

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/US2016/045946	International filing date (day/month/year) 08.08.2016	Priority date (day/month/year) 10.08.2015
International Patent Classification (IPC) or both national classification and IPC INV. C07F9/16 A61K31/664 A61P31/18		
Applicant MERCK SHARP & DOHME CORP.		

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 Sáez Díaz, R 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>1-22</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-22</u>
Industrial applicability (IA)	Yes: Claims	<u>1-22</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

Re Item V

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

- 1 The present application relates a β -amino acid ester phosphodiamide derivatives of formula (I) as prodrugs of tenofovir for use in the treatment of HIV infection.
- 2 Claims 16-18 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.
- 3 Reference is made to the following documents:
 - D1 WO 2008/005555 A1
 - D2 PERTUSATI FABRIZIO ET AL: "PMPA and PMEA prodrugs for the treatment of HIV infections and human papillomavirus (HPV) associated neoplasia and cancer", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 78, 2014, pages 259-268, XP028847859
 - D3 WO 01/47935 A2
- 4 No prior art document discloses derivatives of the present formula (I). The structurally closest compound can be found in document D2 (prodrug 12). This prior art compound shows, however, an α -aminoacid instead of a β -aminoacid attached to the phosphodiamide tenofovir moiety. Therefore, the subject-matter of claims 1-22 is novel and meets the requirements of Article 33(2) PCT.

Document D1 generally discloses β -amino acid ester phosphodiamide derivatives of formula (I) as the ones of present claim 1. It is noted that the presently claimed compounds of general formula (I) represent a novel selection from D1, because they are generally but not specifically disclosed therein. The structurally closest compound of document D1 is example AR, which differs from the ones presently claimed through the substitution pattern of the purine ring and the phosphodiamide moiety (α - instead of β -aminoacid).

Document D3 shows β -amino acid ester phosphodiamide prodrugs of unrelated compounds (example 52.33).

- 5 Document D2 is considered to be the closest prior art to the subject-matter of claims 1-22 as it discloses α -amino acid ester phosphodiamide derivatives of tenofovir as prodrugs for use in the treatment of HIV infection (prodrug 12, table 1). The difference between the example compound of D2 and the presently claimed compounds resides in the aminoacid chain attached to the tenofovir moiety (α -instead of a β -aminoacid). The problem to be solved by the present invention may therefore be regarded as the provision of alternative phosphodiamide derivatives of tenofovir for use in the treatment of HIV infection. The compounds described in present claims 1-13 are structurally very similar to the ones described in D2. Since no effect seems to be associated to the minor structural variation, no inventive step can be recognized on the basis of such variation. This observation finds further support in that D1 already teaches that the alkyl chain between the amine and the carboxylic group of the aminoacid can be varied without affecting the activity of the compounds (see claim 1). Furthermore, β -amino acid ester phosphodiamide prodrugs are known in the art (see example 52.33 of D3). Considering the teachings of D1-D3, the person skilled in the art would have expected the claimed to maintain the activity of the compounds explicitly disclosed in said documents. This information would provide the person skilled in the art with a reasonable expectation of success to try to modify the compounds described in D2 to find alternative prodrugs of tenofovir and would arrive at the presently claimed subject-matter without exercising any inventive skill. Therefore, the subject-matter of claims 1-22 does not involve an inventive step within the sense of Article 33(3) PCT.

Re Item VII

Certain defects in the international application

- 6 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D2 is not mentioned in the description, nor are these documents identified therein.