

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.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/US2015/022011	International filing date (day/month/year) 23.03.2015	Priority date (day/month/year) 24.03.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D417/14 C07D487/04 A61P31/04 A61K31/427 A61K31/496 A61K31/4439 A61K31/454 A61K31/437		
Applicant NOVARTIS AG		

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 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 66.1*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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Telephone No. +49 89 2399-0 
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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:

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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>4, 5, 7-17, 19, 21-27</u>
	No: Claims	<u>1-3, 6, 18, 20, 28-36</u>
Inventive step (IS)	Yes: Claims	<u>8-17, 19, 21, 23-25</u>
	No: Claims	<u>1-7, 18, 20, 22, 26-36</u>
Industrial applicability (IA)	Yes: Claims	<u>1-36</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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

1 Reference is made to the following document:

D1 EP 0 093 376 A2 (1983-11-09)

Re Item IV

2 Lack of unity

2.1 The present application refers to compounds of formula I (claim 1) and IA (claim 2), compositions comprising them (claim 29) and a second therapeutic agent (claim 36), and their medical use (claim 33) in the treatment of Gram-negative bacterial infections (claim 30).

2.2 This Authority considers that there are at least 3 inventions covered by the claims indicated as follows:

- compounds of formula I, wherein Het is a 5-membered heteroaryl ring and subject-matter referring to them
- compounds of formula I, wherein Het is a ring substituted with oxo and subject-matter referring to them
- compounds not falling within the 1st or 2nd invention and subject-matter referring to them

2.3 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The closest prior art for the present application is D1. D1 discloses compounds of a formula (claim 1), compositions comprising them and a carrier (claim 34), compositions comprising them and a beta-lactam antibiotic (claim 35), and their medical use in the treatment of Gram-negative bacterial infections (inhibitory activity on *Enterobacter cloacae*, or *Klebsiella pneumoniae*; page 85-87, entry 3 of table on page 87). The compounds of claim 1 of D1 and the presently claimed compounds show a certain overlap. A specific compound which falls within the overlapping area and within the scope of claims 1-3, 6, 18, 20, and 28 has also been disclosed in D1 (example 9 and 3rd entry in the table on page 87).

2.4 The technical problem underlying the present application can be seen in the provision of further compounds useful to treat bacterial infections. As a solution of the aforementioned technical problem, the present application provides compounds of formula I. However such compounds are already known from D1 (see e.g. compound of example 9 of D1).

- 2.5 Compounds according to dependent claims 8-13, 19, 21, and 23-25 differ from the compounds of D1 due to their 5-membered heteroaromatic ring Het. Neither this nor a corresponding structural feature is present in compounds of dependent claims 14-17, which carry a saturated ring substituted with an oxo group at the corresponding position.
- 2.6 Thus, in view of example 9 of D1, the requirement of a technical feature relationship as defined in Rule 13(2) PCT, involving one or more of the same or corresponding special technical features (i.e. technical features which define a contribution over the prior art) are not met. In other words, the compounds according to present claims 8-13, 19, 21, and 23-25 on the one side and according to claims 14-17 on the other side do not share any common special technical feature that distinguishes them over the prior art, and the application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Re Item V

- 3 Claims 30-32 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 be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Authorities other than the EPO, for example the USPTO might accept such claims as patentable.
- 4 Novelty
- At least the subject-matter of claims 1-3, 6, 18, 20, and 28-36 is not new over D1 (see paragraph 2.3, above).
- 5 Inventive step
- 5.1 D1 is regarded as being the prior art closest to the subject-matter of the present application. The subject-matter of claims 1-3, 6, 18, 20, 28-36 is not new and hence cannot be inventive.
- 5.2 The compounds of present claims 4, 5, 7, 22, 26, and 27 overlap with the compounds of claim 1 of D1 and can be considered as selections from the compounds disclosed in D1 for the same use. Such selections can only be regarded as inventive if the presently claimed compounds exhibit unexpected effects or properties in relation to the rest of compounds of D1. Since no such effects or properties are indicated and supported in the application, the

subject-matter of claims 4, 5, 7, 22, 26, and 27 does not involve an inventive step within the meaning of Article 33(3) PCT. In order to show any such unexpected effect(s) vis-à-vis the said prior art, comparative tests could be performed using compounds with the maximum structural similarity, i.e. the compound of example 9 of D1. In addition, it should be credibly shown that the effect occurs over the whole claimed range.

- 5.3 The compounds of claims 8-13, 19, 21, and 23-25 differ from the compounds of D1 due to their 5-membered heteroaryl ring Het, and the compounds of claims 14-17 due to their saturated ring Het. The problem to be solved by the subject-matter of claims 8-17, 19, 21, and 23-25 may therefore be regarded as the provision of alternative antibacterial compounds.
- 5.4 In view of the data provided in tables A and B (pages 247-281), it seems credible that compounds according to claims 8-17, 19, 21, and 23-25 exhibit anti-bacterial activity. Compounds of formula I, wherein Het is a saturated heterocycle or a 5-membered heteroaryl have not been proposed as anti-bacterials and a skilled person starting from D1 could not necessarily expect that they exhibit the desired activity despite the replacement of a pyridinio residue by a saturated heterocycle or a 5-membered heteroaryl. Inventive step can therefore be acknowledged for these compounds and subject-matter referring to them. The problem has however been solved in two different ways, i.e. the solution is not unitary (see paragraph 2, above).

Re Item VII

- 6 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

- 7 Independent claim 33 correctly claims a compound for use as a medicament. However, the dependent claims 34-35 refer to it as if it were a claim to the compounds per se, giving rise to an internal inconsistency, contrary to Art. 6 PCT. This objection could be overcome by rephrasing claims 34 and 35 as follows: "The compounds for use of claim 33, wherein..."
- 8 The vague and imprecise statement in the last paragraph of page 282 of the description implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.