PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	16.11.2017
Applicant's or agent's file reference: P17023-DHWA	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/KR2017/008576	08.08.2017	23.08.2016

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

C07C271/24(2006.01)i, C07C269/06(2006.01)i, C07C269/08(2006.01)i

Applicant

DONG WHA PHARM. CO., LTD.

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 43*bis*.1(a)(i) with regard to novelty, inventive step or 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 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 66.1*bis*(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/KR	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/KR2017/008576

Box No. I Basis of this 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 43*bis*.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:

☐ in the form of an Annex C/ST.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/KR2017/008576

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

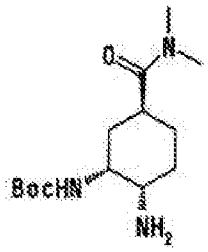
Novelty (N)	Claims	1-9	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	None	NO

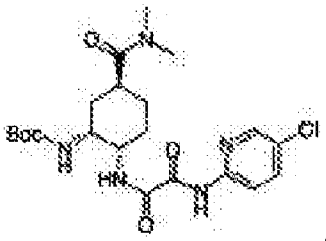
2. Citations and explanations:

Reference is made to the following document:

D1: KR 10-2005-0110612 A (DAIICHI PHARMACEUTICAL CO., LTD.) 23 November 2005

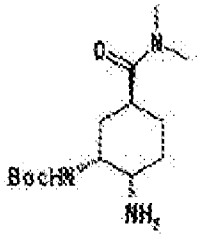
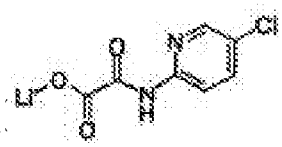
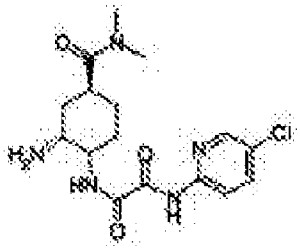
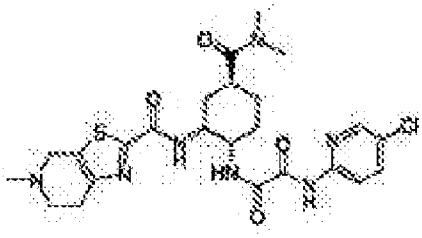
2.1. Novelty and Inventive Step

D1 discloses a compound (reference example 144, 

) (see paragraphs [1184]-[1186]); a compound (

, reference example 434), prepared from the compound of

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**

reference example 144 () and the compound of reference example 433 () (see paragraphs [2363]-[2369]); a compound ( , reference example 435), prepared by separating a Boc group from the compound of reference example 434 (see paragraphs [2371]-[2373]); and a compound (), prepared from the compound of reference example 435 and a compound of reference example 10 () in embodiment 310 (see paragraphs [0621]-[0623] and [4380]-[4382]).

2.1.1. Claim 1

The compound represented by chemical formula 2 in claim 1 is different from the compound of reference example 144 in D1 in that the former compound is a succinate salt (see paragraphs

[1184]-[1186]). However, D1 provides organic acid salts such as oxalate salts, succinate salts, glutarate salts, tartrate salts, malate salts, etc., as examples of salts of the compound represented by chemical formula 1 (see paragraph [0183]). Furthermore, the present invention and D1 both relate to a compound having the same effect of exhibiting anticoagulant effects by inhibiting an activated blood coagulation factor X (FXa) (see paragraph [0001]). Thus, a person skilled in the art could easily select succinic acid from the organic acids to prepare a succinate salt of the compound, without any technical difficulty; and the effect resulting therefrom could be sufficiently predicted.

Therefore, claim 1 is novel under PCT Article 33(2), but lacks an inventive step under PCT Article 33(3) in light of D1.

2.1.2. Claims 2 and 3

Claims 2 and 3 relate to a compound represented by chemical formula 3 or 4, respectively. Each of the compounds is different from the compound of reference example 144 in D1 in that the former compounds are a tartrate salt or a citrate salt, respectively (see paragraphs [1184]-[1186]). However, as stated in item 2.1.1. above, D1 provides organic acid salts such as oxalate salts, succinate salts, glutarate salts, tartrate salts, malate salts, etc., as examples of salts of the compound represented by chemical formula 1 (see paragraph [0183]). Furthermore, the present invention and D1 both relate to a compound having the same effect of exhibiting anticoagulant effects by inhibiting an activated blood coagulation factor X (FXa) (see paragraph [0001]). Thus, a person skilled in the art could easily select tartaric acid or

citric acid from the organic acids to prepare a tartrate salt or a citrate salt of the compound, without any technical difficulty; and the effect resulting therefrom could be sufficiently predicted.

Therefore, claims 2 and 3 are novel under PCT Article 33(2), but lack an inventive step under PCT Article 33(3) in light of D1.

2.1.3. Claim 4

Claim 4 is different from D1 in that the claim relates to a method for preparing an acid addition salt, comprising: adding succinic acid, tartaric acid or citric acid to a reaction solution in which a compound represented by chemical formula 1 is dissolved in an organic solvent to prepare a mixture or sludge; and then heating and stirring the mixture or sludge. However, as stated in items 2.1.1. and 2.1.2. above, D1 discloses the compound of reference example 144 corresponding to the compound represented by chemical formula 1 in claim 4 (see paragraphs [1184]-[1186]), and provides organic acid salts such as oxalate salts, succinate salts, glutarate salts, tartrate salts, malate salts, etc., as examples of salts of the compound (see paragraph [0183]). Furthermore, the present invention and D1 both relate to a compound having the same effect of exhibiting anticoagulant effects by inhibiting an activated blood coagulation factor X (FXa) (see paragraph [0001]). Thus, a person skilled in the art could easily select succinic acid, tartaric acid or citric acid from the organic acids to prepare a succinate salt, a tartrate salt, or a citrate salt of the compound, without any technical difficulty; and the effect resulting therefrom could be

sufficiently predicted. In addition, the first step, second step and third step in claim 4 correspond to typical preparation steps used for preparing a salt compound, and thus could be derived by a person skilled in the art without any technical difficulty.

Therefore, claim 4 is novel under PCT Article 33(2), but lacks an inventive step under PCT Article 33(3) in light of D1.

2.1.4. Claims 5 to 8

Claim 5 referring to claim 4 limits the type of organic solvent, and said limitation is not disclosed in D1. However, an organic solvent to be used for preparing a salt compound could be derived by a person skilled in the art without any technical difficulty. It is not deemed that a remarkable effect is predicted therefrom.

Claims 6 to 8 refer to claim 4. Claim 6 limits the concentration range of the compound of chemical formula 1. Claim 7 limits the content of succinic acid, tartaric acid or citric acid with respect to the compound of chemical formula 1. Claim 8 limits the heating temperature. Said claims are different from D1 in that said limitations are not disclosed in D1. However, said difference could be optimized by a person skilled in the art through repeated experiments, without any technical difficulty. It is not deemed that said numerical limitations pose any particular technical difficulty, and it is not deemed that said numericals limitations have any critical significance. Thus, said difference could be easily implemented from D1, without any technical difficulty.

Therefore, claims 5 to 8 are novel under PCT Article 33(2), but lack an inventive step under PCT Article 33(3) in light of D1.

2.1.5. Claim 9

Claim 9 is different from D1 in that the claim uses, in the first step, an acid addition salt represented by any one of chemical formulas 2 to 4. However, as stated in items 2.1.1. and 2.1.2. above, D1 discloses the compound of reference example 144 corresponding to the compound represented by chemical formula 1 in claim 4 (see paragraphs [1184]-[1186]), and provides organic acid salts such as oxalate salts, succinate salts, glutarate salts, tartrate salts, malate salts, etc., as examples of salts of the compound (see paragraph [0183]). Furthermore, the present invention and D1 both relate to a compound having the same effect of exhibiting anticoagulant effects by inhibiting an activated blood coagulation factor X (FXa) (see paragraph [0001]). Thus, a person skilled in the art could easily select succinic acid, tartaric acid or citric acid from organic acids to prepare a succinate salt, a tartrate salt, or a citrate salt of the compound, without any technical difficulty; and the effect resulting therefrom could be sufficiently predicted. In addition, D1 discloses, in example 310, a compound prepared from the compound of reference example 435 and the compound of reference example 10, which corresponds to edoxaban represented by chemical formula A in claim 9 (see paragraphs [0621]-[0623] and [4380]-[4382]).

Therefore, claim 9 is novel under PCT Article 33(2), but lacks an inventive step under PCT Article 33(3) in light of D1.

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**

2.2. Industrial Applicability

The invention as set forth in claims 1 to 9 is industrially applicable under PCT Article 33(4).

[Note]

- Edoxaban represented by chemical formula A in claim 9 is a compound prepared from "the acid addition salt represented by any one of formulas 2 to 4 prepared according to claim 4." However, the substitution site of "N,N-dimethylcarbamoyl" in the acid addition salt of chemical formulas 2 to 4 and the substitution site of "N,N-dimethylcarbamoyl" in edoxaban of chemical formula A are inconsistent with each other. Thus, in order to make the subject matter clearer, it would be desirable to make the substitution sites of "N,N-dimethylcarbamoyl" of these chemical formulas consistent. (For reference, the present international search report and written opinion have been established under the assumption that the substitution site of "N,N-dimethylcarbamoyl" in edoxaban represented by chemical formula A in claim 9 is the substitution site of chemical formulas 2 to 4 in claim 4.)