



- (51) International Patent Classification:
C07D 235/06 (2006.01) C07D 417/04 (2006.01)
- (21) International Application Number:
PCT/IN2018/050675
- (22) International Filing Date:
18 October 2018 (18.10.2018)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
201821032495 30 August 2018 (30.08.2018) IN
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF THIABENDAZOLE

(57) Abstract: The present invention relates to an improved process for preparing thiabendazole of formula (I) with high yield, high purity, in economical and commercially viable manner for agricultural and pharmaceutical use.

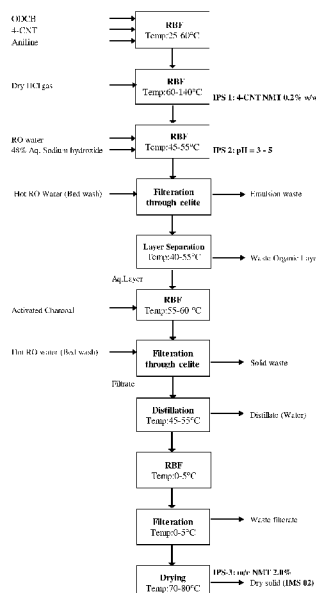
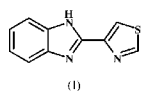


Figure 1



MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *of inventorship (Rule 4.17(iv))*

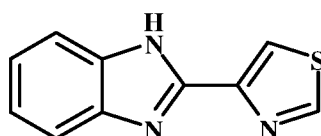
Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *upon request of the applicant, before the expiration of the time limit referred to in Article 21(2)(a)*
- *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

AN IMPROVED PROCESS FOR THE PREPARATION OF THIABENDAZOLE

FIELD OF INVENTION

The present invention relates to an improved process for preparing thiabendazole of formula (I) with high yield, high purity, in an economical and commercially viable manner for agricultural and pharmaceutical use.



(I)

BACKGROUND OF INVENTION

Thiabendazole, 2-(4'-thiazolyl)-benzimidazole (TBZ) (I) is an important anthelmintic and fungicidal agent widely used in pharmaceutical, agriculture and food industry. Owing to the commercial importance of thiabendazole, the various synthetic routes are disclosed in the literature for preparing this pharmacologically and fungicidally active compound.

The various literature discloses the synthesis of thiabendazole by using aniline, 4-cyanothiazole and hydrogen chloride in polychlorobenzene such as dichloro- or a trichlorobenzene solvent under high pressure reaction conditions to obtain N-phenyl-(thiazole-4-amidine)-hydrochloride (amidine hydrochloride). This amidine hydrochloride is then treated with hypohalites such as sodium or potassium hypochlorite, sodium hypobromite and calcium hypochlorite in presence of base such as alkali or alkaline earth metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide; or an alkali metal carbonate or bicarbonate such sodium carbonate, sodium bicarbonate to obtain thiabendazole.

The US patent no. US 3,274,208 discloses the process for preparation of amidine hydrochloride by reacting 4-cyanothiazole and aniline in presence of aluminum chloride at 180 °C. The amidine hydrochloride is purified by acid base treatment.

The US patent no. US 3,299,081 (henceforth patent '081) discloses the process for preparation of N-phenyl-(thiazole-4-amidine)-hydrochloride (amidine hydrochloride) and thiabendazole by heating together 4-cyanothiazole and aniline hydrochloride and purging of excess dry hydrogen chloride gas under pressure (15 psig) reaction condition in a 1,2-dichlorobenzene solvent at 135 to 140 °C using closed reactor. The amidine hydrochloride is isolated by filtration and it is then cyclized to N-chloro-N'-phenyl-(thiazole-4-amidine) intermediate by reaction with sodium hypochlorite in water-methanol solvent, further the intermediate is then converted to thiabendazole by treatment with potassium hydroxide in ethanol. The preferred embodiment of the said patent discloses the use of excess hydrogen chloride in a polychlorobenzene medium to achieve higher yields of amidine hydrochloride. The reaction with gas under pressure is exothermic, so the reaction is unsafe.

As per the background of the patent '081, the prior art processes were disclosed that the N-aryl amidines could be prepared by reacting together a nitrile and an aromatic amine in the presence of a metal catalyst such as aluminum chloride or zinc chloride. The process involved the use of a metallic halide as an additional substance in the reaction mixture with the result that metal complexes are obtained which have to be decomposed and the metal removed before pure amidine compounds can be recovered. It was also known to prepare N-aryl amidines by reacting the nitrile and the aromatic amine hydrochloride in a solvent such as ether in the absence of metallic halide. The process referred to affords only poor yields of the desired amidine. Hence, neither of these methods are entirely satisfactory.

The US patent no. US 3,299,082 discloses the process for preparation of N-phenyl-(thiazole-4-amidine)-hydrochloride (amidine hydrochloride) by reacting aniline and 4-cyanothiazole in the presence of a Friedel Crafts type catalyst such as aluminum chloride at temperature 180 °C. The amidine hydrochloride is reacted with hydroxylamine hydrochloride, in presence of base such as sodium bicarbonate and water as solvent to obtain N-phenyl-(thiazole-4-hydroxyamidine) which is then treated with alkyl or aryl sulfonyl halide such methane sulfonyl chloride in the presence of a base such as pyridine to obtain thiabendazole.

The US patent no. US 3,325,506 discloses the process for preparation of thiabendazole by reacting amidine hydrochloride with hypohalites such as sodium or potassium hypochlorite, sodium hypobromite and calcium hypochlorite in presence of base such as alkali or alkaline earth metal hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide; or an alkali metal carbonate or bicarbonate such sodium carbonate, sodium bicarbonate in water or mixtures of water and organic solvents to obtain thiabendazole.

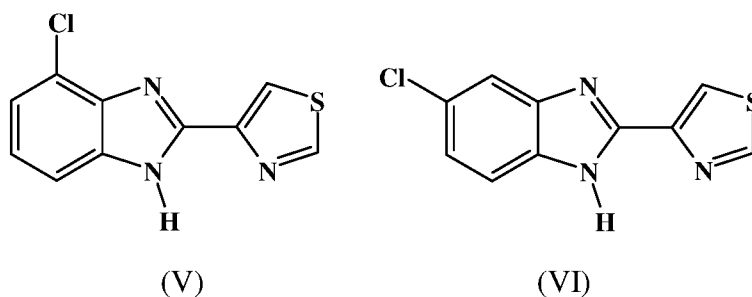
The significance of by-products from reactions in process development work arises from the need to control or eliminate their formation which might affect product cost, process safety, product purity and environmental health. Very few reactions go to 100% completion in the desired sense. Even when conversion is 100% selectivity is not 100%. Most reactions are accompanied by by-products which arise as a direct consequence of a primary synthetic step including work-up and isolation and as a result of various types of side reactions. By-products from the latter type also include tars, polymeric materials, and coloring matters. The level of some by-products from side reactions depends frequently on the batch size.

In the pharmaceutical industry, an impurity is considered as any other inorganic or organic material, or residual solvents other than the drug substances, or ingredients, arise out of synthesis or unwanted chemicals that remains with APIs. Organic impurities are those substances which are formed in the drug substance during the process of synthesis of drug product or even formed during the storage of drug product. This type of impurity includes intermediate, starting material, degradation product, reagents, ligands, catalyst and by product. Inorganic impurities present mainly include heavy metals, residual solvents, inorganic salts, filter aids, charcoal, reagent, ligands and catalyst.

Impurity profiling includes identification, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations. Impurity profiling has gained importance in modern pharmaceutical analysis since an unidentified, potentially toxic impurities are hazardous to health and the presence of unwanted impurities may influence bioavailability, safety and efficacy of APIs. Now days, not only purity profile but also impurity profile has become mandatory according to various

regulatory authorities. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products, and residual solvents.

The prior art processes for preparing thiabendazole suffer from inherent drawbacks and inconveniences, such as low yields, additional reaction steps, high-pressure and unsafe reaction conditions. Moreover, the prior art processes for preparation of thiabendazole are end up with surplus level of potential impurities such as 4-chloro thiabendazole (V) or 5-chloro thiabendazole (VI). Also, the prior processes are silent about these impurities. Since, the strict regulations of the regulatory authorities pertaining to the presence of impurities in the active ingredient, it is highly essential to align the research inline with the guidelines of the regulatory authorities in accordance to appropriate regulations and limits to register and commercialize the product in respective countries.



Hence, with objective of developing the short process, more direct and less expensive methods, significant improvement in the art for preparation of thiabendazole with controlled level of 4-chloro thiabendazole or 5-chloro thiabendazole impurities, residual solvents (methanol, benzene) and heavy metals (selenium, cobalt, molybdenum), the inventors of the instant invention are motivated to pursue the research to synthesize thiabendazole in under atmospheric conditions with high yield and high chemical purity for agricultural and pharmaceutical use.

Therefore, a person skilled in the art will never be motivated to arrive at the claimed process even in view of the combined teachings of the aforesaid prior arts. In addition, the instant invention submits that a person skilled in the art will never be able to achieve the objectives of the claimed invention even after combining the teachings of the prior art documents, as none of them provides remedies to the deficiencies of the other.

Further, the instant invention provides a simple, an economical and commercially viable process for preparation of thiabendazole.

OBJECTIVES OF THE INVENTION

The main object of the present invention is to provide an improved process for the preparation of thiabendazole of formula (I), which is simple, economical, user- friendly and commercially viable.

Another objective of the present invention is to provide a process for the preparation of thiabendazole of formula (I), at atmospheric pressure condition with controlled impurity profile, which would be easy to implement on commercial scale.

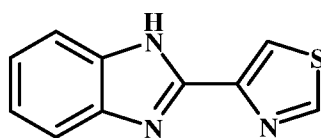
Yet another objective of the present invention is to provide a process for the preparation of thiabendazole of formula (I), with controlled level of residual solvents and heavy metals.

Yet another objective of the present invention is to provide a process for the preparation of a compound of formula (I) with a high yield and high chemical purity.

Yet another objective of the present invention is to provide a process for the preparation of a compound of formula (I) in which the solvents and reagents are recycled and reused for successive synthesis process.

SUMMARY OF THE INVENTION

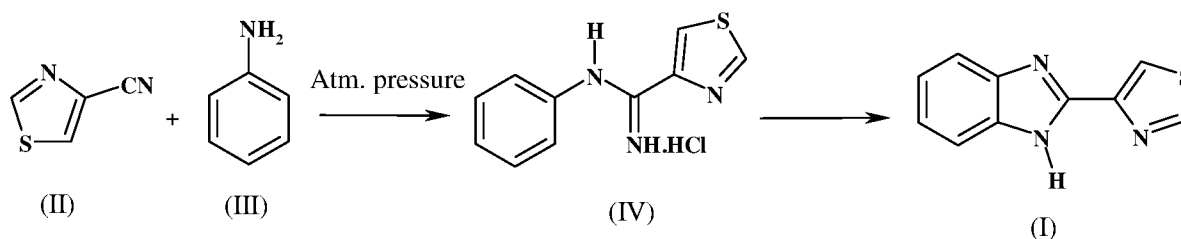
Accordingly, the present invention provides an improved process for the preparation of thiabendazole of formula (I), which comprises the steps of:



(I)

- (a) reacting 4-cyanothiazole of formula (II) with aniline of formula (III) in presence of hydrogen chloride gas and o-dichlorobenzene at atmospheric pressure, at a temperature between 135 to 150°C to obtain amidine hydrochloride of formula (IV);
- (b) treating amidine hydrochloride of formula (IV) with 1.07 to 1.17 equivalents of sodium hypochlorite in presence of sodium carbonate, to control an amount of 4-chloro thiabendazole and/or 5-chloro thiabendazole impurities, to obtain crude thiabendazole of formula (I); and
- (c) purification of crude thiabendazole to pure thiabendazole of formula (I).

The above process is illustrated in the following general synthetic scheme:



BRIEF DESCRIPTION OF DRAWINGS:

Figure 1. Illustrates the process flow diagram for preparation of amidine hydrochloride (IV)

Figure 2. Illustrates the process flow diagram for preparation of crude thiabendazole (I)

Figure 3. Illustrates the process flow diagram for purification of thiabendazole (I)

DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter. Indeed, the invention may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. As used in the specification, and in the appended claims, the singular forms “a”, “an”, “the”, include plural referents unless the context clearly dictates otherwise.

In accordance with the objectives wherein the present invention provides an improved process for the preparations of thiabendazole (I) by (a) reacting 4-cyanothiazole of formula

(II) with aniline of formula (III) in presence of hydrogen chloride and o-dichlorobenzene at atmospheric pressure, at a temperature between 135 to 150°C to obtain amidine hydrochloride of formula (IV); (b) treating amidine hydrochloride of formula (IV) with 1.07 to 1.17 equivalents sodium hypochlorite in presence of sodium carbonate, to control an amount of 4-chloro thiabendazole and/or 5-chloro thiabendazole impurities, to obtain crude thiabendazole of formula (I); and (c) purification of crude thiabendazole to pure thiabendazole of formula (I).

The process for the preparations of thiabendazole (I) is illustrated by following figures:

Figure 1. Illustrates the process flow diagram for preparation of amidine hydrochloride (IV)

Figure 2. Illustrates the process flow diagram for preparation of crude thiabendazole (I)

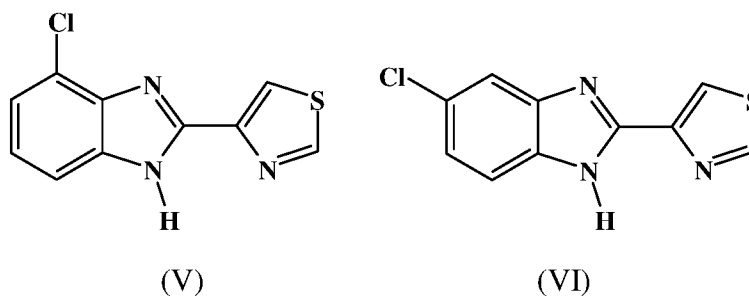
Figure 3. Illustrates the process flow diagram for purification of thiabendazole (I)

In the step (a), the pH of the solution is adjusted between pH 3 to 5, before separation of o-dichlorobenzene, to avoid carry of unreacted aniline into the amidine hydrochloride product. The adjustment of pH before separation of o-dichlorobenzene in the formation of amidine hydrochloride is essential as the unreacted aniline may come with product as an aniline hydrochloride.

The instant invention for preparation of thiabendazole is involving the important aspect to control the level of impurities, residual solvents, heavy metals and purification of thiabendazole. Residual solvents are the solvents that may be organic or inorganic liquids used during the process of manufacturing of pharmaceutically active ingredient. The metals, such as selenium, cobalt, molybdenum, nickel, etc. may be used or introduced during manufacturing, so it is important to control such metals in the final product as impurities.

In another embodiment of the present invention wherein the 1.07 to 1.17 equivalents of sodium hypochlorite are used in step (b) to control an amount of impurities 4-chloro thiabendazole (V) or 5-chloro thiabendazole (VI). The individual level of 4-chloro thiabendazole (V) or 5-chloro thiabendazole (VI) impurities are preferably not more than 0.80% w/w, more preferably not more than 0.50% w/w, analyzed by HPLC. The 1.07 to 1.17

equivalents of sodium hypochlorite are used in instant invention as the excess quantity of sodium hypochlorite in the reaction mass is utilized for the aromatic ring chlorination of thiabendazole at position 4 and 5, thus the 4-chloro thiabendazole (V) or 5-chloro thiabendazole (VI) impurities are formed in high level.



Further, the high flow rate of sodium hypochlorite results in formation of higher impurity profile. The temperature of also plays a crucial role in impurity formation. The temperature must be maintained to prevent reaction of sodium hypochlorite with N-chloro amidine, prematurely creating thiabendazole, which further reacts with sodium hypochlorite to form 4-chloro thiabendazole and 5-chloro thiabendazole impurities. The low temperature may also result in unreacted amidine which leaves excess of hypochlorite to react with thiabendazole and form 4-chloro thiabendazole and 5-chloro thiabendazole impurity.

The structural details of the 4-chloro thiabendazole (V) and 5-chloro thiabendazole (VI) impurities are as follow.

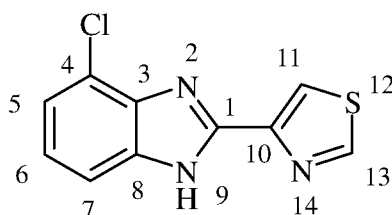
1. 4-Chloro thiabendazole:

(a) **FT-IR study:** The FT-IR spectrum was recorded in the KBr pellet using ABB FTLA-2000 FT-IR Spectrometer. The IR data is tabulated below.

Frequency (cm ⁻¹)	Assignment (s)
1576.37	C=C stretching
1309.16	C-N stretching
3073.38	N-H stretching

(b) NMR spectral data:

NMR experiment was carried out on 400 MHz Bruker spectrometer using DMSO as solvent. The chemical shifts are reported on the δ scale in ppm relative DMSO at 2.5 ppm. The ^1H spectra displayed in respectively. The NMR assignment of 4-chloro thiabendazole is shown below.

**Proton assignments of 4-Chloro thiabendazole:**

Sr. No	No. of Proton	Chemical shift value in ppm	Multiplicity	^1H Position on Carbon
1	3	7.18-7.22, 7.26-7.28, 7.47-7.49	t, d, d	C6, C7, C5
2	3	8.56-8.57, 9.345-9.349, 13.33	d, d, s	C11, C13, 9NH

s-singlet, *d*-doublet, *t*-triplet, *q*-quartet, *dd*-doublet of doublet, *br*-broad, *m*-multiplet.

2. 5-Chloro thiabendazole:**(a) FT-IR study:**

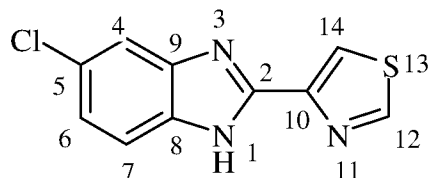
The FT-IR spectrum was recorded in the KBr pellet using ABB FT/LA- 2000 FT-IR Spectrometer. The IR data is tabulated below.

Frequency (cm^{-1})	Assignment (s)
1620.6, 1390.7	C=C Aromatic stretching
2949.5-2857.9	C-H Aromatic stretching
3103	N-H stretching

(b) NMR spectral data:

NMR experiment was carried out on 400 MHz Bruker spectrometer using DMSO- d_6 as solvent. The chemical shifts are reported on the δ scale in ppm relative DMSO- d_6 at 2.50

ppm. The ^1H spectra displayed in respectively. The NMR assignment of 5-chloro thiabendazole is shown below.



Proton assignments 5-Chloro thiabendazole:

Sr. No.	No. of Proton	Chemical shift value in ppm	Multiplicity	^1H Position on Carbon
1	1	7.21-7.24	dd	C6
2	2	7.57	br s	C7 & C4
3	2	8.48-8.49 & 9.341-9.345	d, d	C14 & C12
4	1	12.55	br s	-NH

s-singlet, d-doublet, q-quartet m-multiplet, br-broad.

In another embodiment of the present invention wherein in the step (b), the amidine hydrochloride of formula (IV) is treated with first lot of 1.07 to 1.17 equivalents of sodium hypochlorite at temperature 10 to 15 °C in presence of sodium carbonate and second lot of sodium hypochlorite at temperature 60 to 65 °C to control level of impurities 4-chloro thiabendazole or 5-chloro thiabendazole. The N-chlorination is highly selective at the aforesaid temperature, however, during the second lot of sodium hypochlorite addition, if temperature of the reaction mass is higher than the defined temperature, the selectivity decreases due to the formation of 4-chloro thiabendazole and 5-chloro thiabendazole.

Solvents play a crucial role in chemical and pharmaceutical industry as reaction media and they are also used for cleaning, purification and other purposes. Major use of bulk solvents is in these industries. The recent health, safety and environmental concerns will limit their use in future and are already beginning to do so. However, safe solvents will continue to be used in chemical industry since solvents are necessary in various contexts and are very convenient to use. In many cases it is possible to avoid them altogether though they are often used

routinely more out of habit than necessity. Many reactions can be done without a solvent in liquid or even solid phase or in an aqueous medium but isolation of product and its purification may require the use of a solvent unless the product is obtained pure by a simple distillation, filtration or phase separation.

Use of solvents permits variation of rates of addition, agitation, discharge or quenching, temperature, concentration, pH etc. and enables easy control of exothermic reactions. Crystallization from a solvent is often a necessary operation to get rid of colored and other impurities in a product. Most importantly, the major reason for use of solvents is their ability to profoundly influence reaction rates and to change the course of reactions.

In another embodiment of the present invention wherein in the step (b), the water and methanol are used as solvent. The reason of selection of these optimized quantities of these solvents is that they have higher E_T values. Importantly polarity plays a crucial role and E_T values are most useful measure of polarity according to the scale developed by Dimroth and Reichardt. The E_T value for water is 63.1 and methanol is 55.4, which is higher as compared to the other solvents, leads to more polarity and better solvation effects. In addition to this dipole moment and dielectric constant are also high for water and methanol. For water the dipole moment is 6.07 and dielectric constant is 78.39, however for methanol the dipole moment is 5.67 and dielectric constant is 32.70.

Further, the instant invention for preparation of thiabendazole wherein, an amount of residual solvents methanol and benzene are not more than 3000 ppm, not more than 2 ppm, respectively.

The instant invention for preparation of thiabendazole wherein, an amount of selenium is not more than 30 ppm, cobalt not more than 5 ppm, molybdenum not more than 300 ppm.

In another embodiment of the present invention wherein the purification of thiabendazole in step (c) comprises (i) converting crude thiabendazole to solid thiabendazole hydrochloride using concentrated hydrochloric acid in water, (ii) charcoalizing (15.0% w/w w.r.t to 4-

cyanothiazole) thiabendazole hydrochloride, (iii) filtering the solid thiabendazole hydrochloride, (iv) dispersing thiabendazole hydrochloride in water, (v) further treating with aqueous ammonia solution to obtain free thiabendazole, (vi) isolating pure thiabendazole by filtration.

In another embodiment of the present invention wherein the solvents such as o-dichlorobenzene, methanol and reagents are recycled and reused for successive synthesis process.

In another embodiment of the present invention wherein the one step or all step may be performed in in-situ manner.

The invention is further illustrated by the following examples, which should not be construed to limit the scope of the invention in anyway.

Examples

Example 1: Preparation of amidine hydrochloride (IV)

To the 4-neck, 1 lit RBF, fixed with thermo pocket, condenser and hydrogen chloride (HCl) gas inlet, 100 g (0.908 moles, 1.0 eq) of 4-cyanothiazole, 386 (3.86 V) ml of 1,2-dichlorobenzene and 86.02 (0.924 moles, 1.02 eq) g of aniline were charged. The reaction mass was heated to 55 to 60 °C and hydrogen chloride (HCl) gas was purged till exotherm ceased. Then the temperature of the reaction mass was raised to 135 to 140 °C and again dry HCl gas was purged till 4-cyanothiazole was reduced to less than 0.2 % (w/w) analyzed by HPLC. The reaction mass was cooled to 45 to 50° C and 500 mL of water was charged and the reaction mass was stirred for half an hour. The pH of the reaction mass was adjusted between 3 to 5 using caustic lye. The reaction mass was filtered through hyflo bed, and bed was washed with 50 (0.5 V) mL of water. The organic layer was separated, and the aqueous layer was charged back to the RBF. 20 g of activated charcoal was added in aqueous layer under stirring at 45 to 50 °C. The reaction mass was heated to 55 to 60 °C and maintained under stirring for 1.0 hour. The reaction mass was filtered through the hyflo bed under

vacuum, and bed was washed with 50 mL of hot water and suck dried till no more filtrate collected. 300-400 mL of water was distilled from the aqueous layer at 55 °C under 50 m bar of vacuum. Then the reaction mass was cooled to 0 to 5 °C and maintained under stirring for 1 hour. The obtain amidine hydrochloride was filtered by using Buckner funnel and suck dried till no more filtrate collected from it. The wet cake was dried under vacuum at 55 to 60 °C to get 189 g (86.83% yield, HPLC purity 99.85%) of amidine hydrochloride.

Example 2: Preparation of thiabendazole (I)

The 5 lit RBF was fixed with over head stirrer, thermo pocket, condenser and addition funnel. 185 g (0.772 moles, 1.0 eq.) of amidine hydrochloride and 1536 mL (7.33V) of water were charged. The reaction mass was cooled to 0 to 5 °C. 1233 mL of methanol was added to the mass and the pH of the reaction mass was adjusted between 9 to 10 by using 5N sodium carbonate solution. The reaction mass was warmed to 10 to 15 °C and 415.35 g (12.57 % w/w, 0.91 eq.) sodium hypochlorite was slowly added by maintaining temperature between 10 to 15 °C. The reaction mass was stirred at same temperature for half an hour. Then the reaction mass was heated to 60 to 65 °C and 46.15 g (12.57 % w/w, 0.1 eq) sodium hypochlorite was added. The reaction mass was stirred at 60 to 65 °C for 1.0 hour and the reaction mass was cooled to 30 to 40 °C. The reaction mass was filtered, the bed was washed with 925 mL of water (5.0 V) and suck dried for 10 minutes to get 238 g (152 g on dry basis, 97.82 % yield, HPLC purity 99.77%) of thiabendazole.

Example 3: Purification of thiabendazole (I)

The 5 lit RBF was fixed with over head stirrer, thermo pocket, condenser and addition funnel. 224 g of wet crude thiabendazole (145 g on dry basis) was charged at 25 to 30 °C. 2392 mL (16.5 V) of water was charged and the reaction mass was heated to 75 to 80 °C. The pH of the reaction mass was adjusted between 1 to 2 by adding concentrated hydrochloride. Then 21.75 g (15 %, w/w) activated charcoal was added and the reaction mass was stirred for 1.0 hour at 75 to 80 °C. The reaction mass was filtered through hyflo bed and the bed was washed with 1445 mL (1.0 V) of hot water. The aqueous layer was charged back to clean RBF and cooled to 0 to 5 °C and stirred for 10 hours. The solid was filtered and suck dried under vacuum to get 224 g wet cake of thiabendazole hydrochloride (135 g on dry basis).

1261 mL (10 V w.r.t dry thiabendazole hydrochloride) was charged and then 224 g wet cake of thiabendazole hydrochloride was added. The reaction mass was heated to 70 to 80 °C and maintained under stirring for half an hour to get clear solution. The pH of the reaction mass was adjusted to 7 to 8 by using liquor ammonia. The reaction mass was cooled to 25 to 30 °C and stirred for 1.0 hour. The reaction mass was filtered, and the wet cake was slurry washed twice with 1350 mL (10V x 2 times). Then the bed was washed with 675 mL (5.0 V) water. The solid was dried under vacuum at 60 to 70 °C to afford 119 g (79.33% yield, HPLC purity 99.96%) of pure thiabendazole.

Abbreviations

Aq	:	Aqueous
CDCl ₃	:	Deuterated Chloroform
cm ⁻¹	:	Per centimetre
4-CNT	:	4-cyanothiazole
DMSO	:	Dimethyl sulfoxide
eq	:	Equivalent
g	:	Gram
FS	:	Finished substance
FT-IR	:	Fourier-transform infrared
GC	:	Gas chromatography
h	:	Hour/s
HCl	:	Hydrogen chloride
HPLC	:	High performance liquid chromatography
IMS	:	Intermediate specification
IPS	:	In process specification
IR	:	Infrared
KBr	:	Potassium bromide
Kg	:	Kilogram
L	:	Litre
LOD	:	Loss on drying

m/c	:	Moisture content
ml	:	Millilitre
MLR	:	Mother liquor
MS	:	Mass spectrometry
Na ₂ CO ₃	:	Sodium Carbonate
NaOCl	:	Sodium hypochlorite
NMT	:	Not more than
NMR	:	Nuclear magnetic resonance
OAB	:	On anhydrous basis
ODCB	:	O-dichlorobenzene or 1,2-dichlorobenzene
psig	:	Pounds per square inch gauge
RBF	:	Round bottom flask
RM	:	Reaction mixture
RO	:	Reverse osmosis
RS	:	Relative substances
rt	:	Room temperature
TBZ	:	Thiabendazole
TLC	:	Thin layer chromatography
V	:	Volume
VTD	:	Vacuum tray dryer
w.r.t	:	With respect to

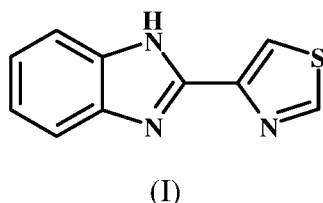
Advantages of the present invention

1. The instant invention consists of a process which provides thiabendazole with high yield and high chemical purity.
2. The process of instant invention does not involve the use of a metallic halide in the preparation of amidine hydrochloride.
3. The instant invention consists of a process in which the reaction is performed at atmospheric pressure, hence makes the process more environmental friendly, economical, safer and thereby commercially viable.

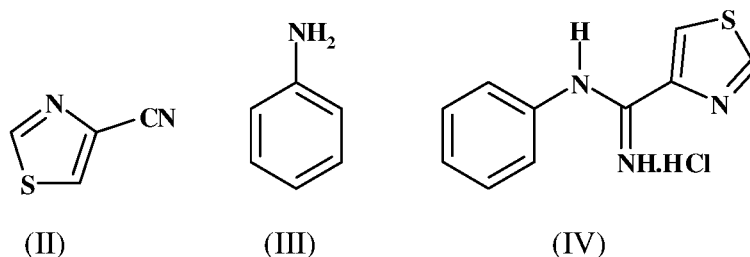
4. The instant invention consists of an improved process for preparation of thiabendazole with controlled amount of 4-chloro thiabendazole or 5-chloro thiabendazole impurities.
5. The process of the present invention is economically and commercially viable process and significantly reducing the production cost of thiabendazole.
6. In the instant process solvents can be recycled and reused for successive synthesis process.
7. The instant robust invention leads to low effluent generation, hence makes the process more environmental friendly, safer and thereby commercially viable.

We claim:

1. An improved process for the preparation of thiabendazole of formula (I), which comprises the steps of:



(a) reacting 4-cyanothiazole of formula (II) with aniline of formula (III) in presence of hydrogen chloride gas and o-dichlorobenzene at atmospheric pressure, at a temperature between 135 to 150°C to obtain amidine hydrochloride of formula (IV);

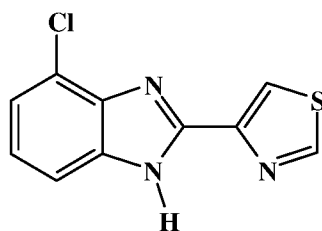


(b) treating amidine hydrochloride of formula (IV) with 1.07 to 1.17 equivalents of sodium hypochlorite in presence of sodium carbonate to control an amount of 4-chloro thiabendazole and/or 5-chloro thiabendazole impurities, to obtain crude thiabendazole of formula (I); and

(c) purification of crude thiabendazole to pure thiabendazole of formula (I).

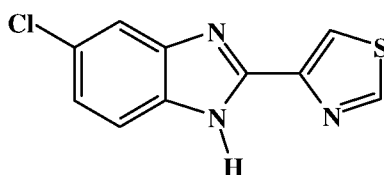
2. The process as claimed in claim 1 wherein, the lot wise addition of sodium hypochlorite is preferred in the said step (b).

3. The process as claimed in claim 1 wherein, an amount of 4-chloro thiabendazole (V) impurity is preferably not more than 0.80% w/w, more preferably not more than 0.50% w/w.



(V)

4. The process as claimed in claim 1 wherein, an amount of 5-chloro thiabendazole (VI) impurity is preferably not more than 0.80% w/w, more preferably not more than 0.50% w/w.



(VI)

5. Thiabendazole as prepared by the process claimed in claim 1 wherein, an amount of 4-chloro thiabendazole (V) impurity is preferably not more than 0.80% w/w, more preferably not more than 0.50% w/w.

6. Thiabendazole as prepared by the process claimed in claim 1 wherein, an amount of 5-chloro thiabendazole (VI) impurity is preferably not more than 0.80% w/w, more preferably not more than 0.50% w/w.

7. Thiabendazole as prepared by the process claimed in claim 1 wherein, an amount of residual solvent methanol is not more than 3000 ppm and benzene is not more than 2 ppm.

8. Thiabendazole as prepared by the process claimed in claim 1 wherein, an amount of selenium is not more than 30 ppm, cobalt is not more than 5 ppm and molybdenum is not more than 300 ppm.

9. The process for purification of thiabendazole which comprises;

- (i) converting crude thiabendazole to solid thiabendazole hydrochloride using concentrated hydrochloric acid in water;
- (ii) charcoalizing thiabendazole hydrochloride;

- (iii) filtering the solid thiabendazole hydrochloride;
- (iv) dispersing thiabendazole hydrochloride in water;
- (v) further treating with aqueous ammonia solution to obtain free thiabendazole; and
- (vi) isolating pure thiabendazole by filtration.

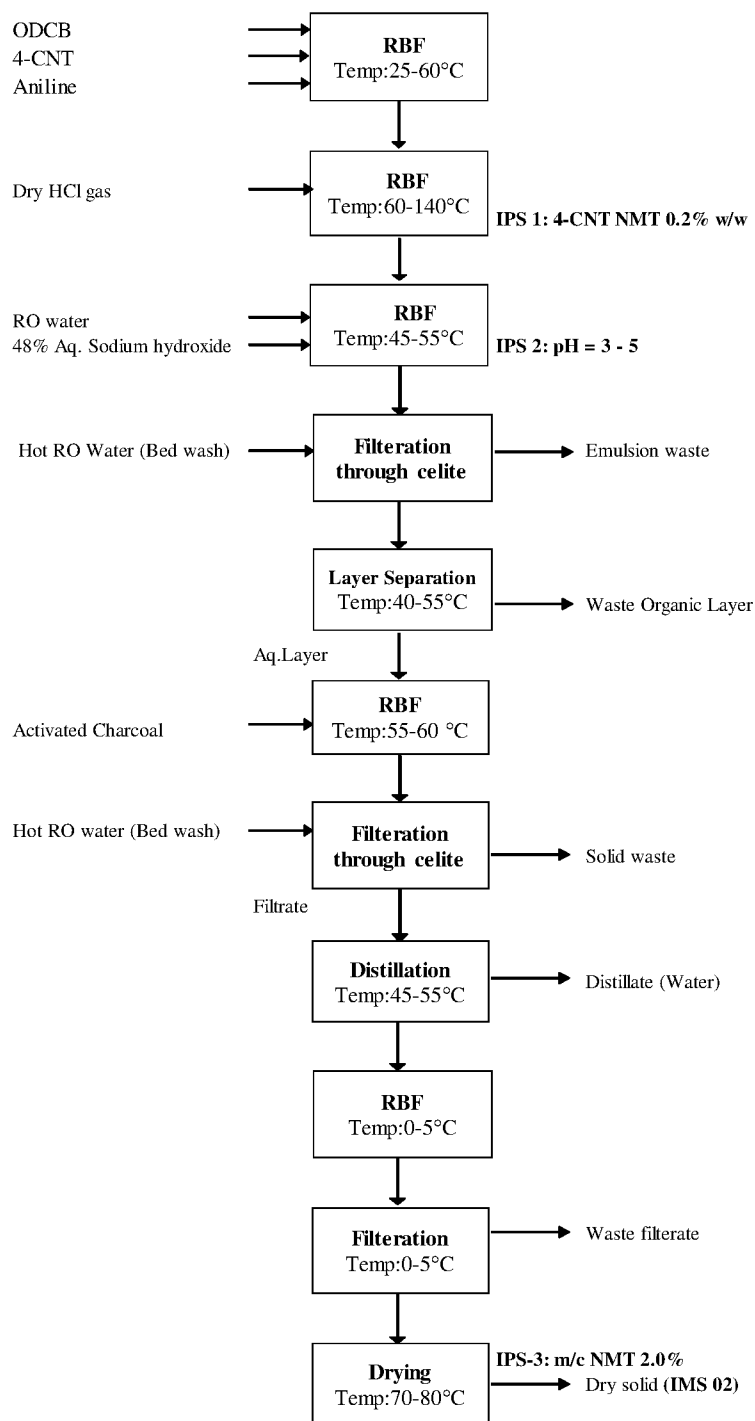


Figure 1

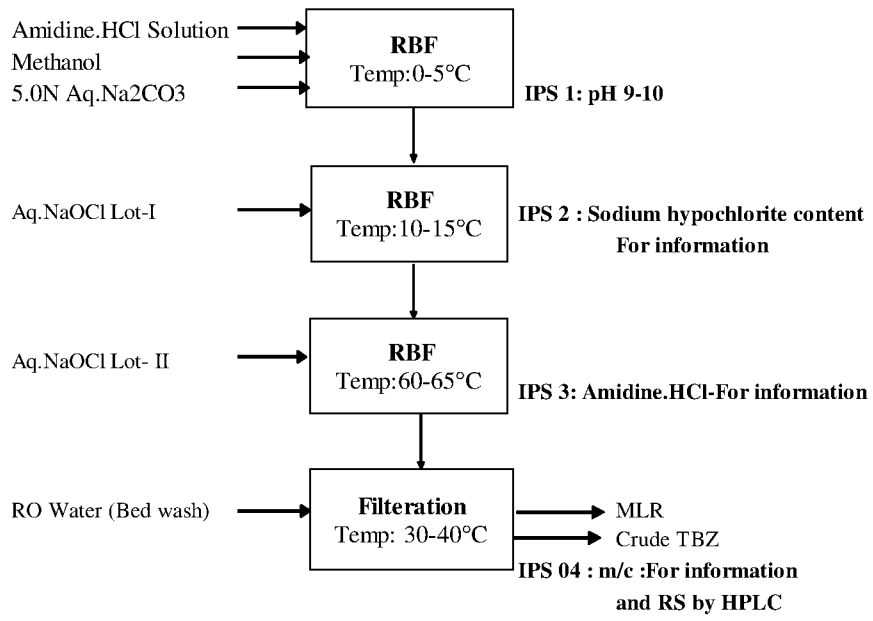


Figure 2

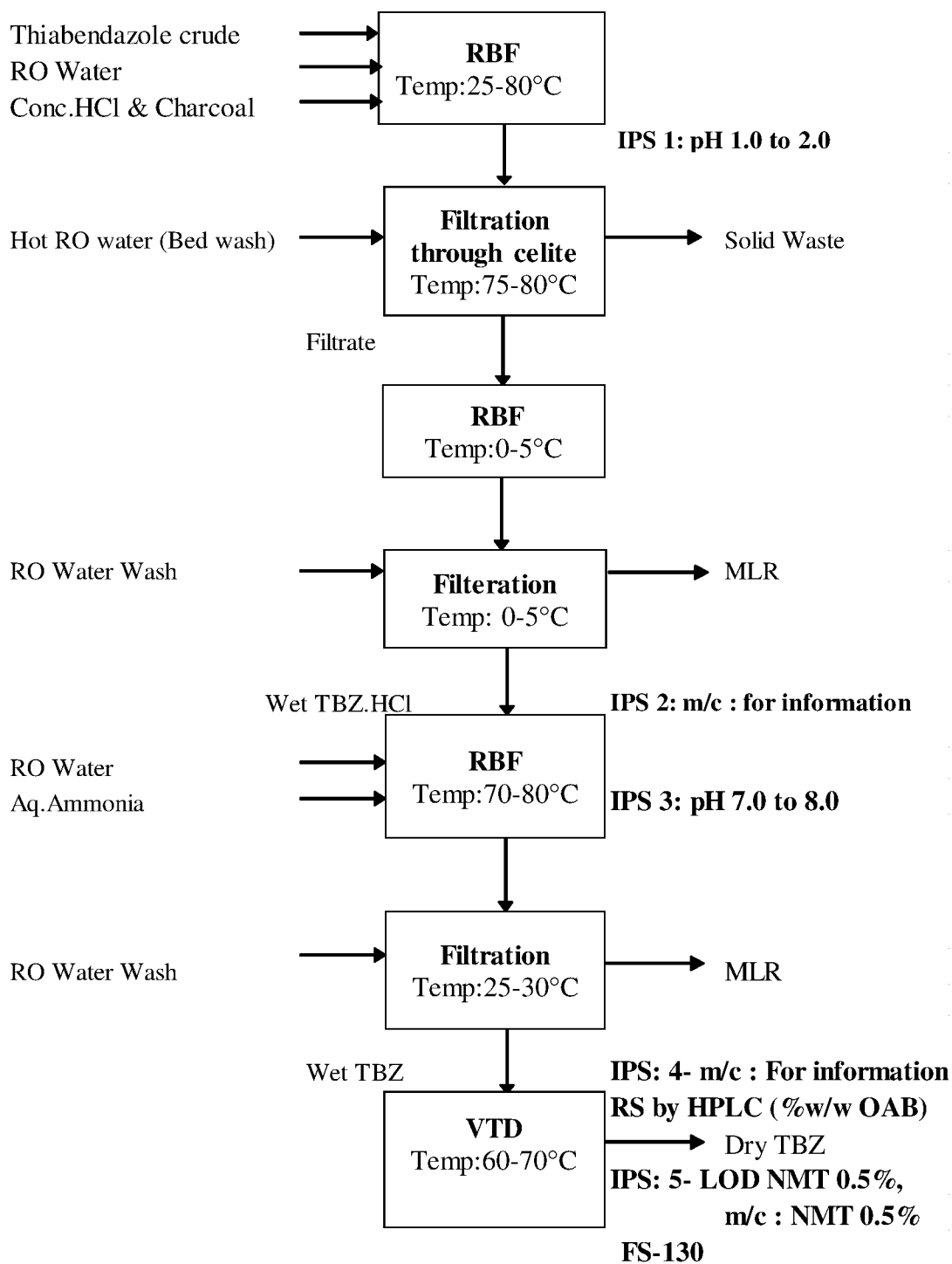


Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/050675

A. CLASSIFICATION OF SUBJECT MATTER
C07D235/06, C07D417/04 Version=2018.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

TotalPatent One, STN, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	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. *table 1, 4a; pg. 3477, point 17*	1-8
Y	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. *fig.1; pg. 545, lest column, second para*	2-8
Y	GRENDA, V. J., JONES, R. E., GAL, G., & SLETZINGER, M., "NOVEL PREPARATION OF BENZIMIDAZOLES FROM N-ARYLAMIDINES. (Y: 2-8) NEW SYNTHESIS OF THIABENDAZOLE.", THE JOURNAL OF ORGANIC CHEMISTRY, 1965, 30(1), 259-261. *pg. 259, left column last para to right column first para; pg. 260, Conversion of the N-Chloro	2-8



Further documents are listed in the continuation of Box C.



See patent family 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 application or patent 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

Date of the actual completion of the international search

31-12-2018

Date of mailing of the international search report

31-12-2018

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2018/050675

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Intermediate IIa to IIIa*	
Y	US 3299081 A (MERCK AND CO INC) 17 JANUARY 1967 (17.01.1967) *examples 1,4*	2-8
X	CA 744727 A (MERCK AND CO INC) 18 OCTOBER 1966 (18.10.1966) *example 15* FAMILY: [NONE]	9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/050675

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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)

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking (Box III)

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:

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2018/050675

Citation	Pub.Date	Family	Pub.Date
US 3299081 A	17-01-1967	DE 1468351 A1	29-10-1970
		GB 1076028 A	19-07-1967