PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	31-12-2018
Applicant's or agent's file reference PCT0055	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN2018/050675	18-10-2018	30-08-2018

International Patent Classification (IPC) or both national classification and IPC
C07D235/06,C07D417/04 Version=2018.01

Applicant
HIKAL LIMITED

1. This opinion contains indications relating to the following items:

- [x] 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
- [x] Box No. IV Lack of unity of invention
- [x] 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
- [x] 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/	Date of completion of this opinion	Authorized officer
Indian Patent Office Plot No. 32, Sector 14, Dwarka,New Delhi-110075 Facsimile No.	31-12-2018	Vishakha Gupta Telephone No. +91-1125300200

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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:

   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:

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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:

This International Searching Authority found multiple inventions in this international application, as follows:
Group I: Claims 1-4 (fully); Claims 5-8 (partially)

These claims relate to an improved process for the preparation of thiabendazole.

Group II: Claim 9 (fully); Claims 5-8 (partially)

These claims relate to a process for the purification of thiabendazole.

These groups of inventions are not so linked as to form a single general inventive concept as required under Rule 13.1 of PCT for the following reasons:

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

   ☒ all parts.

   ☐ the parts relating to claims Nos. _____

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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**

1. Statement

Novelty (N)	Claims	2-9	YES
	Claims	1	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	NONE	NO

2. Citations and explanations:

Reference is made to the following documents:

D1 PATIL, V., BARRAGAN, E., PATIL, S. A., PATIL, S. A., & BUGARIN, A., "A PRACTICAL METHOD, NAOCL-MEDIATED, TO PREPARE THIABENDAZOLES VIA INTRAMOLECULAR AMINATION REACTION", TETRAHEDRON LETTERS, 2017, 58(35), 3474-3477.

D2 ELLSWORTH, R. L., MERTEL, H. E., & VANDENHEUVEL, W. J., "SYNTHESIS AND MASS SPECTROMETRY OF ISOTOPICALLY LABELED ISOPROPYL 2-(4-THIAZOLYL)-5-BENZIMIDAZOLECARBAMATE (CAMBENDAZOLE).", JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, 1976, 24(3), 544-549.

D3 GRENDA, V. J., JONES, R. E., GAL, G., & SLETZINGER, M., "NOVEL PREPARATION OF BENZIMIDAZOLES FROM N-ARYLAMIDINES. NEW SYNTHESIS OF THIABENDAZOLE.", THE JOURNAL OF ORGANIC CHEMISTRY, 1965, 30(1), 259-261.

D4 US 3299081 A (MERCK AND CO INC) 17 JANUARY 1967 (17.01.1967)

D5 CA 744727 A (MERCK AND CO INC) 18 OCTOBER 1966 (18.10.1966)

The present application is directed to a process for the synthesis of thiabendazole of formula I and its purification. The synthetic route comprises (a) reacting 4-cyanothiazole with aniline in the presence of HCl (g), o-dichlorobenzene at atmospheric pressure and at a reaction temperature around 135-150 degrees Celsius, (b) converting the obtained amidine hydrochloride in step (a) to crude thiabendazole via treatment with NaOCl (1.07-1.17 eq) and Na2CO3 and (c) purifying the crude thiabendazole to obtain the pure compound. The purification process involves the following steps in sequence i.e. treatment of crude thiabendazole with conc. HCl,

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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:

1. Claims 5-8 define a product in terms of its production process. A claim defining a product in terms of a production process must be construed as a claim directed to the product per se (PCT/GL/ISPE/7, Part II, 5.26). Claims for products defined in terms of a process of production are allowable only if the product as such fulfills the requirements for patentability, i.e. they are novel and inventive. A product is not novel simply because it was produced using a novel production process.

2. The use of expression 'not more than' in claims 3-8 renders the subject matter of claims unclear since it introduces an ambiguity into these claims. Therefore, claims 3-8 do not fulfil the requirements of Article 6 PCT.

3. Claims 7-8 lack antecedent basis as the process claimed in independent claim 1 does not specify the reaction parameters such as solvents eg. methanol, benzene or the use of reagents containing selenium or molybdenum. So, the relevance and intended limitations posed by these claims are not clear. Thus, claims 7-8 do not meet the requirements of PCT Article 6 and Rule 6.4.

4. The claimed range of sodium hypochlorite in claim 1 is inconsistent with that used in example 2 of the specification. Example 2 uses a total of 1.01 eq of NaOCl (0.91+0.1 eq) whereas the claimed range is in between 1.07-1.17 eq. Thus, there is lack of clarity and support in the sense of Article 5 and 6 of PCT.

Supplemental Box

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

Continuation of Not Complied(Box4)

The special technical feature is an essential feature common to all embodiments of the claimed invention (and responsible for the inventive effect) and which defines a contribution with each of the claimed inventions over prior art (Rule 13.2 of PCT). Upon prior art search, it was found that thiabendazole of formula I is already known in the prior art. The only linking feature between these groups of inventions is the compound thiabendazole which is already known. Hence, here it is considered that the common technical link in the above mentioned groups is not novel. Therefore, the above mentioned groups lack a common feature which could be regarded as the 'special technical feature' providing unity to the claims. Consequently, the application may be objected for lacking unity a posteriori.

Continuation of Citation and Explanation(Box5)
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charcoalizing, filtering the solid, dispersing in water, treating with aqueous ammonia and filtering pure thiabendazole.

D1 discloses preparation of thiabendazole starting from 4-cyanothiazole and aniline. The process involves reacting 4-cyanothiazole and aniline in o-dichlorobenzene at 135 degrees Celsius with purging excess dry HCl. The product of this step i.e. amidine hydrochloride adduct (31 mmol) was subjected to treatment with NaOCl (31 mmol) and sodium carbonate to provide crude thiabendazole which was further purified (See table 1, 4a; pg. 3477, point 17).

D2 teaches hydrogen chloride catalysed reaction of aniline and 4-cyanothiazole to provide amidine which upon treatment with sodium hypochlorite followed by basification resulted in thiabendazole (See fig.1; pg. 545, lest column, second para).

D3 provides ring closure reaction of amidine hydrochloride (Ia) with 1 mole of sodium hypochlorite and 1 eqiv. of base to give substituted benzimidazole (or thiabendazole) in 98% yield (See pg. 259, left column last para to right column first para; pg. 260, Conversion of the N-Chloro Intermediate IIa to IIIa).

D4 discloses preparation of amidine hydrochloride via reaction of aniline and 4-cyanohiazole in o-dichlorobenzene and hydrogen chloride(g) at 140 degrees Celsius (See example 1,4).

D5 teaches preparation of 2-(4-thiazolyl)-5-methoxybenzimidazole

(or 5-methoxy thiabendazole) from amidine hydrochloride followed by its purification. The process comprises (a) adding conc. HCl, (b) filtering the solid, (c) dispersing in HCl, (d) treating with decolorizing charcoal, (e) adjusting pH with NaOH and (f) recovering the pure product by filtration (See example 15).

2.1 NOVELTY (Article 33(2) of PCT)

2.1.1 Claim 1 of the present application does not meet the requirements of Article 33(2) of PCT for the following reasons:
D1 discloses an identical process for preparing thiabendazole which consists of all the steps (a) to (c) as claimed in instant application in the same sequence. D1 teaches synthesis of amidine hydrochloride as obtained in present step (a) via reaction of 4-cyanothiazole (formula II) with aniline (formula III) in HCl(g) at atmospheric pressure. The reaction temperature (135C) employed in D1 also falls within the range of present claims. Further, the amount of NaOCl required for conversion of amidine hydrochloride to thiabendazole is also same in both the documents (31:31 or 1:1 mole ratio of amidine and NaOCl in D1). The crude compound was finally purified via column chromatography. Thus, present claim 1 is anticipated by D1.

2.1.2 Claims 2-8 are novel over D1-D4 as none of the documents identify the impurities 4-chloro thiabendazole and/or 5-chloro thiabendazole existing in crude thiabendazole.

Further, the purification process as claimed in claim 9 differs from the process of D5 in that D5 does not disclose the use of aqueous ammonia for neutralizing the pH of solution. Rather, D5 employs sodium hydroxide for this purpose.
Therefore, claims 2-9 meet the requirements of PCT Article 33(2).

2.2 INVENTIVE STEP (Article 33(3) of PCT)

2.2.1 Since the subject matter of claim 1 is not novel, inventive step cannot be acknowledged for this claim.

2.2.2 Claims 2-8 do not involve an inventive step over D1 or D2-D4 and common general knowledge.

D1 may be regarded as the closest state of the art pertaining to subject matter of these claims. Starting from D1, the problem to be solved by the present application may be seen in the provision of a further process for the synthesis of thiabendazole in high yield and which involves fewer impurities. However, D1 discloses a similar process which is carried out at atmospheric pressure and

which involves the same reaction parameters (temperature, pressure, solvent) and reagents as employed in instant case (pg. 3477, point 17 of D1). Similarly, D2 discloses the entire claimed process with reference to D3 for the transformation of amidine hydrochloride to thiabendazole. Further, D4 discloses synthesis of amidine hydrochloride which in combination with D3 yields the claimed process. It is to be noted that all of these documents D1-D4 comment upon the importance of using optimum amounts of NaOCl (about 1 equivalent) during step (b) so as to achieve highly pure compounds (eg. 98% in D3; 96% in D4). Thus, the proposed technical problem appears to have been solved in prior arts.

The present application differs in that none of the documents D1-D4 identify the compounds (V) and (VI) or solvents which lead to the impurity. However, identification of the chemical structure of the impurities can be carried out by any person skilled in the art who is well aware of the routine characterization techniques such as IR, NMR etc. Thus, a mere detection of compounds (V) and (VI) may not be regarded as a distinguishing feature leading to any technical advancement to the already known process. Consequently, claims 2-8 are obvious over D1 or D2-D4 in combination with general art.

Regarding claim 9, D5 appears to be the closest prior art. D5 discloses all the steps as claimed in present claim, the difference being that it teaches purification of 5-methoxy thiabendazole. Further, D5 differs in that it teaches a different base i.e. NaOH for neutralizing the solution (corresponding to step (V) of claim 9). However, it is obvious for any person skilled in the art to assume that a known process for the purification of a derivative of thiabendazole could be used to purify thiabendazole as well. Additionally, the purpose of aqueous ammonia in instant step (V) is the same as that of NaOH in D5 i.e. to adjust the pH of the reaction mass. So, any person skilled in the art will be prompted to try another base for this purpose so as to arrive at a novel process without any inventive ingenuity. Consequently, the process as claimed in claim 9 is obvious over D5 and common general knowledge.

2.3 INDUSTRIAL APPLICABILITY (Article 33(4) of PCT)

The subject-matter of Claims 1-9 is considered to be industrially applicable and thus fulfils the requirements of Article 33(4) PCT.