

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 123429-08420	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2020/039346	International filing date (<i>day/month/year</i>) 24 June 2020 (24.06.2020)	Priority date (<i>day/month/year</i>) 27 June 2019 (27.06.2019)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant BIOGEN MA INC.		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i> . I(a).																								
2.	This REPORT consists of a total of 7 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	This report contains indications relating to the following items: <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 10%; text-align: center;">☒</td> <td style="width: 30%;">Box No. I</td> <td style="width: 80%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	Box No. I	Basis of the report	☐	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 Article 35(2) 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
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44 <i>bis</i> .3(c) and 93 <i>bis</i> .1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44 <i>bis</i> .2).																								

	Date of issuance of this report 28 December 2021 (28.12.2021)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Cécile Chatel e-mail ro.ib@wipo.int

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/US2020/039346	International filing date (day/month/year) 24.06.2020	Priority date (day/month/year) 27.06.2019
International Patent Classification (IPC) or both national classification and IPC INV. C07D231/56 C07D401/12 C07D405/14 C07D471/04 C07D487/04 C07D519/00 A61K31/416 A61P29/00 A61P35/00 A61K31/4439 A61K31/437 A61K31/4985 A61P3/00 A61P25/00		
Applicant BIOGEN MA INC.		

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:  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 Moriggi, J 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>3-8, 13, 14, 16-19, 24, 26-36</u>
	No: Claims	<u>1, 2, 9-12, 15, 20-23, 25, 37-41</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-41</u>
Industrial applicability (IA)	Yes: Claims	<u>1-41</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

Item V.

Claims 39-41 relate to subject-matter considered by this Authority to be covered by the provisions 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. Nevertheless, the present application deals with the subject-matter of said claims 39-41.

1. Reference

Reference is made to the following documents:

D1: Chem. Soc. 2018, 9, 655-659

D2: WO 2014/107771

D3: CN 105503863

D4: WO 2014/143666

D5: WO 2016/083433

D6: WO 2017/009798

D7: WO 2017/148902

2. Novelty

Document D1 discloses compound 4I that falls within formula (I') of claim 1 of the present application.

Formula I of claim 1 of document D2, wherein L is C(O)-NH and A¹ is N-(CH₂)_n-R¹, and formula (I') of claim 1 of the present application, in which R¹ is alkyl and R³ is option ii, overlap. Document D2 explicitly discloses compounds 14, 18 and 20 that fall within the chemical area defined by the structural overlap. In addition, document D2 discloses their use in the treatment of neurodegenerative diseases.

Formula I of claim 1 of document D3, wherein X is NHX¹, and formula (I') of claim 1 of the present application, in which R¹ is heterocycle, R² is alkyl and X¹ is N, overlap. In addition, document D3 discloses at least compounds I-3, I-6, I-16 and I-42 that fall within the chemical area defined by the structural overlap. In addition, D3 discloses pharmaceutical compositions (claim 9) and the use for treating cancer (claim 10).

Formula I of claim 1 of document D4 and formula (I') of claim 1 of the present application, in which R^3 is option ii and at least one R^4 is NH_2 , overlap. It is questionable whether, for example, compound A13 falls within the chemical area defined by the structural overlap. In fact, it would correspond to a compound of formula (I') of the present application wherein R^1 is C_1 alkyl and is substituted with a C_6 heterocycle (see item VIII for the clarity issue associated with the term heterocycle). In any case, document D4 discloses compounds A16 and A24 that certainly fall within the chemical area defined by the structural overlap (when R^1 of the present application is -alkyl-cycloalkyl). In addition, document D4 discloses pharmaceutical compositions (claim 110) and a method for the treatment of neurological disorders and inflammatory diseases (claim 119).

The present application does not meet the requirements of Article 33(2) PCT.

For the sake of completeness, it should be noted that:

Documents D5-D7 disclose IRAK4 inhibitors. They differ from the compounds according to formula (I') of claim 1 of the present application through the orientation of the amide group: it is attached to the indazole ring via its carbonyl group in the present application and via its nitrogen atom in the compounds of D5-D7.

3. Inventive Step

Firstly, it is reminded that subject-matter that is not novel cannot be inventive. Secondly, the applicant's attention is drawn to the fact that, when determining which document could be considered as the closest prior art, it has to be borne in mind that the primary aim of the application is to provide pharmaceutical compounds useful for the treatment or prevention of certain disorders, and that the pathway or mechanism by which these pharmaceuticals achieve the desired effect is of only secondary interest. As a result, document D4, which relates to the treatment of neurological disorders and inflammatory diseases just like the present application, is regarded as the closest prior art.

At first, the problem to be solved by the novel subject-matter of the present application could be seen in the provision of indazole derivatives useful for treating neurological disorders and inflammatory diseases that possess unexpected properties over the prior art.

There is, however, no experimental data or any other information supporting the presence of an unexpected effect associated with the novel subject-matter of the present application over D4. The technical problem must therefore be reformulated into a less ambitious problem, namely the mere provision of alternative indazole derivatives useful for the treatment of neurological disorders and inflammatory diseases.

The data provided on pages 199-202 seem to indicate that at least the exemplified compounds according to formula (I') of current claim 1 actually solve the technical problem. However, in view of the structural overlap with D4, the person skilled in the art of medicinal chemistry would have considered obvious the compounds of formula (I') of current claim 1.

The present application does not meet the requirements of Article 33(3) PCT.

Item VIII.

Throughout the claims, the term "heterocycle" is sometimes preceded or followed by the adjective saturated (be it fully or partially saturated) but sometimes it is used on its own. It is reminded that according to IUPAC, "heterocycle" also includes heteroaryl rings. The claims are therefore inconsistent and unclear (Article 6 PCT). In addition, the term "may" is sometimes used, i.e. "*may be fully or partially saturated*". Since "may" is not restrictive, the claims are also ambiguous and do not meet the requirements of clarity of Article 6 PCT.

Option vi of the current definition of R³ is not necessarily limited to a carbon-only ring system and, as a result, option vi is partially redundant with option v. Claim 1 does not fulfil the requirements of conciseness set down in Article 6 PCT.

The claims must be self-contained and cannot refer, for example, to the description in order to define the subject-matter for which protection is sought. As a result, current claim 36 does not meet the requirements of Article 6 PCT. The actual examples must be explicitly recited in claim 36.