(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 February 2021 (25.02.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/033172 A1

(51) International Patent Classification:
C07D 401/04 (2006.01)

(21) International Application Number:
PCT/IB2020/059172

(22) International Filing Date:
30 September 2020 (30.09.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201941033579 20 August 2019 (20.08.2019) 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, IT, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, 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, 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).

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(54) Title: PROCESS FOR THE PREPARATION OF CHLORANTRANILIPROLE

(57) Abstract: The present invention relates to two novel, efficient and one-pot methods for synthesizing chlorantraniliprole. In the first scheme, Chlorantraniliprole is prepared by a novel telescopic process starting from 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid a key raw material-A (Key RM-A). In the second scheme, starting from Key RM-A, the process steps use of a novel variant of anthranilic acid (Methyl 2-amino-5-chloro-3-methylbenzoate), to get Chlorantraniliprole. Furthermore, the present invention also relates to the synthesis of key starting material for the synthesizing chlorantraniliprole in-situ. All the in-situ steps of the disclosed synthesis methods obtain good yield, without using any expensive reagent or base or harsh reaction conditions, which makes the process simple, environment friendly and more cost effective. With this process the production cost of chlorantraniliprole and its intermediates is substantially reduced; fewer by-products are formed during its synthesis and since it's a one-pot reaction, isolation and purification are easy to achieve.

WO 2021/033172 A1

TITLE OF THE INVENTION:

PROCESS FOR THE PREPARATION OF CHLORANTRANILIPROLE

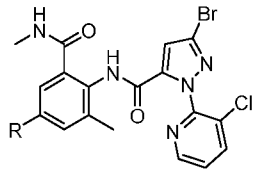
This Non-provisional patent application claims the priority of the provisional patent application numbered 201941033579 filed on August 20, 2019.

Field of Invention

The present invention relates to a field of agricultural pesticides, and more specifically to Insecticides acting on an insect ryanodine receptor.

Background

Anthranilic diamide are new important class of insecticides. This class of insecticides is highly potent, selective, less toxic, and safe. These insecticides work through an action on a novel target, a ryanodine receptor. Chlorantraniliprole, an anthranilic diamide, developed and commercialized worldwide by DuPont has excellent control over lepidopteran pests, low mammalian toxicity and a favorable environmental profile. A pesticide is applicable for a broad range of crops to control a wide range of pests belonging to Lepidoptera, Coleoptera, Diptera and Isoptera species. Few of its derivatives, example Cyantraniliprole (**2**) is also highly effective against insects.



R = Cl, Chlorantraniliprole (1)

R = CN, Cyantraniliprole (2)

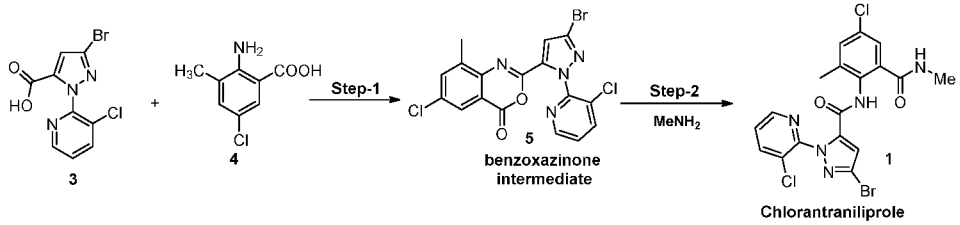
In the past, a number of methods and processes have been reported for the preparation of Chlorantraniliprole. Also, modifications based on Cyantraniliprole structure have long been enthusiasm of researchers but there are few reports on improving the process for Cyantraniliprole manufacture.

Current routes to this anthranilic diamide involve complex multi-step synthesis and are often reliant on toxic reagents generating intermediates, which need wasteful purification steps to be isolated. In order to complement existing methodologies, a convenient telescopic process is highly desirable.

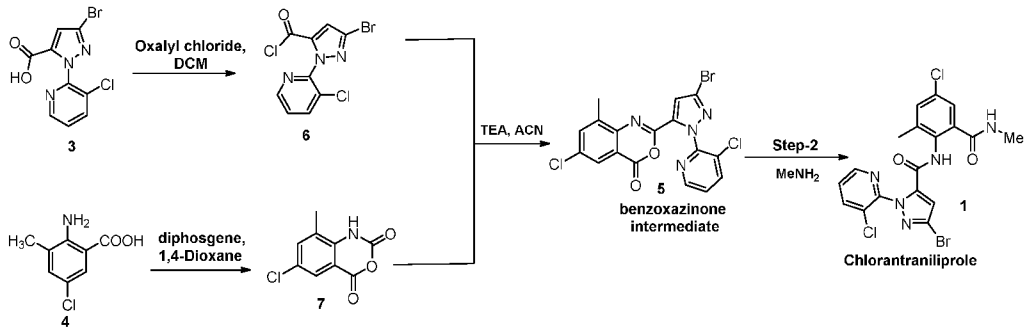
The reported routes for preparation of Chlorantraniliprole include a patent application WO/2003/015519 filed by DuPont claiming Chlorantraniliprole as a product. This patent application describes its preparation using two of its advanced intermediates in two steps. In the first step, a reaction of 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (**3**) with 2-amino-5-chloro-3-methylbenzoic acid (**4**) in the presence of methane sulfonyl chloride and pyridine as base gives a cyclic intermediate 2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-8-methyl-4H-enzo[*d*][1,3]oxazin-4-one (**5**). In the second step, a ring opening of resulting cyclized product i.e. 2-(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl)-6-chloro-8-methyl-4*H*-enzo[*d*][1,3]oxazin-4-one (**5**) by reaction with methyl amine as shown in **Scheme 1**. The WO/2003/015519 patent application also

describes the synthesis of cyclic intermediate benzoxazinone (**Scheme 2**) by treating isatoic anhydride for example, 6-chloro-8-methyl-1*H*-benzo[d][1,3]oxazine-2,4-dione (**7**) with acid chloride (**6**) in the presence of base pyridine. The disclosed process of preparation (Scheme 1 & 2) of Chlorantraniliprole and its intermediate in the WO/2003/015519 patent application has several sequential steps and uses harsh and toxic chemicals and reagents and moderate yields.

Scheme 1:



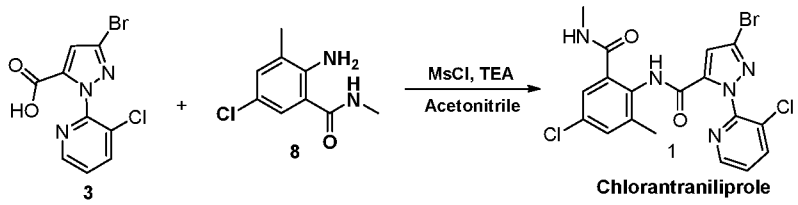
Scheme 2:



US7528260 (B2) granted to DuPont describes that Chlorantraniliprole can be prepared by reacting 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (**3**) with 2-amino-5-chloro-N, 3-dimethylbenzamide (**8**) using methanesulfonyl chloride as a reagent for

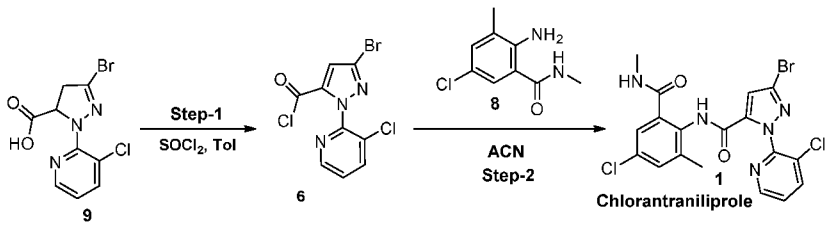
amide coupling in the presence of pyridine and/or substituted pyridine such as 2-picoline, 3-picoline, 2,6-lutidine as bases in acetonitrile as a solvent (Scheme 3). The patent further claims the process for preparation of Chlorantraniliprole by coupling of acid (**3**) and anthraniliamide (**8**) using methanesulfonyl chloride as a coupling reagent in the presence of β-picoline as base in acetonitrile as a solvent (Scheme 3).

Scheme 3:



Similarly, US8217179 (B2) granted to Shenyang Sinochem Agrochemicals in the year 2012, discloses preparation of Chlorantraniliprole **Scheme 4** by reacting 3-bromo-1-(3-chloropyridin-2-yl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid (**9**) with 2-amino-5-chloro-N, 3-dimethylbenzamide (**8**) with simultaneous acyl halide formation and oxidation of dihydro pyrazole ring using thionyl chloride followed by reaction with anthranilamide (**8**) to get Chlorantraniliprole.

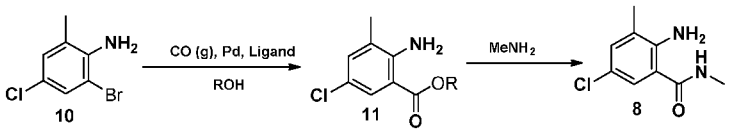
Scheme 4:



This patent claims the process for preparation of Chlorantraniliprole using advanced intermediate pyrazolic acid without having double bond in pyrazole ring, hence, saving one oxidation step using thionyl chloride as a reagent in toluene or acetonitrile as a solvent and without use of any base. Similar approach is required to reduce the number of process steps in preparation of Chlorantraniliprole.

Another patent US8871939 (B2) granted to DuPont discloses a method of preparation of one of the advanced intermediate anthranilamide 2-amino-5-chloro-N, 3-dimethylbenzamide (**8**) by carbonylative amidation of substituted halo anilines (**10**) using palladium catalyst for example palladium (II) acetate and ligand 1,4-bis(diphenylphosphino)butane (dppb) **Scheme 5**. The disclosed method for the synthesis is cumbersome and requires use of certain toxic gases and expensive catalyst.

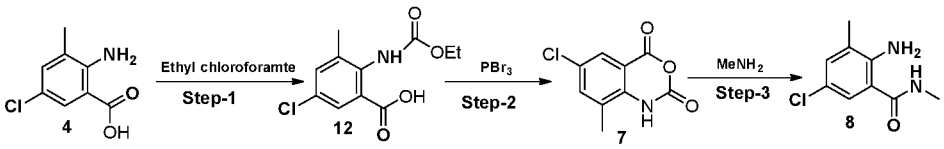
Scheme 5



Similarly, US8153844 (B2) granted to FMC Corp. discloses a method of preparation one of the advanced intermediate anthranilamide for example 2-amino-5-chloro-N, 3-dimethylbenzamide (**8**) by converting carbamate derivatives of anthranilic acid (**12**) using phosphorus tribromide into isatoic anhydride (**7**) and thereafter ring opening by

alkyl amine for example, methyl amine **Scheme 6**. Phosphorus Tribromide is a corrosive chemical and its contact can severely irritate and burn the skin and eyes with possible eye damage. When heated to decomposition, it emits toxic fumes of hydrogen bromide and phosphorous oxides. Similarly, Ethyl chloroformate used in this reaction is highly toxic and is a strong eye and skin irritant.

Scheme 6



Chlorantraniliprole is specific in its action, has low toxicity for other living beings, excellent environmental safety profile, high efficacy, and unique mode of action, therefore, an increasing global demand of Chlorantraniliprole has been observed over the years. As per a new report by QY Research, titled "Global Chlorantraniliprole Sales Market Report 2018," the global chlorantraniliprole market is expected to expand at a moderate CAGR of 4.4% during the seven-year forecast period 2018-2025. By the end of 2025, the market is expected to attain a valuation of US$ 2,120 Mn. In 2017, it was valued at a US$ 1,500 Mn.

Therefore, there is a need to research and develop new efficient, cost effective, robust, and safe processes for preparation of high quality Chlorantraniliprole, which addresses the increasing demand and the environmental issues generated due to the traditional manufacturing processes.

Object of the Invention:

The primary object of the invention is to develop an efficient, telescopic, and environment friendly process for the preparation of chlorantraniliprole and its intermediates.

Another object of the invention is to disclose efficient/novel schemes for the in-situ production of a key raw material and key starting material essentially used for the production of chlorantraniliprole.

Another object of the invention is to disclose use of novel intermediate compounds to achieve production process efficiency.

It is therefore a further object of the present invention is to develop a process that uses ecofriendly reagents having low toxicity for the production of chlorantraniliprole.

Yet another object of the invention is to develop a process that produces fewer by-products and can be carried out in a single pot.

The present invention therefore also provides methods to reduce the production cost of chlorantraniliprole and improve its quality.

Statement of invention:

The invention discloses two novel, efficient and one-pot method for synthesizing chlorantraniliprole, and its intermediates. In the first scheme, Chlorantraniliprole is prepared by a novel telescopic process starting from 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (**3**). In the second scheme, starting from 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (**3**), the process steps use a novel variant of pyrazolic acid (Methyl 2-amino-5-chloro-3-methylbenzoate), to get Chlorantraniliprole. All the in-situ steps of the disclosed synthesis method obtain good yield, without using any base or harsh reaction conditions, which makes the process simple, environment friendly and more cost effective. With this process, the

production cost of chlorantraniliprole and its intermediates is substantially reduced; fewer by -products are formed during its synthesis and since it is a one-pot reaction, isolation and purification are easy to achieve.

Summary of Invention

The invention provides two novel, efficient and one-pot method for synthesizing chlorantraniliprole. The invention also provides efficient/novel schemes for the in-situ production of the KRMs viz. 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (**3**), 2-Amino-5-chloro-N,3-dimethylbenzamide (**8**), Methyl 2-amino-5-chloro-3-methylbenzoate (**13**). In the first scheme, Chlorantraniliprole is prepared by a novel telescopic process starting from 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (**3**), the process steps include in-situ preparation of acid chloride (**6**) using stoichiometric amount of oxalyl chloride or thionyl chloride at ambient temperature followed by coupling with anthranilic amide without using any base.

In the second scheme, starting from 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (**3**), the process steps include in-situ preparation of acid chloride, methyl ester of chlorantraniliprole (**14**) followed by reaction with methyl amine to get Chlorantraniliprole in one-pot. This scheme uses a novel variant of pyrazolic acid (Methyl 2-amino-5-chloro-3-methylbenzoate) (**13**) to get Chlorantraniliprole. Furthermore, all the in-situ steps of the disclosed synthesis method obtain good yield, without using any base or harsh reaction conditions, which makes the process simple, environmentally benign and more cost effective. Moreover, with this process the production cost of chlorantraniliprole and its intermediates is substantially reduced; fewer

by-products are formed during its synthesis and since it is a one-pot reaction, isolation and purification are easy to achieve.

Brief description of schemes of the invention

Scheme-7.1 Provides the details of reactants and reaction conditions for the in-situ preparation of chlorantraniliprole using 2-amino-5-chloro-N,3-dimethylbenzamide.

Scheme-7.2 Provides the details of reactants and reaction conditions for the in-situ preparation of chlorantraniliprole using methyl 2-amino-5-chloro-3-methylbenzoate.

Scheme-8 Provides the details of reactants and reaction conditions for the preparation of pyrazole acid **(3)** using dichloropyridine (DCP).

Scheme-9 Provides the details of the reactants and reaction conditions for the preparation of 2-amino-5-chloro-N,3-dimethylbenzamide using *m*-Toluic acid.

Scheme-10 Provides the details of the reactants and reaction conditions for the preparation of methyl 2-amino-5-chloro-3-methylbenzoate using 3-methyl-2-nitrobenzoic acid.

Detailed description of schemes of the invention

As used herein, the terms "includes," "including," "has," "having," "contains", "containing," or any other variation thereof, are intended to cover a non-exclusive inclusion, subject to any limitation explicitly indicated. For example, a process, method that comprises a list of

compounds is not necessarily limited to only those compounds but may include other compounds not expressly listed or inherent to such process, method.

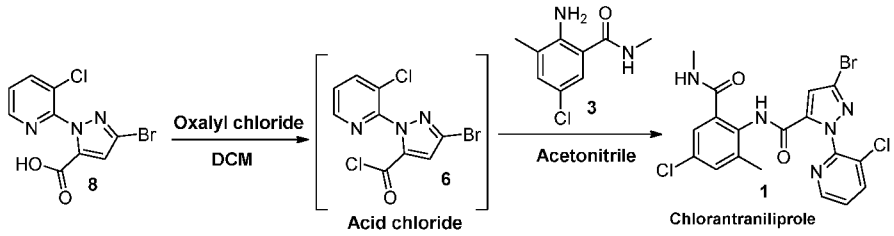
The use of numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about". In this manner, slight variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. Also, the disclosure of these ranges is intended as a continuous range including each and every value between the minimum and maximum values.

In a preferred embodiment, a telescopic process for the preparation of Chlorantraniliprole (Formula 1) takes place in the following manner:

To a solution of 3-Bromo-1-(3-chloropyridin-2-yl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid (**8**) (1 g, 0.033 mol) in DCM (10 ml) was added catalytic amount of DMF and oxalyl chloride (1.26 g, 0.0099 mol) at room temperature. The reaction mixture was stirred for 12-14 hours (h) at room temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, the DCM was recovered and acetonitrile (10 ml) and 2-amino-5-chloro-N,3-dimethylbenzamide (3) (1 eq.) was added. The reaction mixture was stirred for 3-4 h at 60-70°C. The progress of the reaction was monitored by HPLC. After completion of the reaction, Acetonitrile was recovered at a reduced pressure. Product was isolated by adding water to a residue and filtration of resulting solid to get crude product. Crude product was purified by slurry wash with acetone. Yield: 78% and purity: 98%. (Scheme 7.1)

^{1}H NMR (DMSO-d_6) 2.12 (s, 3H), 2.62 (d, 3H, J = 4.4 Hz),7.31 (d, 1H, J = 2 Hz), 7.36 (s, 1H), 7.43 (d, 1H, J = 2 Hz), 7.57, (dd, 1H, J = 4.4 Hz), 8.14 (d, 1H, J = 8 Hz), 8.24 (d, 1H, J = 4.4Hz), 8.46 (d, 1H, J = 4.8 Hz), 10.24 (s, 1H). ^{13}C NMR (DMSO-d_6) 18.13, 26.55, 125.79, 127.01, 127.28,128.30, 131.40, 131.61, 131.97, 136.41, 139.20, 139.66, 139.81,147.51, 148.86, 156.01, 156.65.

Scheme 7.1



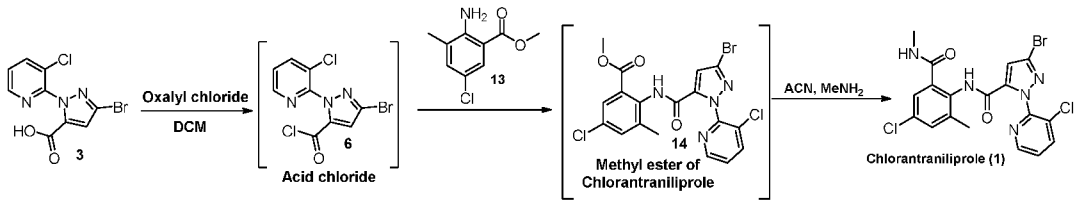
In another preferred embodiment, the telescopic process for the preparation of Chlorantraniliprole (Formula 1) takes place in the following manner:

To a solution of 3-bromo-1-(3-chloropyridin-2-yl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid (8) (1 g, 0.033 mol) in DCM (10 ml) was added catalytic amount of DMF and oxalyl chloride (1.26 g, 0.0099 mol) at room temperature. The reaction mixture was stirred for 12-14 h at room temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, methyl 2-amino-5-chloro-3-methylbenzoate (13) and triethyl amine was added. The reaction mixture was stirred for 3-4 h at room temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, DCM was recovered at a reduced pressure. To the residue, acetonitrile was added and cooled to 0-10°C. Aqueous solution of methyl amine was added at 0-10°C and the reaction mixture was stirred for 3-4 h at

room temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, solvent was recovered at reduced pressure. Product was isolated by adding water to the residue and filtration of resulting solid to get crude product. Crude product was purified by slurry wash with acetone. Yield: 70% and purity: 98%. (Scheme 7.2)

^{1}H NMR (DMSO-d_6) 2.12 (s, 3H), 2.62 (d, 3H, J = 4.4 Hz),7.31 (d, 1H, J = 2 Hz), 7.36 (s, 1H), 7.43 (d, 1H, J = 2 Hz), 7.57,(dd, 1H, J = 4.4 Hz), 8.14 (d, 1H, J = 8 Hz), 8.24 (d, 1H, J = 4.4Hz), 8.46 (d, 1H, J = 4.8 Hz), 10.24 (s, 1H). ^{13}C NMR (DMSO-d_6) 18.13, 26.55, 125.79, 127.01, 127.28, 128.30, 131.40, 131.61, 131.97, 136.41, 139.20, 139.66, 139.81,147.51, 148.86, 156.01, 156.65.

Scheme 7.2



In an embodiment, the process for the preparation of 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (3) takes place in the following manner:

Step-1: Preparation of 3-chloro-2-hydrazinylpyridine (Scheme 8)

To a solution of 2,3-Dichloropyridine (DCP) (1 kg, 0.0067 mol) in 1,4-Dioxane (2 lit) was added 10% aqueous solution of hydrazine hydrate (1.69 kg, 0.0337 mol) at room temperature. The reaction mixture was heated at 100-110°C and stirred for 24 h at the same temperature. The progress of the reaction was monitored by HPLC. After completion of

the reaction, cool the reaction mass to room temperature. The solid product was isolated by adding water to a reaction mass and filtering resultant solid product. Yield: 94% and purity: 97.3%, melting range165-166°C.

Step-2: Preparation of ethyl 2-(3-chloropyridin-2-yl)-5-oxopyrazolidine-3-carboxylate

To a solution of sodium ethoxide (745 g) and 3-chloro-2-hydrazinylpyridine (300 g) in ethanol (900 ml) was added diethyl maleate (396 g) at 70-80°C. Stir the reaction mass for 1 -2 h at 75-80°C. The progress of the reaction was monitored by HPLC. After completion of the reaction, cool the reaction mass to 40-50°C. Acetic acid (313 g) was added to the reaction mass at 40-50°C and then cool the reaction mass to room temperature. Recovered the solvent at reduced pressure at 40-45°C. Added water (3 liters) to the residue and extracted the product in DCM. DCM was recovered at reduced pressure at 40-45°C to get the crude product. The crude was purified by recrystallization using IPA as solvent. Yield: 70%, and purity: 97% and melting range-138-139°C.

Step-3: Preparation of Ethyl 3-bromo-1-(3-chloropyridin-2-yl)-4, 5-dihydro-1H-pyrazole-5-carboxylate

To a solution of Ethyl 2-(3-chloropyridin-2-yl)-5-oxopyrazolidine-3-carboxylate (300 g, 1.12 mol) in DCM (3 lit) and TEA (394 g, 3.89 mol) was added Methanesulfonyl chloride (191.2 g, 1.67 mol) at -10°C to 0°C. The reaction mass was stirred for 2-3 h at 0°C to 5°C. The progress of the reaction was monitored by HPLC. After completion of the reaction, reaction mass was washed with water (1.5 lit). To DCM layer, HBr in acetic acid (33%) (895 g, 3.32 mol) was added at 0°C to -10°C. The reaction mixture was stirred for 1-2 h at 0-5°C. The

progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mass was washed with saturated aq. $NaHCO_3$ (3.3 lit). DCM was recovered at a reduced pressure at 30-40°C afforded Ethyl 3-bromo-1-(3-chloropyridin-2-yl)-4, 5-dihydro-1H-pyrazole-5-carboxylate. Yield: 90% and HPLC purity: 90%.

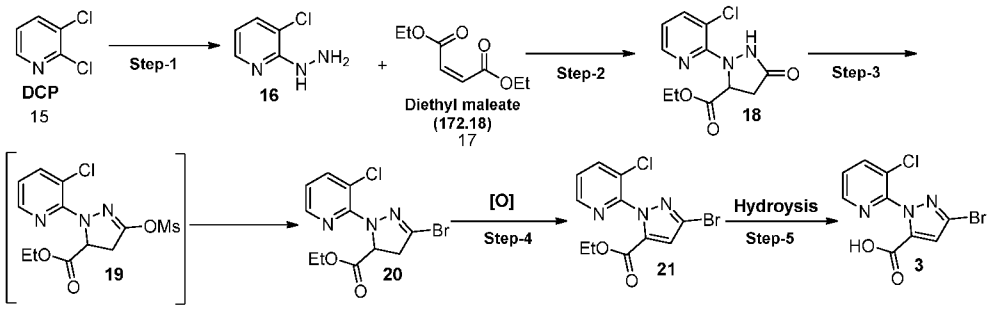
Step-4: Preparation of ethyl 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylate

To a solution of ethyl 3-bromo-1-(3-chloropyridin-2-yl)-4,5-dihydro-1H-pyrazole-5-carboxylate (324 g, 0.97 mol) and concentrated Sulfuric acid (191 g, 1.94 mol) in acetonitrile was added Potassium persulfate (394.6 g, 1.46 mol) at room temperature. The reaction mixture was heated to 80-85°C and stirred for 2-3 h at the same temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was cooled to room temperature. Filtered-off inorganics and recovered acetonitrile under reduced pressure at 40-45°C. The solid product was isolated by addition of water to the residue. Yield: 99%, Purity: 95% and a melting range:113-115°C.

Step-5: Preparation of 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid

To a solution of Ethyl 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylate (315 g, 0.95 mol) in Methanol (1.57 lit) was added aqueous solution of sodium hydroxide (57 g, 1.43 mol) at 0°C to 5°C. The reaction mass was stirred for 1-2 h at room temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, methanol was recovered at reduced pressure at 30-40°C. Water was added to the residue and acidified with 6 N hydrochloric acid. The resulting solid product was isolated by filtration and drying. Yield: 88% and HPLC purity: 95%.

Scheme 8: Preparation of acid (3)



In an embodiment, the process for the preparation of 2-Amino-5-chloro-N,3-dimethylbenzamide (8) takes place in the following manner:

Step-1: 3-Methyl-2-nitrobenzoic acid (Scheme 9)

m-Toluic acid (100 g) was added to fuming nitric acid (200 ml) at -10 to -5°C in portion wise manner. After addition, the reaction mixture was stirred for 2-3 h at -10 to -5°C. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was poured into ice water and stirred for 1-2 h. The solid product was isolated by filtration and washed with water to get crude product. The crude product was purified by crystallization in ethanol to get pure 3-methyl-2-nitrobenzoic acid. Yield: 45% and purity: 97%.

Step-2: Preparation of *N*,3-dimethyl-2-nitrobenzamide

To a solution of 3-methyl-2-nitrobenzoic acid (5 g, 0.027 mol) in Toluene was added thionyl chloride (6.6 g, 0.055 mol) at room temperature. The reaction mass was heated to 90-100°C and stirred for 2-3 h at the same temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, Toluene and excess of thionyl chloride were recovered under reduced pressure at

40-50°C. The residue was dissolved in DCM and DCM solution was slowly added to aqueous solution of methyl amine (40%, 4.3 g, 0.055 mol) at 0-10°C. The reaction mixture was stirred for 1-2 h at 0-10°C. The progress of the reaction was monitored by HPLC. After completion of the reaction, product was extracted in DCM. The DCM layer was washed with brine solution and recovered the DCM to get N,3-dimethyl-2-nitrobenzamide. Yield: 90% and purity: 97%.

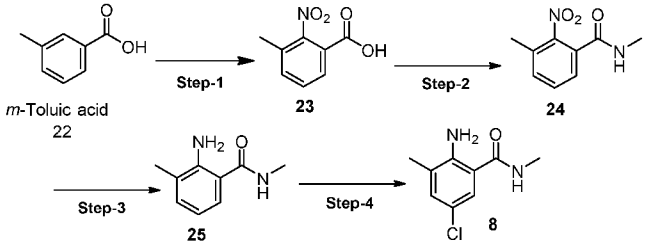
Step-3: 2-amino-*N*,3-dimethylbenzamide

To a solution of N,3-dimethyl-2-nitrobenzamide (5 g) in methanol was added Pd/C (10%, 500 mg). The reaction mixture was flushed with hydrogen and stirred under pressure of hydrogen (1-2 kg) for 10-12h. The progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mass filtered through a pad of Celite. Methanol was recovered at under reduced pressure at 40-50°C to get 2-amino-N,3-dimethylbenzamide. Yield: 90% and HPLC purity: 97%.

Step-4: 2-Amino-5-chloro-N,3-dimethylbenzamide

To a solution of 2-amino-N,3-dimethylbenzamide (4 g, 0.023) and hydrochloric acid (8 ml) in acetic acid (12 ml) was added hydrogen peroxide (30%, 0.032 mol) at 5-10°C. The reaction mixture was stirred for 5-6 h at room temperature. The progress of the reaction was monitored by HPLC. After completion of the reaction, water was added into the reaction mixture. The resultant solid product was isolated by filtration and washed with water. Yield: 85% and purity: 95%.

Scheme 9: Preparation of 8



In an embodiment, the process for the preparation of Methyl 2-amino-5-chloro-3-methylbenzoate (13) is performed in the following manner:

Step-1: Preparation of 2-Amino-3-methylbenzoic acid (Scheme 10)

To a solution of 3-methyl-2-nitrobenzoic acid (50 g) in methanol was added Pd/C (10%, 5 g). The reaction mixture was flushed with hydrogen and stirred under pressure of hydrogen (1-2 kg) for 10-12 h. The progress of reaction was monitored by HPLC. After completion of the reaction, the reaction mass is filtered through a pad of Celite. Recovered methanol at reduced pressure at 40-50°C to get 2-Amino-3-methylbenzoic acid. Yield: 90% and HPLC purity: 97%.

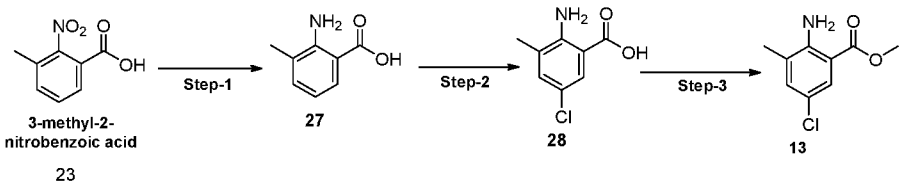
Step-2: Preparation of 2-amino-5-chloro-3-methylbenzoic acid

To a solution of 2-Amino-3-methylbenzoic acid (200 g) and concentrated hydrochloric acid (400 ml) in acetic acid (600 ml) was added Hydrogen peroxide (H_2O_2) (30%) (202.5 g) at 20-30°C. The reaction mixture was stirred for 12-15 h at 20-30°C. The progress of the reaction was monitored by HPLC. After completion of the reaction, water was added to the reaction mixture. The resulting solid product was isolated by filtration and drying. Yield: 79%, HPLC purity: 95% and melting range: 233-237°C.

Step-3: Preparation of methyl 2-amino-5-chloro-3-methylbenzoate

To a mixture of 2-Amino-5-chloro-3-methylbenzoic acid (175 g, 0.95 mol) and K_2CO_3 (137.06 g, 0.99 mol) in DMF (525 ml) was added Dimethyl sulfate (119 g, 0.95 mol) at room temperature. The reaction mixture was heated and stirred for 9-10 h at 100-110°C. The progress of the reaction was monitored by HPLC. After completion of the reaction, DMF was recovered under reduced pressure at 60-70°C. Water was added to the residue and product was isolated by extraction in ethyl acetate and recovering of ethyl acetate. Yield: 78%, purity: 98%.

Scheme 10: Preparation of 13



3-methyl-2-nitrobenzoic acid
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This written description discloses the invention, including the best mode, and also to enable any person skilled in the art to practice the invention, including making and using and performing any incorporated methods. The patentable scope the invention is defined in the claims, and may include other examples that occur to those skilled in the art.

Claims

We claim:

1. A telescopic process for preparation of Chlorantraniliprole and its intermediates, said process comprising the steps of:

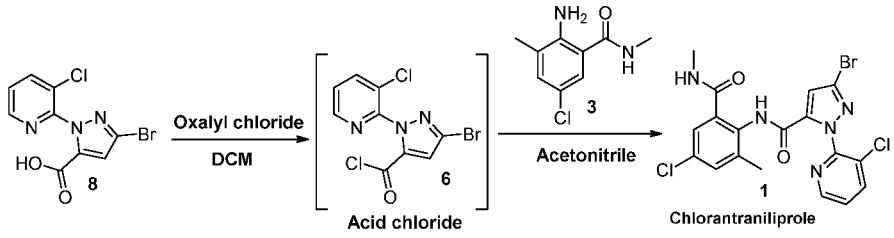
a) reacting compound (3) in DCM or EDC with catalytic amount of DMF and oxalyl chloride, or thionyl chloride, or methane sulfonyl chloride or any reagent which can form the corresponding acid chloride/bromide such as $POCl_3$, $POBr_3$ between 0-40°C.

b) stirring the reaction mixture for 4-24 h between 0-40°C;

c) adding acetonitrile or DMF or THF and compound (8) and stirring the reaction mixture for 1-10 h at 40-80°C;

d) isolating the product by adding water to the residue and filtration of resulting solid to get crude product; and

e) purifying the crude product by slurry wash with acetone, methyl ethyl ketone, methanol, ethanol, IPA, ethyl acetate, acetonitrile to get pure chlorantraniliprole.



2. The process for preparing chlorantraniliprole as claimed in claim 1 wherein 60-85% of yield and 95-98% of purity is achieved.

3. The process for preparing chlorantraniliprole as claimed in claim 1 wherein the solvents DCM, EDC, DMF, DMA THF and acetonitrile are recovered from the reaction mixture sequentially.

4. The process for preparing chlorantraniliprole as claimed in claim 1 wherein preparation of key raw material compound 8 (2-Amino-5-chloro-N,3-dimethylbenzamide) is achieved through a process comprising the steps of:

Step-1: Synthesis of 3-methyl-2-nitrobenzoic acid:

a) reacting *m*-Toluic acid to fuming nitric acid at -30 to 0°C;
b) stirring reaction mixture for 1-10 h at -30 to 0°C;
c) pouring reaction mixture into ice water followed by stirring for 1-12 h;
d) isolating the solid product by filtration and washing with water to get crude product; and
e) purifying the crude product by crystallization in any alcoholic solvent such as methanol, or ethanol or IPA to get 97% pure 3-methyl-2-nitrobenzoic acid with yield of 20-80% and purity of 97% and above.

Step-2: Synthesis of *N*,3-dimethyl-2-nitrobenzamide:

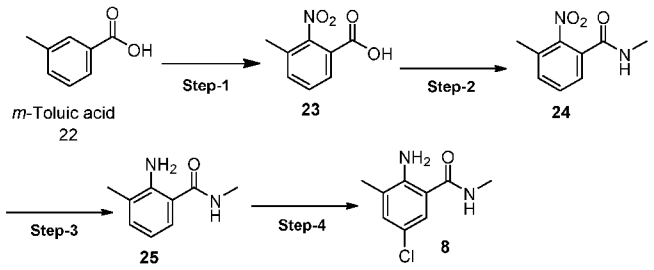
a) reacting 3-methyl-2-nitrobenzoic acid in Toluene or DCM or EDC with thionyl chloride or oxalyl chloride;
b) reaction mixture is heated to 30-110°C and stirred for 2-3 h at the same temperature;
c) slowly adding a solution of resulting acid chloride in DCM or EDC into aqueous solution of methyl amine at -10 to 10°C or methyl amine solution in organic solvents such methanol, THF
d) stirring the reaction mixture for 1-12 h at -10 to 10°C; and
e) extracting the product in DCM or EDC and evaporation solvent to get *N*,3-dimethyl-2-nitrobenzamide with a yield of 80-95% and purity of above 97%.

Step-3: Synthesis of 2-Amino-*N*,3-dimethylbenzamide:

a) reacting *N*,3-dimethyl-2-nitrobenzamide in methanol or ethanol or IPA with Pd/C; Raney Ni
b) flushing the reaction mixture with hydrogen and stirring under pressure of hydrogen (1-10 kg) for 5-24 h
c) filtering the reaction through pad of Celite; and
d) recovering solvent at reduced pressure at 40-50°C to get 2-amino-N,3-dimethylbenzamide with a yield of 80-90% and HPLC purity of above 97%.

Step-4: Synthesis of 2-amino-5-chloro-*N*,3-dimethylbenzamide:

a) reacting 2-amino-*N*,3-dimethylbenzamide with hydrochloric acid in acetic acid;
b) adding hydrogen peroxide at -5 to 10°C;
c) stirring the reaction mixture for 4-12 h at room temperature; and
d) adding water to reaction mixture to get a solid product which is filtered and washed with water to get a yield of 70-85% and a purity of above 95%.



5. A telescopic process for preparing chlorantraniliprole and its intermediates, said process comprising the steps of:

a) reacting compound (3) in DCM or EDC with catalytic amount of DMF and oxalyl chloride, or thionyl chloride, or methane sulfonyl chloride at room temperature;

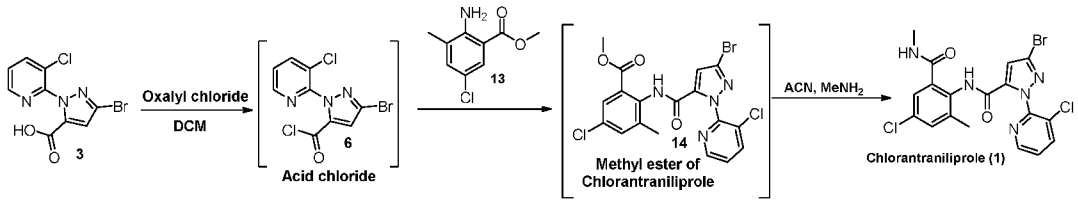
b) after completion of reaction, compound (13) and triethyl amine is added;

c) stirring the reaction mixture for 1-10 h at room temperature;

d) aqueous solution of methyl amine or methyl amine solution in organic solvent is added at -10 to10°C and reaction mixture was stirred for 1-12 h at room temperature;

e) isolating the product by adding water to the residue and filtration of resulting solid to get crude product; and

f) purifying the crude product by slurry wash with acetone, methyl ethyl ketone, MIBK, ethyl acetate, methanol, ethanol, IPA, acetonitrile to get pure chlorantraniliprole.



6. The process for preparing chlorantraniliprole as claimed in claim 5 wherein a novel variant of anthranilic acid (compound 13, Methyl 2-amino-5-chloro-3-methylbenzoate) is used to get chlorantraniliprole with a purity of 95-98%.

7. The process for preparing chlorantraniliprole as claimed in claim 5 wherein preparation of key raw material compound 3 (3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid) is achieved through a process comprising the steps of:

Step-1: Synthesis of 3-chloro-2-hydrazinylpyridine:

a) reacting 2,3-Dichloropyridine (DCP) with aqueous solution of hydrazine hydrate (70-90%) at 50 to 110°C in non-polar a

protic acid such as 1,4-dioxane, acetonitrile, DMF, DMSO or protic polar solvent such as water, or methanol, or ethanol or IPA or butanol

stirring reaction mixture for 6-26 h at 50 to 110°C; pouring reaction mixture into water followed by stirring for 1-12 h;

isolating the solid product by filtration and washing with water to get pure product with good yield: 94% and purity: 97.3%,

Step-2: Synthesis of ethyl 2-(3-chloropyridin-2-yl)-5-oxopyrazolidine-3-carboxylate

a) reacting 3-chloro-2-hydrazinylpyridine with diethyl maleate at 40 to 90°C in protic polar alcoholic solvents such as methanol, or ethanol or IPA or butanol in the presence of base sodium hydride, or sodium metal or sodium ethoxide, or sodium ethoxide or pot-*t*-butoxide
b) stirring reaction mixture for 1-10 h at 50 to 100°C;
c) neutralizing reaction mixture with acetic acid or formic acid or citric acid
d) recovering solvent and isolation of pure product by recrystallization in IPA or ethanol with good yield: 50-80%, and purity: 95-97%

Step-3: Synthesis of Ethyl 3-bromo-1-(3-chloropyridin-2-yl)-4, 5-dihydro-1H-pyrazole-5-carboxylate

a) reacting ethyl 3-bromo-1-(3-chloropyridin-2-yl)-4,5-dihydro-1H-pyrazole-5-carboxylate with methane sulfonyl chloride or *p*-Toluene sulfonyl chloride at -10 to 10°C in halogenated solvents such as DCM or EDC in the presence of organic base triethyl amine or di-isopropyl ethylamine
b) washing reaction mixture with water

c) treating organic layer in-situ with HBr at -10 to 10°C

d) neutralizing reaction mixture with aqueous sodium bicarbonate

e) recovering solvent to get product with good yield: 80-90%, and purity: 90-92%

Step-4: Synthesis of ethyl 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylate

a) reacting Ethyl 2-(3-chloropyridin-2-yl)-5-oxopyrazolidine-3-carboxylate with concentrated Sulfuric acid and Potassium persulfate at 60 to 100°C in polar solvent such as DMF, acetonitrile, DMSO

b) filtering reaction mixture

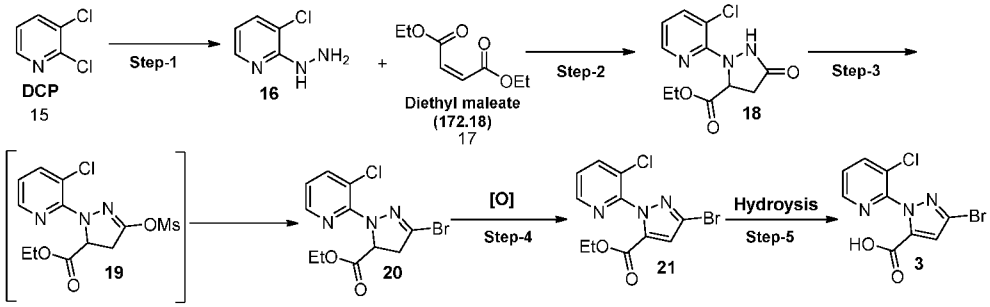
c) recovering solvent and treating residue with water to get product with good yield: 90-99%, and purity: 92-95%

Step-5: Synthesis of 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid

a) reacting Ethyl 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylate with aqueous NaOH at 0 to 50°C in polar solvent such as methanol, or THF and water

b) acidifying reaction mixture with aqueous hydrochloric acid

c) isolating solid product by filtering reaction mixture with good yield: 90-95%, and purity: 95-97%



8. The process for preparing chlorantraniliprole as claimed in claim 5 wherein preparation of intermediate compound **13** (Methyl 2-amino-5-chloro-3-methylbenzoate) is achieved through a process comprising the steps of:

Step-1: Synthesis of 2-Amino-3-methylbenzoic acid:

a) reacting 3-methyl-2-nitrobenzoic acid in methanol or ethanol or IPA or acetic acid to Pd/C or Raney Ni
b) flushing the reaction mixture with hydrogen and stirred under pressure of hydrogen (1-10 kg) for 5-24 h;
c) filtering the reaction mass through pad of Celite; and
d) recovering solvent at reduced pressure at 40-50°C to get 2-Amino-3-methylbenzoic acid with an yield of 90% and HPLC purity of 97%.

Step-2: synthesis of 2-amino-5-chloro-3-methylbenzoic acid:

a) reacting 2-Amino-3-methylbenzoic acid with concentrated hydrochloric acid in acetic acid or formic acid;
b) adding Hydrogen peroxide (H_2O_2) at 0-50°C;
c) stirring the reaction mixture for 6-15 h at 0-30°C;
d) adding water to the reaction mixture to get a solid product; and

e) filtrating and drying of the solid product to get yield of 79%, HPLC purity of 95%

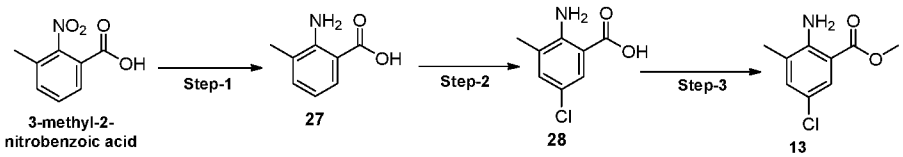
Step-3: synthesis of methyl 2-amino-5-chloro-3-methylbenzoate:

a) reacting a mixture of 2-Amino-5-chloro-3-methylbenzoic acid and K_2CO_3 or Cesium carbonate or sodium carbonate in DMF or acetonitrile with Dimethyl sulphate or Methyl iodide or methyl bromide at room temperature; or

b) heating the reaction mixture with constant stirring for 5-24 h at 80-120°C;

c) after recovering DMF under reduced pressure, water is added to the residue; and

d) extraction of product in ethyl acetate and concentration of solvent to get pure product yield: 70-78% purity: 95-98%.



3-methyl-2-nitrobenzoic acid
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9. The process for preparing chlorantraniliprole as claimed in claim 1 wherein the compound 8, 2-Amino-5-chloro-N,3-dimethylbenzamide is synthesized using the process described in claim 4.

10. The process for preparing chlorantraniliprole as claimed in claim 5 wherein, the compound 3, 3-Bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid) and intermediate compound 13, Methyl 2-amino-5-chloro-3-methylbenzoate is synthesized using the process described in claim 7 & 8.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/059172

A. CLASSIFICATION OF SUBJECT MATTER
C07D401/04 Version=2021.01

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, 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.
Y	WO2003015519A1 (E.I.DU PONT DE NEMOURS AND COMPANY (US)), 27 FEBRUARY 2003 (2003-02-27) (See Schemes 1-3)	1-10
Y	US8217179B2 (SHENYANG RESEARCH INSTITUTE OF CHEMICAL INDUSTRY Co. (CN)), 10 JULY 2012 (2012-07-10) (See Abstract, Claim 1)	1-10

☐ 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
"D" document cited by the applicant in the international application
"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	Date of mailing of the international search report
27-01-2021	27-01-2021
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Vikas Verma Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/059172

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:

The subject-matter of claims 1-10 comprises two distinct groups of inventions which are not linked to show the single inventive concept.
Group 1 : Claims 1-4.

The subject matter of claims 1 -4 is related to preparation of chlorantraniliprole by the reaction of compound 6 with amide compound.

Group 2 : Claims 5-10.

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.

International application No.
PCT/IB2020/059172

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

The subject matter of claims 5-10 is related to preparation of chlorantranilirole by the reaction of compound 6 with ester compound.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2020/059172

Citation	Pub.Date	Family	Pub.Date
WO 2003015519 A1	27-02-2003	US 20070225336 A1	27-09-2007
		EP 1416797 B1	12-05-2004
US 8217179 B2	10-07-2012	WO 2009121288 A1	08-10-2009