

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2022/073889

International filing date (day/month/year)
29.08.2022

Priority date (day/month/year)
03.09.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C07D409/14 C07C309/04 A61P7/02 A61K31/4178

Applicant
BAYER AKTIENGESELLSCHAFT

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-12</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-12</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-12</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Claims 6, 10 and 12 and certain passages of the description relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims relating to the use of a compound in medical treatment, but may allow claims relating to a product, in particular substance or compositions for a first or further use in medical treatment.

1. Relevant prior art

The following documents D1-D3 are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1 WO 2009/103440 A1 (SANOFI AVENTIS [FR]; FOLLMANN MARKUS [DE] ET AL.) 27 August 2009 (2009-08-27), cited in the application
- D2 JEROME MENEYROL ET AL: "5-Chlorothiophene-2-carboxylic Acid [(S)-2-[2-Methyl-3-(2-oxopyrrolidin-1-yl)benzenesulfonylamino]-3-(4-methylpiperazin-1-yl)-3-oxopropyl]amide (SAR107375), a Selective and Potent Orally Active Dual Thrombin and Factor Xa Inhibitor",
JOURNAL OF MEDICINAL CHEMISTRY,
vol. 56, no. 23, 12 December 2013 (2013-12-12), pages 9441-9456, XP055283783,
US ISSN: 0022-2623, DOI: 10.1021/jm4005835, cited in the application
- D3 WO 2014/174102 A1 (SANOFI SA [FR]) 30 October 2014 (2014-10-30), cited in the application

2. Novelty

The present application relates to 2-(1-methyl-1H-imidazol-2-yl)ethyl 3-[(5-chlorothiophene-2-carbonyl)amino]-N {2-ethyl-3-[(3S)-3-hydroxy-2-oxopyrrolidin-1-yl]benzene-1-sulfonyl}-S-alaninate of the formula (I), the salts or solvates thereof and to their medical applications.

The present compound of formula (I) is novel over D1-D3 on account of 1-methyl-1H-imidazol-2-yl)ethyl-oxo group (ester).

The whole subject-matter claimed is considered novel (Article 33(2) PCT).

3. Inventive step

Any of D1-D3 can represent the closest prior art as they all disclose compounds which are dual inhibitors of thrombin and factor Xa. The compounds of D1-D3 are amide derivatives while the present compound of formula (I) is one particular ester at the corresponding site, namely 1-methyl-1H-imidazol-2-yl-ethyl ester. No esters are suggested as final compounds with the desired activity in D1-D3.

The technical problem to be solved by the present invention may be regarded as a provision of further compounds with dual inhibitory activity of thrombin and factor Xa which are useful in the treatment of thrombotic or thromboembolic disorders.

The solution to that problem is the provision of the compounds of formula (I) defined in claim 1. Data demonstrating the ability of the synthesized compounds of formula (I) to inhibit thrombin (factor IIa) and factor Xa is given in tables 2b and 3b on pages . Thus, the problem has been solved.

Starting with the compounds of D1-D3 the technical contribution of the present invention resides in the replacement of amide with a particular ester moiety.

Such a kind of modification is neither disclosed nor suggested by the cited prior art.

Given the structural differences between the compounds of the present application and the compounds of D1-D3, the skilled person would not have predicted the qualitative retention of the desired activity for the compounds of the present application.

Therefore, the solution to the given problem appears to be non obvious in the light of D1-D3 rendering the presently claimed subject-matter inventive (Article 33(3) PCT).