PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: MICHAEL ASAM
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	14 APR 2014
Applicant's or agent's file reference 68011-WO-PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2013/074522	12 December 2013	13 December 2012

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C07D 213/803 (2014.01)
USPC - 546/327

Applicant DOW AGROSCIENCES LLC

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 or 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 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 66.1*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/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	24 March 2014	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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Box No. I Basis of this 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 filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

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 in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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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)	Claims	1, 2	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1, 2	NO
Industrial applicability (IA)	Claims	1, 2	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1 and 2 lack an inventive step under PCT Article 33(3) as being obvious over Balko et al. (hereafter Balko) in view of Heinzman et al. (hereafter Heinzman).

Regarding claim 1, Balko discloses a process for the isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl) pyridine-2-carboxylic acid (Col. 39, Lns. 1-3, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (compound 100)) which comprises: (a) neutralizing an aqueous solution of an alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid with hydrochloric acid at a temperature from about 45 to about 90 °C to produce an aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (Col. 38, Lns. 48-52, A solution of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-(2,2-difluroethoxy)phenyl)pyridine-2-carboxylic acid methyl ester (0.300 g, 0.0008 mol) in methanol (5 mL) and sodium hydroxide (1N, 2 mL) was heated to reflux 1 hour and then acidified to pH 3 (concentrated hydrochloric acid); Col. 38, Lns. 57-58, The following compounds were prepared according to the procedure of Example 61 and Col. 39, Lns. 1-3); (b) cooling the aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid to about 10 to about 25 °C to crystallize the 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (Col. 38, Ln. 53, ... allowed to cool), and (c) collecting the crystalline 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylic acid (Col. 38, Lns. 53-54, ... resulting solid was collected and dried). Balko fails to explicitly disclose neutralizing with an excess of 85 - 99 percent formic acid. However, Heinzman is in the field of synthesis of acids from carboxylic acid esters (Heinzman Title, Synthesis of amido acids from carboxylic acid esters and amino acid salts) and teaches neutralizing with an excess of 85 - 99 percent formic acid (Heinzman Pg. 17, Para. 2, Step C. Neutralization of amido acid sodium salt - Formic acid 96% (50.35 g, 1.05 mol) is added ...; Heinzman Pg. 10, Para. 4, Typically a molar ratio of acid to amido acid salt of about 1.1 is used). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Blako to replace hydrochloric acid with 96% formic acid, as taught by Heinzman. The motivation would be to take advantage of solubility of formates and ease of removal of formic acid (Heinzman Pg. 10, Para. 4).

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Regarding claim 2, Balko discloses a process for the preparation and isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl) pyridine-2-carboxylic acid (Col. 39, Lns. 1-3, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (compound 100)) which comprises: (a) contacting an ester of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid of Formula I, as shown, in which R1 represents H, and R2 represents C1 alkyl (Col. 34, Lns. 55-57, 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid methyl ester (Compound 42); Col. 38, Lns. 48-52, A solution of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-(2,2-difluroethoxy)phenyl)pyridine-2-carboxylic acid methyl ester ...; Col. 38, Lns. 57-58, The following compounds were prepared according to the procedure of Example 61 and Col. 39, Lns. 1-3) with an aqueous solution of an alkali metal or alkaline earth metal hydroxide (Col. 38, Ln. 51, ... sodium hydroxide (1N, 2 mL) ...) in a C1-C4 alcohol at a temperature from about 45 to about 100 °C (Col. 38, Lns. 50-52, ... in methanol ... was heated to reflux ...) to produce an aqueous alcoholic solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, (b) optionally removing most of the C1-C4 alcohol from the aqueous alcoholic solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, (c) neutralizing the aqueous solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid with hydrochloric acid at a temperature from about 45 to about 90 °C to produce an aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl) pyridine-2-carboxylic acid (Col. 38, Lns. 48-52, A solution of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-(2,2-difluroethoxy)phenyl) pyridine-2-carboxylic acid methyl ester (0.300 g, 0.0008 mol) in methanol (5 mL) and sodium hydroxide (1N, 2 mL) was heated to reflux 1 hour and then acidified to pH 3 (concentrated hydrochloric acid)), (d) cooling the aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid to about 10 to about 25 °C to crystallize the 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (Col. 38, Ln. 53, ... allowed to cool), and (e) collecting the crystalline 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid (Col. 38, Lns. 53-54, ... resulting solid was collected and dried). Balko fails to explicitly disclose neutralizing with an excess of 85 - 99 percent formic acid. However, Heinzman is in the field of synthesis of acids from carboxylic acid esters (Heinzman Title, Synthesis of amido acids from carboxylic acid esters and amino acid salts) and teaches neutralizing with an excess of 85 - 99 percent formic acid (Heinzman Pg. 17, Para. 2, Step C. Neutralization of amido acid sodium salt - Formic acid 96% (50.35 g, 1.05 mol) is added ...; Heinzman Pg. 10, Para. 4, Typically a molar ratio of acid to amido acid salt of about 1.1 is used). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Blako to replace hydrochloric acid with 96% formic acid, as taught by Heinzman. The motivation would be to take advantage of solubility of formates and ease of removal of formic acid (Heinzman Pg. 10, Para. 4).

Claims 1 and 2 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.