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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2017/057588	01.12.2017	01.12.2016

International Patent Classification (IPC) or both national classification and IPC
INV. C07H21/00 C07H21/02 A61K31/7084 A61P35/00

Applicant
TAKEDA PHARMACEUTICAL COMPANY LIMITED

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 notifed 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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Mezzato, Stefano Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2017/057588

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. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-100, 105, 107-109, 111-120, 126-128, 142-200
	No:	Claims	101-104, 106, 110, 121-125, 129-141
Inventive step (IS)	Yes:	Claims	32-100, 142-200
	No:	Claims	1-31, 101-141
Industrial applicability (IA)	Yes:	Claims	1-200
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

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

   and / or

2. Non-written disclosures (Rules 43*bis*.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

Reference is made to the following documents:

D1 WO 2014/189805 A1 (AURO BIOTECH INC [US]; UNIV CALIFORNIA [US]) 27 November 2014 (2014-11-27)cited in the application

D2 WO 2014/179335 A1 (SLOAN KETTERING INST CANCER [US]; UNIV ROCKEFELLER [US]; UNIV RUTGERS) 6 November 2014 (2014-11-06)cited in the application

D3 WO 2017/027646 A1 (MERCK SHARP & DOHME [US]; ALTMAN MICHAEL D [US]; ANDRESEN BRIAN [US];) 16 February 2017 (2017-02-16)cited in the application

D4 WO 2017/161349 A1 (IMMUNE SENSOR LLC [US]; UNIV TEXAS [US]) 21 September 2017 (2017-09-21)

D5 WO 2016/096174 A1 (INVIVOGEN [FR]) 23 June 2016 (2016-06-23)cited in the application

D6 YAN H ET AL: "Synthesis and immunostimulatory properties of the phosphorothioate analogues of cdiGMP", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 18, no. 20, 15 October 2008 (2008-10-15), pages 5631-5634, XP025562123, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2008.08.088 [retrieved on 2008-08-29]

1 **Re Item IV**

Lack of unity of invention

1.1 This Authority considers that the application does not meet the requirements of unity of invention and that there are 4 inventions covered by the claims indicated as follows:

1. claims: 1-31
Compounds of formula (I)

2. claims: 32-100
Compounds of formula (XIV)

3. claims: 101-143
Compounds of formula (XL)

4. claims: 144-200
Compounds of formula (XLI)

1.2 The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows.

According to Rule 13.2 PCT in an International patent application the requirement of unity of invention as referred to in Rule 13.1 PCT is fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features, the latter expression designating those features which define a contribution which each of the claimed inventions considered as a whole makes over the prior art.

The problem underlying the present invention is the provision of further cyclic dinucleotides having STING (stimulator of interferon genes) agonistic activity, which may be useful as agents for the prophylaxis or treatment of cancer and related diseases.

D1 discloses (D1, figure 2A; compounds 9a-9f; claim 1) cyclic dinucleotides having STING (stimulator of interferon genes) agonistic activity.

The subject-matter of independent claim 1 differs from these compounds of D1 in that one of the nucleobases has the structure given in the proviso at the end of present claim 1.

The subject-matter of independent claim 32 differs from these compounds of D1 in that the cyclic dinucleotides are connected to an antibody A through a linker L.

The subject-matter of independent claim 101 differs from these compounds of D1 in that the cyclic dinucleotides are connected to a group R28 through a linker L1.

The subject-matter of independent claim 144 differs from these compounds of D1 in that the cyclic dinucleotides are connected to a drug delivery agent DA.

The technical effects derived from those differences against D1 are unknown. Therefore, the present inventions solve the problem of providing further cyclic dinucleotides having STING agonistic activity.

The inventions above are characterised by the following special technical features: a different nucleobase, group A, group R28, group DA.

Those special technical features are neither the same nor corresponding. Consequently, the four different inventions are not linked by a single general inventive concept and the application does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

Invention 1 claims: 1-31

Compounds of formula (I)

2 **Re Item V**

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

2.1 **Independent claims**

Compound claim 1

2.2 **Novelty (Article 33(2) PCT)**

2.2.1 Document D1-D2 disclose (D1, figure 2A; compounds 9a-9f; claim 1; D2, claims 1, 33) cyclic dinucleotides having STING (stimulator of interferon genes) agonistic activity.

However, the present compounds of claim 1 fall within the scope of the claims of D1-D2. The subject-matter of independent claim 1 differs from these compounds of D1-D2 in that one of the nucleobases has the structure given in the proviso at the end of present claim 1, which is not specifically disclosed by D1-D2 (a selection from at least two different lists of variables is necessary to arrive at the purine base of the proviso of present claim 1). The present compounds of claim 1 are thus a new selection from those disclosed by D1-D2.

Claims 1-31 are new.

2.3 **Inventive step (Article 33(3) PCT)**

2.3.1 Either document D1 or D2 can be considered as the closest prior art, as they both disclose cyclic dinucleotides having STING agonistic activity with the most structural features in common.

The technical effect derived from this new selection of present claim 1 is unknown. The problem to be solved by the present invention is thus the provision of further cyclic dinucleotides having STING agonistic activity.

D1-D2 (D1, claim 1; D2, claims 1, 33) already suggest the selection of features of present claims 1-31. The skilled person would thus have regarded those selections as obvious modifications of D1-D2.

Claims 1-31 are hence not inventive.

To substantiate the presence of an inventive the step, the applicant should show that the present compounds possess an unexpected activity over the compounds of D1-D2.

3 **Re Item VI**

Certain documents cited

Document D3-D4 (D3, page 388, last line; claim 22; page 389, line second; claim 22; D4, page 291; claim 10; compounds 2-3; page 292; claim 10; compounds 1-3; page 293; claim 10; compounds 1, 3; page 294; claim 10; compound 1; page 299; claim 10; compound 3; claims 28-31, 37) disclose cyclic dinucleotides having STING agonistic activity. The subject-matter of independent claim 1 differs from these compounds of D3-D4 in that one of the nucleobases has the structure given in the proviso at the end of present claim 1, which is not specifically disclosed by D3-D4. The present compounds of claim 1 are thus new over D3-D4.

Should the priority of the present application not be valid, D3-D4 would become relevant for the assessment of inventive step.

4 **Re Item VII**

Certain defects in the international application

4.1 The wording "incorporated by reference" should be removed from the description.

Invention 2 claims: 32-100

Compounds of formula (XIV)

5 **Re Item V**

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

5.1 **Independent claims**

Compound claim 32

5.2 **Novelty (Article 33(2) PCT)**

5.2.1 Document D1-D2, D5-D6 disclose (D1, figure 2A; compounds 9a-9f; claim 1; D2, claims 1, 33; D5, claims 1-2; D6, page 5632; compounds 7a, 7b) cyclic dinucleotides having STING (stimulator of interferon genes) agonistic activity.

5.2.2 Independent claim 32 differs from D1-D2, D5-D6 in that:

- an antibody, antibody fragment, or antigen-binding fragment is connected through a linker to the sulphor atom on the phosphate (i.e. group A of claim 32 is an antibody, antibody fragment, or antigen-binding fragment).

Present claims 32-100 are thus new.

5.3 **Inventive step (Article 33(3) PCT)**

5.3.1 Any one of documents D1, D2, D5, D6 can be considered as the closest prior art, as they all disclose cyclic dinucleotides having STING agonistic activity.

The technical effect derived from this difference is (see par. [1052] of the present description) that the compound is used as a payload in an antibody- or (antigen recognition sequence)-drug conjugate. The problem to be solved by the present invention is thus how to modify the cyclic dinucleotides of D1, D2, D5, D6 so that they can function as payloads in an antibody- or (antigen recognition sequence)-drug conjugate.

Although it would be straightforward to connect the cyclic dinucleotides to an antibody or an antigen, there is in the prior art no hint at how this connection could be obtained through a sulphor atom of the phosphate group. D1, D2, D5, D6 are silent as to possible drug conjugates of those known cyclic dinucleotides, but only disclose compositions comprising antibodies as additional separate components (i.e. not conjugated to the cyclic dinucleotides).

Therefore, present claims 32-100 are inventive.

6 **Re Item VII**

Certain defects in the international application

6.1 **Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy**

Claims 84-87 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) and Article 34(4)(a)(I) PCT.

For the assessment of the present claims 84-87 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for use in a new medical treatment.

Although claims 84-87 are directed to a method of treatment of the human/ animal body, the present examination has been carried out and based on the alleged effects of the compounds/compositions.

6.2 The wording "incorporated by reference" should be removed from the description.

7 **Re Item VIII**

Certain observations on the international application

7.1 The terms "linker" and "spacer" used in claims 32-100 are vague and unclear and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

Invention 3 claims: 101-143

Compounds of formula (XL)

8 **Re Item V**

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

8.1 **Independent claims**

Compound claim 101

8.2 **Novelty (Article 33(2) PCT)**

8.2.1 D5 discloses (D5, claims 1-2) compounds of claim 101, wherein R28 is NH2 (see group R1 of claim 1 of D5).

Present claims 101-104, 106, 110, 121-125, 129-141 are not new over D5.

8.2.2 D6 discloses (D6, page 5632; compounds 7a, 7b) compounds of claim 101, wherein R28 is CN.

Present claims 101-104, 106, 110, 121-125, 129-141 are not new over D6.

8.3 **Inventive step (Article 33(3) PCT)**

8.3.1 D5 can be considered as the closest prior art, as its discloses S-protected derivatives of cyclic dinucleotides, which have STING agonistic activity.

8.3.2 Claims 105, 107-109, 111-120, 126-128, differ from D5 (D5, claims 1-2) in minor modifications of the nucleobase or of the carbohydrate rings. The technical effect derived from those modification is unknown. The problem to be solved by the present invention is thus the provision of further S-protected derivatives of cyclic dinucleotides, which have STING agonistic activity.

Those minor structural modifications are obvious to the skilled person.

Therefore, present claims 105, 107-109, 111-120, 126-128 are hence not inventive.

8.4 Claims 142-143 differ from D5 in that:

- R28 is a succinamide group.

Prior art documents D1, D2, D5, D6, all related to cyclic dinucleotides having STING agonistic activity, do not disclose similar modifications on the S-phosphate, nor would the skilled person have been prompted to introduce a succinimide group without hindsight.

Therefore, present claims 142-143 are inventive.

9 **Re Item VII**

Certain defects in the international application

9.1 The wording "incorporated by reference" should be removed from the description.

10 **Re Item VIII**

Certain observations on the international application

10.1 The terms "linker" and "spacer" used in claims 101-142 are vague and unclear and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.

Invention 4 claims: 144-200

Compounds of formula (XLI)

11 **Re Item V**

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

11.1 **Independent claims**

Compound claim 144

11.2 **Novelty (Article 33(2) PCT)**

11.2.1 Document D1-D2, D5-D6 disclose (D1, figure 2A; compounds 9a-9f; claim 1; D2, claims 1, 33; D5, claims 1-2; D6, page 5632; compounds 7a, 7b) cyclic dinucleotides having STING (stimulator of interferon genes) agonistic activity.

11.2.2 Independent claim 144 differs from D1-D2, D5-D6 in that:

- drug delivery agent is connected (optionally) through a linker to the sulphor atom on the phosphate (i.e. group DA of claim 144 is a drug delivery agent).

Present claims 144-200 are thus new.

11.3 **Inventive step (Article 33(3) PCT)**

11.3.1 Any one of documents D1, D2, D5, D6 can be considered as the closest prior art, as they all disclose cyclic dinucleotides having STING agonistic activity.

The technical effect derived from this difference is (see par. [0169]) that the compound has an enhanced affinity for a selected target. The problem to be solved by the present invention is thus how to modify the cyclic dinucleotides of D1, D2, D5, D6 so that they have an enhanced affinity for a selected target.

Although it would be straightforward to connect the cyclic dinucleotides to a drug delivery agent, there is in the prior art no hint at how this connection could be obtained through a sulphor atom of the phosphate group. D1, D2,

D5, D6 are silent as to possible drug conjugates of those known cyclic dinucleotides, but only disclose compositions comprising additional separate components (i.e. not conjugated to the cyclic dinucleotides).

Therefore, present claims 144-200 are inventive.

12 **Re Item VII**

Certain defects in the international application

12.1 The wording "incorporated by reference" should be removed from the description.

13 **Re Item VIII**

Certain observations on the international application

13.1 The terms "linker", "spacer", "drug delivery agent" used in claims 144-200 are vague and unclear and leave the reader in doubt as to the meaning of the technical feature to which they refer, thereby rendering the definition of the subject-matter of said claims unclear, Article 6 PCT.