

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCHING AUTHORITY

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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/EP2016/070604

International filing date (day/month/year)
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02.09.2015

International Patent Classification (IPC) or both national classification and IPC
INV. C07D403/12 A61K31/496 A61P25/34

Applicant
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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.

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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:
 - ☐ 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 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.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:

see separate sheet

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	
	No: Claims	<u>1-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-12</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the report

The application is directed to a crystalline salt of 1-[4-[2-[[1-(3,4-difluorophenyl)-1H-pyrazol-3-yl]methoxy]ethyl]piperazin-1-yl]ethanone (claims 1-5) and subject matter referring to it (claims 6-12).

For the sake of simplicity, the parent compound 1-[4-[2-[[1-(3,4-difluorophenyl)-1H-pyrazol-3-yl]methoxy]ethyl]piperazin-1-yl]ethanone will be referred to as compound A in the following sections.

Re Item V

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

- 1 Reference is made to the following documents.
- | | |
|----|--|
| D1 | WO 2011/147910 A1, 1 December 2011; cited in the application. |
| D2 | Hilfiker <i>et al.</i> : "Relevance of Solid-state Properties for Pharmaceutical Products" In: HILFIKER (EDITOR): <i>Polymorphism in the Pharmaceutical Industry</i> , 2006 , Wiley-VCH, Weinheim, pages 1-19; XP002528052. |
| D3 | Anderson: "Tools for Purifying the Product: Column Chromatography, Crystallization and Reslurrying", In: <i>Practical Process Research and Development</i> , Academic Press, San Diego, 2000 , pages 223-247; XP002382432. |
| D4 | "Tables of Salt-Forming Acids and Bases" In: <i>Handbook of Pharmaceutical Salts - Properties, Selection, and Use</i> , 2002 , Verlag Helvetica Chimica Acta & Wiley-VCH, Zürich, Weinheim, pages 331-345; XP055247250. |
| D5 | Bastin <i>et al.</i> <i>Organic Process Research and Development</i> 2000 , 4, 427-435; XP008154792. |

2 Novelty

D1 concerns sigma receptor antagonists, the corresponding pharmaceutical compositions and indications (cf. page 4, lines 22-26; claims 12-16). Compound A and pharmaceutical salts thereof are disclosed in **D1** (claim 10, page 61, lines 3 and 22; and page 10, lines 15-29), and 5 of the 7 salt-formers of present claim 3 are disclosed in a single list in **D1**, that is the salts formed with hydrochloric acid, hydrobromic acid, oxalic acid, succinic acid, malic acid, and fumaric acid (cf. page 10, lines 26-29). The present claims are novel over **D1** on account of the feature that the present salts are crystalline.

D2-D5 are not relevant to the question of novelty of the application because compound A and salts thereof are not disclosed therein.

3 Inventive step

The claims do not comply with the requirement of inventive step for the reasons given under items V.3.2 to V.3.4 below.

3.1 Pharmaceutical acceptable salts of compound A are generally taught in **D1** including the salts with hydrochloric acid, hydrobromic acid, oxalic acid, succinic acid, malic acid, and fumaric acid.

The application describes that compound A has a low melting point (46 °C), low aqueous solubility, a pKa of 6.37, and is difficult to crystallise which comes from its low melting point (cf. page 2, lines 18-19; page 5, lines 16-21; page 17, table 1). Furthermore, the application describes salt screening results that gave the crystalline salts of present claim 3. Other acids used in the screen like sulphonic acids and weak acids such as acetic acid, propionic acid, et cetera, did not yield crystalline salts (the application, page 19 et sequence: table 3). Compared with compound A free base, the crystalline salts that have been made and are the subject of claim 3 exhibit a higher, favourable melting point (cf. page 26, table 4) and can be assumed to have a better aqueous solubility than the free base compound A. Hence, in view of **D1** as closest prior art, the problem underlying the application may be seen in the provision of alternative forms of compound A having improved properties.

- 3.2 This problem has not been solved by the subject-matter of claims 1 and 2 (cf. application, table 3: experiments with acids not yielding crystalline salts). Accordingly, the claims 1-2 and 6-10 lack inventive step.
- 3.3 In as far as the claims relate to the crystalline salts of the claims 3-5, the following observations would apply to the criterion of inventive step.

The skilled artisan being involved in developing compound A as an API would make himself familiar with the inherent properties of compound A which are relevant for its manufacture, handling, storage and use. This includes the determination of solubility data; pKa; and its crystallisation behaviour. The latter is important as crystalline forms are most preferred, inter alia because crystallisation usually provides the best purification of the product (cf. common general knowledge **D2**, page 12, penultimate paragraph, first sentence; and **D3**, paragraph bridging pages 233- 234). In doing so, the skilled person would have become aware that compound A suffers from certain drawbacks like low aqueous solubility and a low melting point.

Facing problems with these undesirable properties, he would have looked to forming a salt, as it is known from the general knowledge **D2**, page 8, section 1.4.1, paragraph 1.

The relevant passage reads: "As a rule a salt is chosen if the free acid/base has at least one of the following undesirable properties:

- very low solubility in water;
- apparently not crystallizable;
- low melting point (typical cutoff 80 °C); [...]"

Due to the general knowledge as documented by **D4** (cf. pages 336-337 which lists 69 acids including those to form the salts of present claim 3), he would have been able to narrow the group of potential salt-formers to a finite number of pharmaceutical acceptable salt formers to be tested for improved properties. A possible unpredictability of the respective improved properties would not be equated with non-obviousness here, because there is a finite number of 69 pharmaceutical acceptable salt formers to be tested for improved properties, which would be an acceptable number to "form a reason-

able expectation of success" to arrive at the subject-matter of the present claims 3-5. The present claims do thus not involve an inventive step.

- 3.4 Independent of the assessment of lack of inventive step of the last paragraph of item V.3.3, the document **D1** itself suggests to the skilled person to provide the salts with hydrochloric acid, hydrobromic acid, oxalic acid, succinic acid, malic acid, and fumaric acid, thereby increasing the "reasonable expectation of success". In addition, document **D5**, a review article on salt selection, teaches that hydrochloride salts have often been the first choice for weakly basic drugs (such as the present compound A), since salts can nearly always be formed, and recrystallisation from organic solvents is normally straightforward (cf. page 428, right column, penultimate paragraph). This means that **D1** alone, optionally in combination with **D5**, renders the subject-matter of claims 3-5 obvious to the skilled artisan.

Re Item VIII

Certain observations on the international application

- 1 The application does not comply with Articles 5 and 6 PCT for the following reasons.
- 1.1 Claims 1-2 and 6-10 relate to a very large number of possible crystalline salts of compound A. Support and disclosure within the meaning of Articles 6 and 5 PCT are to be found, however, for only a very small proportion of the crystalline salts claimed, that is the seven entities of present claim 3. Hence, the claims lack support and the application lacks disclosure in as far as they relate to crystalline salts over the full scope of the present claims 1 and 2.
- 1.2 Claim 8 does not comply with Article 6 PCT, because the therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. This objection may be overcome by introducing into the claim a list of pathological conditions cited in the application.

- 1.3 Claim 9 lacks clarity because stress is not a disease but an organism's way of reacting to a challenge. Accordingly, stress does not require treatment and/or prophylaxis, contrary to what is defined in claim 9 (Article 6 PCT). The objection may be overcome by deleting stress from the claim.
- 1.4 The expression "in particular" has no limiting effect on the scope of the claims 9-12. The features following this expression are thus superfluous, thereby resulting in a lack of conciseness of these claims (Article 6 PCT). This objection may be overcome by the deletion of the superfluous features. They can possibly be made the subject of further dependent claims.