

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/US2020/060180

International filing date (day/month/year)
12.11.2020

Priority date (day/month/year)
12.11.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D277/52 C07D417/04 C07D417/12 C07D417/14 A61K31/427

Applicant
GENZYME CORPORATION

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:



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Date of completion of
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:

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>91, 93, 96, 97, 112, 124</u>
	No: Claims	<u>1-90, 92, 94, 95, 98-111, 113-123, 125-138</u>
Inventive step (IS)	Yes: Claims	<u>91, 93, 96, 97, 112, 124</u>
	No: Claims	<u>1-90, 92, 94, 95, 98-111, 113-123, 125-138</u>
Industrial applicability (IA)	Yes: Claims	<u>1-138</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

1. PRIOR ART

Reference is made to the following documents:

- D1 WO 2016/183173 A1 (AVISTA PHARMA SOLUTIONS [US]) 17 November 2016 (2016-11-17)
- D2 JAMES R. HITCHIN ET AL: "Development and evaluation of selective, reversible LSD1 inhibitors derived from fragments", MEDCHEMCOMM, vol. 4, no. 11, 1 January 2013 (2013-01-01), page 1513, XP055440900, United Kingdom
ISSN: 2040-2503, DOI: 10.1039/c3md00226h
- D3 JENKINS JEREMY L ET AL: "A 3D similarity method for scaffold hopping from the known drugs or natural ligands to new chemotypes", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, vol. 47, no. 25, 2 December 2004 (2004-12-02), pages 6144-6159, XP002355651,
ISSN: 0022-2623, DOI: 10.1021/JM049654Z
- D4 WO 03/039451 A2 (FUJISAWA PHARMACEUTICAL CO [JP]; TSUTSUMI HIDEO [JP] ET AL.) 15 May 2003 (2003-05-15)
- D5 WO 96/16650 A1 (HISAMITSU PHARMACEUTICAL CO [JP]; HASHIGUCHI TERUSHI [JP] ET AL.) 6 June 1996 (1996-06-06)
- D6 US 5 449 783 A (SAITA MASARU [JP] ET AL) 12 September 1995 (1995-09-12)
- D7 WO 2018/042316 A1 (NOVARTIS AG [CH]) 8 March 2018 (2018-03-08)
- D8 EP 3 464 282 A1 (ABBVIE SARL [LU]; GALAPAGOS NV [BE]) 10 April 2019 (2019-04-10)

2. GENERAL STATEMENT

Claims 131-138 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1 (iv)/Rule 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize 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 in a first or further medical treatment.

3. NOVELTY

3a) Preliminary remark (see also item VIII) : the present claims relates to an extremely large number of possible compounds. On account of the very general definitions (lacking specific structural definitions) so many documents (see e.g. D1-D6, see passages referred to in the SR) could be retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the processes (see examples of the description where basically R3 systematically denotes a "complex" alkoxy substituent). The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claim (PCT Guidelines 9.19 and 9.23). It should be noted further that many of the dependent claims not appear to contain any substantial restriction.

3b) Accordingly, the search was focused on the concrete embodiments i.e. basically examples where R3 denotes a "complex" alkoxy substituent.

3c) The subject-matter of claim 1 is not considered to be novel (Article 33(2) PCT): D1,D4-D6 form an overlapping part with the presently claimed subject matter of formula (I). In addition to that said documents disclose some compounds falling within the overlapping range or are structurally close. D2 and D3 disclose examples falling under the generic expressions of the current claims are structurally close. An analogous or similar assessment might be carried out for multiple dependent claims.

The subject matter of current claims 91, 93, 96, 97, 112, 124 appears to be novel on account of the specific substitution pattern of the CY unit in view of the cited prior art.

The subject matter of D7 differs in the nature of the central heterocyclic core. The compounds of D8 are structurally remote.

4. INVENTIVE STEP

The subject-matter of the claims 91, 93, 96, 97, 112, 124 appears to fulfil the requirements of Article 33(3) PCT for the following reasons:

The application relates to 5-membered heteroarylaminosulfonamides, the use of such compounds in methods of treating diseases and conditions mediated by deficient CFTR activity, in particular cystic fibrosis.

The closest state of the art for the present application is represented by D7. Said documents disclose structurally similar substituted heteroarylaminosulfonamides having the same properties which do not fall under the present application because of the nature of the central heterocyclic unit.

In the absence of a demonstrated effect the problem of the present application appears to lie in the provision of further heteroarylaminosulfonamides for use in methods of treating diseases and conditions mediated by deficient CFTR activity, in particular cystic fibrosis.

It is shown by means of biological assays that the problem appears to be solved within the claimed scope of claims 91, 93, 96, 97, 112, 124.

Starting from D7 (alone or in combination with D8) the skilled person has no obvious incentive to carry out the modifications leading to the presently claimed subject matter of claims 91, 93, 96, 97, 112, 124 in order to solve the given problem.

Accordingly, inventive step can be acknowledged for claims 91, 93, 96, 97, 112, 124 but not the remaining claims.

Item VIII

-The present claims relates to an extremely large number of possible compounds. On account of the very general definitions (lacking specific structural definitions) so many documents (see e.g. D1-D6, see passages referred to in the SR) could be retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the processes (see examples of the description where basically R3 systematically denotes a "complex" alkoxy substituent). The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claim (PCT Guidelines 9.19 and 9.23).

-Claims 126 and 127 contain vague references to the description and are therefore unclear in scope.