing procedure for manufacturing medicines, and then mixed at 20 rpm for 20 minutes. 1 mg of magnesium stearate was added thereto, and the mixture was further mixed at 20 rpm for 5 minutes. The mixture was compressed into tablets by using a tablet press. Film-coated tablets containing Crystalline Form 1 prepared by coating the obtained tablets with about 10
15 mg of Opadry.

The above procedures were repeated except that Crystalline Form 5 was used instead of Crystalline Form 1 to prepare film-coated tablets containing Crystalline Form 5.

20 3) Dissolution test

Dissolution test was performed for the capsules and tablets prepared above to measure the dissolution rate (%) thereof.

Dissolution test was performed according to Paddle method of U.S.P. Apparatus 2 at a paddle speed of 50 rpm. Acetate buffer, pH 4.0 was used as a dissolution solution,
25 and the capsules or tablets were added when 900 mL of dissolution solution reached 37±0.5°C. At the predetermined time (5 minutes, 10 minutes, 15 minutes and 30 minutes), 1 mL of each sample was taken from the dissolved solution and filtered. The dissolution rate was measured by using HPLC. The test was performed once (N=6).

Mean and standard deviation (S.D.) of the dissolution rates are shown in Table 7 below and Fig. 7.

[Table 7]

	5 minutes		10 minutes		15 minutes		30 minutes	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Tablets (Crystalline Form 1)	61.5	10.5	88.2	8.1	94.4	4.6	98.5	2.4
Tablets (Crystalline Form 5)	53.4	12.5	83.1	5.0	89.6	2.2	96.7	0.4
Capsules	49.7	5.9	87.4	6.8	97.8	3.7	100.0	4.0

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Generally, capsules do not require a large amount of excipient and have the advantage of simple manufacturing process. However, capsules have problems with stability since a capsule itself is vulnerable to humidity and the components in the capsule are not compressed, which results in large surface area, thereby being easily influenced by external environment. Tablets can remedy the shortcomings of capsules, and have advantages of excellent production efficiency and the low production cost. Meanwhile, polymorphs have the same constituent unit of a crystal, but different arrangement thereof, and the solubility thereof may be affected depending on the arrangement.

As shown in Table 7 and Fig. 7, both the tablets and capsules disclosed herein have an excellent dissolution rate of 80% or higher within 10 minutes.

Furthermore, the crystalline forms disclosed herein in capsule form show dissolution rates similar to those in tablet form, which confirms the equivalency of solubility between capsules and tablets. Tablets containing Crystalline Form 1 show dissolution pattern similar to those containing Crystalline Form 5, which confirms that Crystalline Forms 1 and 5 disclosed herein have similar solubility and pharmacological effects.

4) Dissolution test in mass production

Tablets containing Crystalline Forms 1 and 5 disclosed herein were mass-produced (scale up) in order to confirm the similarity of dissolution pattern depending on crystalline forms in mass production. The dissolution test was performed for thus
5 obtained tablets according to the same procedures as described above. Table 8 and Fig. 8 show the results.

[Table 8]

	5 minutes		10 minutes		15 minutes		30 minutes	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Tablets (Crystalline Form 1)	55.2	7.2	86.7	2.3	92.5	1.9	97.3	0.5
Tablets (Crystalline Form 5)	55.2	1.9	82.1	2.3	91.8	0.8	97.5	2.2

10 As shown in Table 8 and Fig. 8, the tablets containing Crystalline Forms 1 and 5 disclosed herein show decreased deviation in the dissolution pattern depending on crystalline forms, which confirms that the crystalline forms disclosed herein have similar solubility and pharmacological effects in mass production.

15 While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

Claims:

[Claim 1]

An anhydrous crystalline 5-chloro-N-((5S)-2-oxo-3-[4-(5,6-dihydro-4H-
5 [1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide
methanesulfonate (GCC-4401C), whose X-ray powder diffraction spectrum using Cu-
K α radiation comprises peaks at an angle of diffraction 2θ of 12.022, 15.721, 15.971,
18.125, 18.928, 19.979, 20.311, 20.726, 21.66, 22.805, 23.18, 23.985, 25.857, 27.25,
27.829, 28, 28.189 and 29.753.

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[Claim 2]

The anhydrous crystalline GCC-4401C of claim 1, which shows a peak at $186\pm 2^\circ\text{C}$
in a differential scanning calorimetry analysis.

15 [Claim 3]

A pharmaceutical composition comprising the anhydrous crystalline 5-chloro-N-
((5S)-2-oxo-3-[4-(5,6-dihydro-4H-[1,2,4]triazin-1-yl)phenyl]-1,3-oxazolidin-5-
yl)methyl)thiophene-2-carboxamide methanesulfonate according to claim 1 or claim 2
as an active ingredient.

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[Claim 4]

The pharmaceutical composition of claim 3, wherein the pharmaceutical
composition further comprises a pharmaceutically acceptable carrier or excipient.

25 [Claim 5]

Use of the anhydrous crystalline GCC-4401C of claim 1 or claim 2, in the
manufacture of a medicament for the prevention or treatment of at least one disease or
symptom selected from the group consisting of thrombosis, myocardial infarction,

arteriosclerosis, inflammation, stroke, angina pectoris, recurrent stricture after
30 angioplasty, and thromboembolism.

[Claim 6]

Use of the pharmaceutical composition of claim 3 or claim 4, in the manufacture
of a medicament for the prevention or treatment of at least one disease or symptom
35 selected from the group consisting of thrombosis, myocardial infarction, arteriosclerosis,
inflammation, stroke, angina pectoris, recurrent stricture after angioplasty, and
thromboembolism.