

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
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INVITATION TO PAY ADDITIONAL FEES
AND, WHERE APPLICABLE, PROTEST FEE
(PCT Article 17(3)(a) and Rule 40.1 and 40.2(e))

	Date of mailing (day/month/year) 27 March 2018 (27-03-2018)
Applicant's or agent's file reference 3817-040PC03	PAYMENT DUE within ONE MONTH from the above date of mailing
International application No. PCT/IB2017/057588	International filing date (day/month/year) 1 December 2017 (01-12-2017)
Applicant TAKEDA PHARMACEUTICAL COMPANY LIMITED	

1. This International Searching Authority

(i) considers that there are 4 (number of) inventions claimed in the international application covered by the claims indicated on an extra sheet:

(ii) therefore considers that **the international application does not comply with the requirements of unity of invention** (Rules 13.1, 13.2 and 13.3) for the reasons indicated on an extra sheet:

(iii) has carried out a partial international search (see Annex) will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
see extra sheet

(iv) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid.

2. Consequently, the applicant is hereby **invited to pay**, within the time limit indicated above, the amount indicated below:

<u>EUR 1.875,00</u>	x	<u>3</u>	=	<u>EUR 5.625,00</u>
Fee per additional invention		number of additional inventions		currency/total amount of additional fees

3. The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest**, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive, where applicable, subject to the payment of a protest fee.
Where the applicant pays additional fees under protest, the applicant is hereby invited, within the time limit indicated above, to pay a protest fee (Rule 40.2(e)) in the amount of EUR 875,00 (currency/amount)

Where the applicant has not, within the time limit indicated above, paid the required protest fee, the protest will be considered not to have been made and the International Searching Authority will so declare.

4. Claim(s) Nos. _____ have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer BößWETTER, Ruth Tel: +49 (0)89 2399-4162
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This International Searching Authority found multiple (groups of) inventions in this international application, 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)

Reference is made to the following document:

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

This Authority considers 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)

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.

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
- see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/189805 A1 (AURO BIOTECH INC [US]; UNIV CALIFORNIA [US]) 27 November 2014 (2014-11-27) cited in the application figure 2A; compounds 9a-9f claim 1 -----	1-31
X	WO 2014/179335 A1 (SLOAN KETTERING INST CANCER [US]; UNIV ROCKEFELLER [US]; UNIV RUTGERS) 6 November 2014 (2014-11-06) cited in the application claims 1, 33 -----	1-31
X,P	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 page 388, last line; claim 22 page 389, line second; claim 22 -----	1-31
X,P	WO 2017/161349 A1 (IMMUNE SENSOR LLC [US]; UNIV TEXAS [US]) 21 September 2017 (2017-09-21) 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 -----	1-31

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Patent Family Annex

Information on patent family members

International Application No

PCT/IB2017/057588

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 2014189805	A1	27-11-2014	AU 2014268836 A1	24-09-2015
			CA 2904536 A1	27-11-2014
			CL 2015002522 A1	30-12-2016
			CN 105228450 A	06-01-2016
			CR 20150616 A	19-04-2016
			CU 20150158 A7	30-05-2016
			DO P2015000281 A	29-02-2016
			EP 2996473 A1	23-03-2016
			HK 1219024 A1	24-03-2017
			HK 1222512 A1	07-07-2017
			JP 2016520085 A	11-07-2016
			KR 20160009039 A	25-01-2016
			PE 00802016 A1	21-02-2016
			PH 12015502438 A1	28-03-2016
			SG 11201508273R A	30-12-2015
			US 2015056224 A1	26-02-2015
			US 2017333552 A1	23-11-2017
WO 2014189805 A1	27-11-2014			

WO 2014179335	A1	06-11-2014	AU 2014260015 A1	15-10-2015
			CA 2908154 A1	06-11-2014
			CL 2015003088 A1	15-04-2016
			CN 105358158 A	24-02-2016
			CR 20150592 A	04-04-2016
			CU 20150149 A7	29-07-2016
			DO P2015000269 A	29-02-2016
			EA 201592074 A1	29-02-2016
			EP 2991655 A1	09-03-2016
			HK 1221414 A1	02-06-2017
			HK 1221652 A1	09-06-2017
			JP 2016524593 A	18-08-2016
			KR 20160024850 A	07-03-2016
			PE 01672016 A1	21-04-2016
			PH 12015502388 A1	22-02-2016
			SG 10201708821R A	28-12-2017
			SG 11201508165V A	27-11-2015
US 2016068560 A1	10-03-2016			
WO 2014179335 A1	06-11-2014			

WO 2017027646	A1	16-02-2017	AU 2016304899 A1	01-02-2018
			TW 201718619 A	01-06-2017
			US 2017044206 A1	16-02-2017
			WO 2017027645 A1	16-02-2017
			WO 2017027646 A1	16-02-2017

WO 2017161349	A1	21-09-2017	NONE	

Application no:
Demande n°: PCT/IB2017/057588
Anmelde-Nr:

DISCLAIMER

The attached provisional opinion on the patentability of the first invention searched serves only as information.
A reply addressing the points raised in the opinion is **not** required and will **not** be taken into account when issuing the final search report and opinion on patentability.

AVERTISSEMENT

L'avis provisoire ci-joint sur la brevetabilité de la première invention recherchée ne sert qu'à titre d'information.
Une réponse abordant les points soulevés dans l'avis n'est **pas** nécessaire et ne sera **pas** prise en compte lors de l'établissement du rapport final de la recherche et de l'avis sur la brevetabilité.

DISCLAIMER

Die beigefügte vorläufige Stellungnahme zur Patentierbarkeit der ersten geprüften Erfindung dient lediglich zur Information.
Eine Antwort auf die erhobenen Punkte in der Stellungnahme ist **nicht** erforderlich und bleibt bei der Erstellung des endgültigen Recherchenberichts und der Stellungnahme zur Patentierbarkeit **unberücksichtigt**.

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)

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.

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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.