

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/US2022/027763

International filing date (day/month/year)
05.05.2022

Priority date (day/month/year)
07.05.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C07D241/08 C07D401/12 C07D405/12 C07D417/12 A61K31/496 A61P29/00

Applicant
MERCK SHARP & DOHME LLC

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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 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:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>1-39</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-39</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-39</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

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

Re Item V

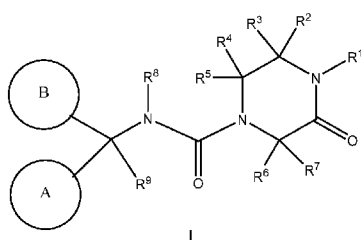
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 2011/026240 A1 (ZALICUS PHARMACEUTICALS LTD [CA]; PAJOUHESH HASSAN [CA] ET AL.) 10 March 2011 (2011-03-10) cited in the application
- D2 WO 2020/092667 A1 (MERCK SHARP & DOHME [US]; ARASAPPAN ASHOK [US] ET AL.) 7 May 2020 (2020-05-07) cited in the application
- D3 WO 2020/092187 A1 (MERCK SHARP & DOHME [US]; BRESLIN MICHAEL J [US] ET AL.) 7 May 2020 (2020-05-07)

Claims 36-39 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 directed 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.

The present application discloses a compound of structural Formula I which find use as NaV1.8 sodium channel inhibitors:



or a pharmaceutically acceptable salt thereof, wherein one of A and B is independently selected from the group consisting of:

- (1) aryl, and
- (2) heteroaryl, and the other of A and B is independently selected from the group consisting of:
 - (1) C₃₋₁₂ cycloalkyl,
 - (2) C₂₋₁₁ cycloheteroalkyl,

- (3) -C₁₋₆alkyl-C₃₋₁₂cycloalkyl,
- (4) -C₁₋₆alkyl-C₂₋₁₁ cycloheteroalkyl,
- (5) -C₁₋₆alkyl-O-C₃₋₁₂cycloalkyl, and
- (6) -C₁₋₆alkyl-O-C₂₋₁₁ cycloheteroalkyl.

V-1. Novelty (Article 33(1) and (2) PCT):

The present compounds differ from those in D1 on account of one of A or B not being aromatic and on account of the present -N(R8)- linking group which is absent in the compounds in D1.

Moreover the present compounds are novel over those in D2 and D3 on account of of the present piperazine which differs from the B heteroaryl in D2 and D3 and the present C(R9)AB group which differs from the group A in D2 and D3.

The present subject-matter can be considered novel in the sense of Article 33(2) PCT.

V-2. Inventive step (Article 33(1) and (3) PCT):

D1, which can be considered the closest prior art, discloses compounds NaV1.8 sodium channel inhibitors.

The difference with the present applications lies in the presence of a phenyl ring instead of the present one of A or B not being aromatic and on account of the absence of a -N(R8)- linking group.

There is no special effect linked to the cited differences and thus the problem to be solved by the present invention may therefore be regarded as the provision of further NaV1.8 sodium channel inhibitors. The solution are the present compounds accroding to the test results disclosed in pages 174-176.

There is no suggestion in D1 nor in other documents to perform the changes as mentioned in order to obtain molecules with the present activity. For instance the present C(R9)AB group with one A or B not being aromatic is not suggested by the corresponding the group A in D2 and D3.

During the international phase the question to which extend the compounds of formula (I) indeed possess the claimed activity will not be addressed. Accordingly it is acknowledged without further investigation that the technical problem defined above has been solved by the provision of compounds of formula (I). However it should be noted that the breath of the claims should be such that it represents a reasonable generalization over the examples provided, and such that substantially all compounds

falling within their scope actually are solutions to the technical problem underlying the invention and only compounds without further condensed rings to the piperazine and R2-R5 being hydrogen (or deuterium) have been exemplified. In this respect it must be noted that most of the compounds claimed cannot be regarded as obvious modification or equivalents of the examples which have been given in the description if the technical problem underlying the application is taken into account.

The present subject-matter can be considered as involving an inventive step in the sense of Article 33(3) PCT.

V-3. Industrial applicability (Article 33(4) PCT):

Claims 1-39 fulfill the requirements of Article 33(4) PCT in respect to their industrial applicability.

Re Item VI

Certain documents cited

- D4 WO 2021/257420 A1 (MERCK SHARP & DOHME [US]; ARASAPPAN ASHOK [US] ET AL.) 23 December 2021 (2021-12-23)
- D5 WO 2021/257490 A1 (MERCK SHARP & DOHME [US]; ARASAPPAN ASHOK [US] ET AL.) 23 December 2021 (2021-12-23)

The documents D4 and D5 have a priority earlier than that of the present application. The present compounds differ from those in D4 and D5 on account of the present piperazine ring. The compounds in D4 and D5 find use as inhibitors of NaV1.8 sodium channel. If the present priority were found not to have validity, these documents would be relevant for the assessment of inventive step of the present application.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D3-D5 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

Claim 2 appear to comprise all the features of claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).