

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference P398584WO	FOR FURTHER ACTION See item 4 below	
International application No. PCT/EP2024/077837	International filing date (<i>day/month/year</i>) 03 October 2024 (03.10.2024)	Priority date (<i>day/month/year</i>) 04 October 2023 (04.10.2023)
International Patent Classification (IPC) or national classification and IPC See relevant information in Form PCT/ISA/237		
Applicant SYNGENTA CROP PROTECTION AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 8 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	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 Article 35(2) 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
4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

	Date of issuance of this report 07 April 2026 (07.04.2026)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Thomas Rochaix e-mail pct.team5@wipo.int

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/EP2024/077837

International filing date (day/month/year)
03.10.2024

Priority date (day/month/year)
04.10.2023

International Patent Classification (IPC) or both national classification and IPC
INV. A01N63/28 A01P3/00 C12N1/20

Applicant
SYNGENTA CROP PROTECTION AG

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

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Galley, Carl

Telephone No. -0



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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
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>10-14</u>
	No: Claims	<u>1-9, 15</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-15</u>
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

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

Reference is made to the following documents:

- D1 WO 2004/065401 A1 (ECOPIA BIOSCIENCES INC [CA]) 5 August 2004
- D2 Park Heung-Soon ET AL: "Screening and Isolation of a Novel Polyene-Producing Streptomyces Strain Inhibiting Phytopathogenic Fungi in the Soil Environment", *Frontiers in Bioengineering and Biotechnology*, vol. 9, 12 July 2021, XP093132997
- D3 Bobek Jan ET AL: "Polyenic Antibiotics and Other Antifungal Compounds Produced by Hemolytic Streptomyces Species", *International journal of molecular sciences*, vol. 23, no. 23, 30 November 2022, page 15045, XP093133000
- D4 WO 2010/107294 A1 (UNIV PUTRA MALAYSIA [MY]) 23 September 2010
- D5 CN 102 533 600 A (SOUTH CHINA SEA INST OCEANOLOG) 4 July 2012
- D6 CN 1 434 115 A (YUNNAN INST OF MICROBIOLOGY [CN]) 6 August 2003
- D7 SINHA ARKADEEP ET AL: "The complete genomic sequence of Streptomyces spectabilis NRRL-2792 and identification of secondary metabolite biosynthetic gene clusters", *Journal of Industrial Microbiology & Biotechnology*, vol. 46, no. 8, 13 June 2019, pages 1217-1223, XP036864648
- D8 SECO E M ET AL: "Starter Unit Choice Determines the Production of Two Tetraene Macrolides, Rimocidin and CE-108, in Streptomyces diastaticus var. 108", *Chemistry & Biology: Current Biology*, vol. 11, no. 3, 1 March 2004, pages 357-366, XP025940223
- D9 WO 2023/017016 A1 (SYNGENTA CROP PROTECTION AG [CH]) 16 February 2023

- 1 Claim 1 attempts to define a polyene compound only by its general molecular formula ($C_{67}H_{115}NO_{25}$) and by maxima peaks in its UV-Vis light absorption spectrum in aqueous acetonitrile solution. However, said information is considered insufficient to identify which compounds from the vast possibilities having the said molecular formula fall within the claim. Thus, it is considered

- that the compound has been insufficiently identified, causing a severe lack of clarity for the skilled person, who also faces undue burden to reach the polyene compound.
- 2 Even when the compound is further defined in that it is obtainable by cultivating a microorganism, i.e. as a so-called "product by process" as in present claims 2–5, not only does this still not clearly identify the product per se, but also the skilled person faces undue burden determining which microorganisms under which conditions, including media, temperature, etc..., are necessary to reach the compound.
- 3 With respect to the 16S rRNA nucleotide sequence of claim 2, while the 16S rRNA gene is highly conserved and extremely useful in determining the phylogenic relationships of bacteria, and consequentially broad functionalities, given that bacteria from the same species and especially same clade will share many properties, the 16S sequence cannot be considered to be causally linked to the effects exhibited by a specific strain, particularly in the case of a "crowded" genus such as *Streptomyces*, many species of which are well reported to produce antifungal polyenes. Thus, for the skilled person's use of the 16S rRNA sequence to attempt to reproducibly identify microorganisms that produce antifungal polyene compounds with the molecular formula as given in claim 1, chance is required. Relying on chance for reproducibility amounts to undue burden in the absence of evidence that such chance events occur and can be identified frequently enough to guarantee success. Similarly, the application fails to provide evidence that any of the sequences SEQ ID NO: 2–49 has a causal link with the production of an antifungal polyene with molecular formula $C_{67}H_{115}NO_{25}$ with the maxima in the UV-Vis spectrum as required, as far as can be understood. As such, the entire claimed subject-matter is considered to lack clarity and sufficiency within the meaning of Articles 5 and 6 PCT.
- 4 Hence, in the absence of a clear and sufficient identification of the polyene (such as the chemical structure), any polyene produced by a *Streptomyces* species may be identical to the claimed polyene. As a consequence, novelty and inventive step of the claimed subject-matter cannot be fully assessed. As such, the search has focussed on the subject-matter where the polyene is a product from the process of cultivating *Streptomyces* strains, particularly those that have been attempted to be defined by the nucleotide sequences and especially the deposited strain *Streptomyces* sp. Saigon413. The applicant

should be aware that further searches may reveal relevant documents in any future procedure.

- 5 As stated previously, the production of active polyene compounds, including those with antifungal activity, from cultivating *Streptomyces* bacteria is well known in the art.

For example, D1 teaches the cultivation of *Streptomyces aizunensis* strains to produce polyene polyketides that demonstrate antifungal activity against, inter alia, *Candida* and *Aspergillus spp.* (claims and examples; Table 6). D2 discloses the screening of 2400 *Streptomyces* strains and identified 149 strains that produce antifungal compounds (abstract; Figure 2). One strain, *S. rubrisoli* Inha 501 was shown to produce a potent antifungal polyene (I-NTF; Figure 5), active against crop phytopathogens causing Fusarium wilt (Table 1). D3 also teaches that *Streptomyces* strains produce a large number of useful antibacterial and antifungal compounds, and provides in Section 1.2, a review into polyene metabolites (Table 1).

Although D1–D3 are silent on the molecular formulae and the UV-Vis light absorption spectrum of the antifungal polyenes taught therein (in particular the references in Table 1 of D3), the burden lies with the applicant to demonstrate that the claimed polyene, whether in cyclic or acyclic form, is different from those known and in what way. As such, the subject-matter of at least claims 1–5 cannot be considered novel over the disclosures of D1–D3 within the meaning of Article 33(2) PCT.

- 6 D4 discloses a *Streptomyces* strain H7372 that produces an antifungal compound, J5, that is disclosed to inhibit *Aspergillus* and *Candida* molds (claims and examples on page 18). The strain is related to *Streptomyces chrestomyceticus* (see figure 6) and comprises a 16S rRNA sequence with 99.73% identity to present SEQ ID NO:1 (as determined by BLAST analysis). The compound J5 is only further defined by its retention in a chromatogram (Figure 7). However, in the absence of evidence to the contrary, D4 is considered to anticipate the subject-matter of at least claims 1–9 and 15 (Article 33(2) PCT).

- 7 D5 discloses a *Streptomyces* strain SCSIO 01689 with deposit number CCTCC M 2011257 that comprises a 16S rRNA sequence also with 99.73% identity to present SEQ ID NO:1 (as determined by BLAST analysis). D5 fails to disclose the production of a polyene, let alone a fungicidal polyene.
- 8 D6 discloses a *Streptomyces albogriseus* *sp. nov.* strain that comprises a 16S nucleotide sequence with 99.46% identity with present SEQ ID NO:1 (as determined by BLAST analysis). D6 teaches that the fermentation broth of the strain has high antifungal activity against powdery mildew (abstract). D6 fails to disclose the production of a polyene.
- 9 D7 discloses the entire genome of a *Streptomyces spectabilis* strain NRRL 2792, that is known to produce antifungal metabolites, and comprises in its genome a nucleotide sequence with 87.93% identity with present SEQ ID NO: 22 (as determined by BLAST analysis). D8 discloses a *Streptomyces diastaticus* var.108 strain that produces the antifungal polyenes (tetraenes) Rimocidin and CE-108, the strain comprising in its genome a nucleotide sequence with 88.64% identity with present SEQ ID NO:23 (as determined by BLAST analysis). D8 also concludes that the production of the polyenes may be manipulated by using different starter units in the fermentation broth; i.e. making the production of new polyenes possible (paragraph bridging pages 364 and 365). Thus, not only is it clear that the production of particular polyenes is dependent on the composition of the fermentation broth, but also, in the absence of evidence to the contrary, D7 and D8 are considered to anticipate the subject-matter of claim 1–9 and 15, as far as can be understood (Article 33(2) PCT).
- 10 The *Streptomyces* strain Saigon413 was deposited on 09-09-2022 according to the Budapest Treaty and the requirements of Rule 13bis PCT and consequentially Article 5 PCT appear to be met with regard to the deposit (see deposit receipt). Said strain appears to be novel within the meaning of Article 33(2) PCT. Nevertheless, with respect to a polyene obtainable from this particular strain, not only is it not clear if it is distinguishable from the many known polyenes produced by other *Streptomyces* strains, but also, given the teaching in D8 that the composition of the fermentation broth affects the

production of polyenes (paragraph bridging pages 364 and 365), it is not clear how the objection with respect to sufficiency of disclosure may be overcome.

- 11 Furthermore, if the production of a specific antifungal polyene is considered to be surprising, it is highly unlikely that any *Streptomyces chrestomyceticus* strain would produce said polyene. As a single mutation may remove the ability of a microorganism to produce certain metabolites, it is highly unlikely that microorganisms with at least 90% identity to the genome of the deposited strain would routinely produce the claimed polyene. Table 2 is not considered sufficient evidence, given the vast number of possible strains encompassed by such definitions. As such, the entire claimed compositions and processes are considered to lack inventive step (Article 33(3) PCT) and sufficiency (Article 5 PCT), respectively.
- 12 Notwithstanding the above argumentation, given that the screening of *Streptomyces* strains for their production of antifungal metabolites, including polyenes appears to be routine in the art. In addition, the use of *Streptomyces* bacteria, their culture broth and the polyenes per se in controlling phytopathogens appears known, for example, from D2, D3 and D9. As such, in the absence of any surprising and/or unexpected effect for the claimed polyene or the strain over other known metabolites and strains, the entire claimed subject-matter appears to lack inventive step within the meaning of Article 33(3) PCT.
- 13 With regard to combinations of the claimed polyene with other actives, such as cyclothiazomycin C, strepimidone and/or malonomycin (see D9: claims), in the absence of any surprising effect, the combination is merely regarded as a juxtaposition of known measures and thus considered obvious for the skilled person (Article 33(3) PCT).
- 14 The industrial applicability of the claimed invention is evident from the application (Article 33(4) PCT).