

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/IB2015/054174	International filing date (day/month/year) 02.06.2015	Priority date (day/month/year) 03.06.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D471/04 A61K31/44 C07D471/14 C07D495/14		
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 Bareyt, Sébastien 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. 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>1-14</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>7</u>
	No: Claims	<u>1-6, 8-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-14</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Reference is made to the following documents:

D1 WO 2012/016930 A1 (Univ. Droit & Santé de Lille [FR]) 09-02-2012

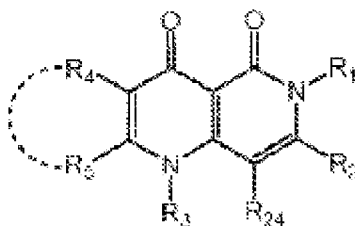
D2 WO 2014/091446 A1 (NOVARTIS AG [CH]) 19-06-2014

Box 5

1 Medical Treatment (Rule 39.1(iv) PCT)

Claims 12-14 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(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.

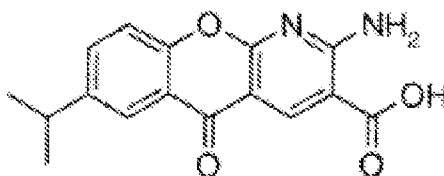
2 Novelty (Article 33(2) PCT)



Due to the invariable presence of the specifically substituted naphthyridinedione moiety (shown here above) the compounds claimed are considered to be novel vis-à-vis the state of the art.

3 Inventive step (Article 33(3) PCT)

D1, which is considered to represent the most relevant state of the art, discloses substituted 5-oxo-5*H*-chromeno[2,3-*d*]pyridine shown below for use in the treatment of nonsense mutation.



No unambiguous comparative data between the compounds of D1 and those presently claimed has been given in the present application. The structural difference can therefore not be linked to any additional effect or property.

The problem to be solved by the present invention may therefore be regarded as providing alternative treatment for nonsense mutations. In view of the biological testing data of present pages 65-72 said problem is considered solved for the specific compounds disclosed therein.

However, the breadth of the claims should be such that it represents a reasonable generalisation of the disclosed examples and be especially such that every compound falling within the scope of the claims actually provides a solution to the problem underlying the invention. On the assumption that the compounds [depicted in pages 37-65 of the present application solve this problem, it clearly appears that they all are of formula (I) wherein R^1 is unsubstituted cyclic and contains 4-6 C and 0-1 N atoms, R^2 is alkyl, R^3 is H or Me, and R^4 - R^5 is thieno or benzo.

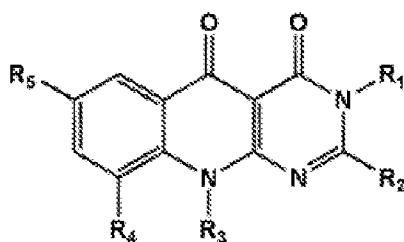
If these characteristics are essential to the specific activity profile on which the acknowledgement of an inventive step is based, the claims should be restricted accordingly. The following statement is limited to the subject-matter for which the technical problem is considered solved (namely the specific compounds and a reasonable generalisation thereof). For the moment the only claim which fulfil this criteria is considered to be claim 7.

In the field of drug design, any structural modification of a pharmacologically active compound is, in the absence of an established correlation between structural features and activity, expected a priori to disturb the pharmacological activity profile of the initial structure. Therefore the present compounds can be considered as non-obvious.

There is no indication in the prior art or in the general knowledge of naphthyridine-dione structure or analogs for use in the treatment of nonsense mutations. Therefore, the present specific compounds (and a reasonable generalisation thereof) are no obvious solution to the present technical problem. A new independent claim may be drafted to include this compounds bearing in mind that the resulting breadth of the claim should be reasonable and credible with respect to the working examples on file. Said claim would be considered to involve an inventive step.

Box 6

D2 discloses pyrimidoquinolindiones shown below for use in the treatment of nonsense mutation.



D2 published on 19-06-2014 claims the priority date of 13-12-2012. If it was not supplied to the EPO. Its content as filed would therefore be comprised in the state of the art for the parts of the present application for which the claimed priority date of 03-06-2014 was challenged. The priority claimed might be considered invalid in a later stage of the proceeding for the subject-matter in which R²⁴ is halogen and/or in which R⁴-R⁵ is not thieno or benzo. The applicant is requested to indicate a base in the original priority document for said subject-matter.