

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/IB2018/056581	International filing date (day/month/year) 29.08.2018	Priority date (day/month/year) 08.09.2017
International Patent Classification (IPC) or both national classification and IPC INV. C07D417/04 C07D417/12 C07D417/14 A01N43/80 A01P3/00		
Applicant PI INDUSTRIES LTD.		

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 Dunet, Guillaume 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>4, 5, 7-16</u>
	No: Claims	<u>1-3, 6, 17, 18</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-18</u>
Industrial applicability (IA)	Yes: Claims	<u>1-18</u>
	No: Claims	

2. Citations and explanations

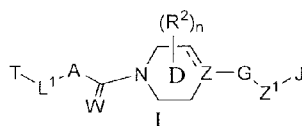
see separate sheet

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

The present application is directed towards fungicidal heterocyclic compounds of formula I



Item V:

Reference is made to the following documents:

- D1 US 6 528 531 B1 (BITFU TESFAYE [US] ET AL) 4 March 2003 (2003-03-04)
- D2 WO 2008/003861 A1 (PASTEUR INSTITUT [FR]; CENTRE NAT RECH SCIENT [FR]; UNIV LILLE 2 UNIVE) 10 January 2008 (2008-01-10)
- D3 EP 2 933 247 A1 (TAKEDA PHARMACEUTICAL [JP]) 21 October 2015 (2015-10-21)
- D4 WANG Y ET AL: "Design and synthesis of ether analogues as potent and selective M² muscarinic receptor antagonists", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 11, no. 7, 9 April 2001 (2001-04-09), pages 891-894, XP004232518, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(01)00100-7
- D5 WO 2009/135581 A2 (MERCK PATENT GMBH [DE]; LERICHE CAROLINE [FR]; CARNIATO DENIS [FR]; RO) 12 November 2009 (2009-11-12)
- D6 JP 2008 179621 A (TAISHO PHARMA CO LTD) 7 August 2008 (2008-08-07)
- D7 US 3 580 912 A (HEIMBERGER WERNER ET AL) 25 May 1971 (1971-05-25)

- D8 EP 1 889 842 A1 (JAPAN TOBACCO INC [JP]) 20 February 2008
(2008-02-20)
- D9 ABDUL WADOOD ET AL: "A Novel Pharmacophore Model to Identify
Leads for Simultaneous Inhibition of Anti-coagulation and Anti-
inflammatory Activities of Snake Venom Phospholipase A2",
CHEMICAL BIOLOGY & DRUG DESIGN.,
vol. 79, no. 4, 30 January 2012 (2012-01-30), pages 431-441,
XP055397997,
GB
ISSN: 1747-0277, DOI: 10.1111/j.1747-0285.2011.01281.x
- D10 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 31 March
2008 (2008-03-31),
retrieved from STN
Database accession no. 1011079-72-3
- D11 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 22 June
2007 (2007-06-22),
retrieved from STN
Database accession no. 938418-21-4
- D12 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 6 August
2012 (2012-08-06),
retrieved from STN
Database accession no. 1386723-21-2
- D13 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 20 June
2007 (2007-06-20),
Database accession no. 938039-83-9

- D14 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1 March
2009 (2009-03-01),
retrieved from STN
Database accession no. 1113102-88-7
- D15 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 26
February 2009 (2009-02-26),
retrieved from STN
Database accession no. 1112438-52-4
- D16 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 19 April
2007 (2007-04-19),
retrieved from STN
Database accession no. 930989-08-5
- D17 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 15
September 2010 (2010-09-15),
retrieved from STN
Database accession no. 1241121-94-7
- D18 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 15
September 2010 (2010-09-15),
retrieved from STN
Database accession no. 1241213-75-1
- D19 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14
September 2010 (2010-09-14),
retrieved from STN
Database accession no. 1240986-09-7

- D20 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 18 July 2016 (2016-07-18),
retrieved from STN
Database accession no. 1954254-17-1
- D21 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 15 July 2016 (2016-07-15),
retrieved from STN
Database accession no. 1952476-33-3
- D22 US 2010/292275 A1 (KAMIREDDY BALREDDY [US] ET AL) 18 November 2010 (2010-11-18) cited in the application
- D23 EP 3 109 248 A1 (BAYER IP GMBH [DE]) 28 December 2016 (2016-12-28)
- D24 US 2011/224258 A1 (PASTERIS ROBERT JAMES [US]) 15 September 2011 (2011-09-15)
- D25 WO 2017/109855 A1 (SDS BIOTECH CORP [JP]) 29 June 2017 (2017-06-29)

1. Novelty

1.1. Compounds falling within the scope of the invention, processes for preparing them and/or composition comprising them are known from D1-D9 (see the passages cited in the SR). Said documents are thus relevant for the novelty of:

- D1: claims 1, 3, 6 and 17;
- D2: claims 1-3, 6 and 17;
- D3: claims 1, 3 and 6;
- D4: claims 1, 6 and 17;
- D5: claims 1, 3 and 6;

- D6: claims 1, 6, 17 and 18;
- D7: claims 1 and 6;
- D8: claims 1, 6 and 17;
- D9: claims 1 and 6.

1.2. Commercial compounds falling within the scope of the invention are also known from D10-D21, which are thus relevant for the novelty of claims 1 (D10-D21) and 3 (D10, D11, and D13-D15)

1.4. Documents D22-D25 disclose compounds that are structurally very close and which are used as fungicidal agent (see the passages cited in the SR); however, none of them discloses a compound falling within the scope of claim 1 (the structural difference essentially lies in the nature of the linker between the piperidine / piperazine ring and moiety "T").

Nonetheless, D2-D24 disclose compounds of formula 4 as defined in claim 18 of the present application (see the passages cited in the SR) and are thus relevant for the novelty of this claim.

1.5. Therefore, only claims 4, 5 and 7-16 seem to be novel (Art. 33(2) PCT)

2. Inventive step

2.1. Any of D22- D25 can be seen as the closest prior art. The compounds of the invention differ from those of the prior art in their structure, in particular in the nature of the linker between the piperidine / piperazine ring and moiety "T". In the absence of any demonstrated advantage / technical effect over the whole scope of protection compared to the compounds disclosed in D22-D25, the problem to be solved can only be seen as the provision of further polycyclic piperidine- / piperazine- based compounds as potential fungicidal agents.

2.2. As mentioned above, compounds that are structurally very close to the compounds of the invention are known for their anti-fungi activity, and the only difference in structure lies in the nature of a linker (e.g. presence of O, S or N instead

of S(O)₂ as in D1). The structural difference is thus so minimal that it is believed that the skilled person looking for alternative compounds would immediately envision using standard bioisosteric linker moieties (like CH₂, NH, O or S as alternative to S(O)₂ or C(O) as disclosed in D1). By doing so, he would arrive at the present compounds without the need of any inventive skill. The compounds of D1 and their use as anti-fungi are thus considered to lack inventiveness (Art. 33(3) PCT).

2.3. The same reasoning applies to the compounds of dependent claims 2-5 and their use against fungi. Said compounds are thus also considered to lack inventiveness (Art. 33(3) PCT)

2.4. Similarly, the process of claim 17 lacks inventiveness in view of the prior art (like D1, D2, D4 or) D6 since the same methodology is used for preparing similar compounds. As corollary, the compounds of claim 18 are also considered to lack inventiveness since no technical effect (e.g. fungicidal activity) is associated to them (Art. 33(3) PCT) and since these compounds are known as intermediates for preparing similar compounds (see D22-D24).

2.5. All in all, none of claims 1-18 is seen as inventive (Art. 33(3) PCT).

Additional note on inventiveness: although the scope claimed encompasses an important number of compound, potentially having significantly different chemical structure, the examples on file are limited to very specific core structures that just cover a tiny portion of the scope claimed. Since it is well established that the anti-fungal activity will greatly depend on the chemical structure of the compounds, it is thus not credible, in view of the evidence on file that all the compounds encompassed in the claims have the desired activity. This is contrary to the requirements of inventiveness.

Item VIII:

3.1. Claim 1: a) Given the structure of the compounds of Formula I, it is not clear how J can be a divalent species (as defined in page 95, lines 5-10). Clarification is needed; b) the use of the term "isomers" is not clear insofar it is so broad that it includes structural isomers, i.e. one does not know which compounds are encompassed or not (Art. 6 PCT).

3.2. Claim 3: No definition is given for groups T1-T47, G1-G63, J1-J82 and Q1-Q99, which renders the exact scope of protection sought unclear (Art. 6 PCT). A possibility to overcome the objection could be to introduce the definition of these groups, e.g. based on pages 16-24 of the description).

3.3. Claim 4: the same remark as for claim 3 applies (Art. 6 PCT).

3.4. Claims 7 and 9: the use of the term "compatible" without a definition of its meaning renders the exact scope of protection sought unclear (what is compatible or not ? Art. 6 PCT).