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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 July 2022 (14.07.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/149098 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *A01P 7/04* (2006.01)
C07B 43/06 (2006.01) *A01N 43/56* (2006.01)
C07B 39/00 (2006.01)

(21) International Application Number:
PCT/IB2022/050124

(22) International Filing Date:
08 January 2022 (08.01.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
202121001255 11 January 2021 (11.01.2021) IN

(71) Applicant: **UPL LIMITED** [IN/IN]; UPL House, 610 B/2, Bandra Village, off Western Express Highway, Bandra-East, Maharashtra, Mumbai 400051 (IN).

(72) Inventors: **PANCHAL, Digish Manubhai**; UPL Limited, UPL House, 610 B/2, Bandra Village, Off Western Express Highway, Bandra-East, Maharashtra, Mumbai 400051 (IN).
DESAI, Jigar Kantilal; UPL Limited, UPL House, 610 B/2, Bandra Village, Off Western Express Highway, Bandra-East, Maharashtra, Mumbai 400051 (IN).

(74) Agent: **MAJUMDAR, Subhatosh** et al.; S. Majumdar & Co., 5, Harish Mukherjee Road, West Bengal, Kolkata 700 025 (IN).

(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).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

WO 2022/149098 A1

(54) Title: PROCESS FOR PREPARATION OF INSECTICIDAL ANTHRANILAMIDES

(57) Abstract: Disclosed herein a convenient process for preparation of insecticidal anthranilamide compounds and intermediate thereof.

TITLE: PROCESS FOR PREPARATION OF INSECTICIDAL ANTHRANILAMIDES

Field of the invention

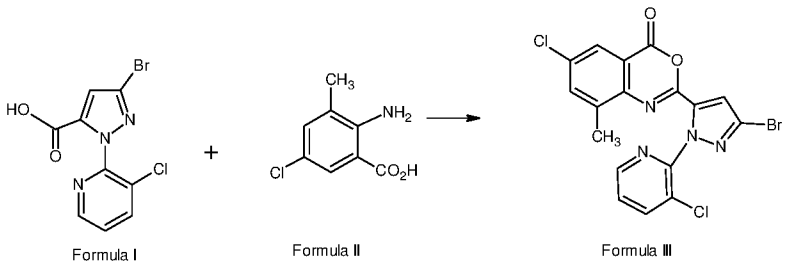
The present invention relates to a convenient one pot process for preparation of insecticidal anthranilamides.

Background of the invention

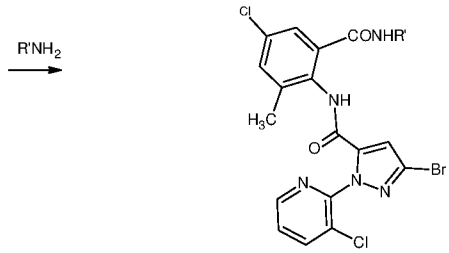
Anthranilamides are a new class of compounds with extremely potent insecticidal activity. These nitrogen-containing aromatic compounds selectively act on targeted ryanodine receptors which form calcium ion channels which are responsible for muscle function in insects.

Examples of insecticidal anthranilamides are cyantraniliprole, chlorantraniliprole, cyclaniliprole, tetrachlorantraniliprole and tetraniliprole. Chlorantraniliprole is a highly potent and selective activator of insect ryanodine receptor with exceptional activity on a broad range of Lepidoptera. It controls a wide range of chewing pests (primarily Lepidoptera, but also some Coleoptera, Diptera and Isoptera species) in a broad range of crops, including fruit, vegetables, vines, cotton, sugar cane, rice and grass.

US7232836 discloses preparation of chlorantraniliprole (E_1, Scheme 1) and US7247647 discloses preparation of cyantraniliprole (E_3, Scheme 2).

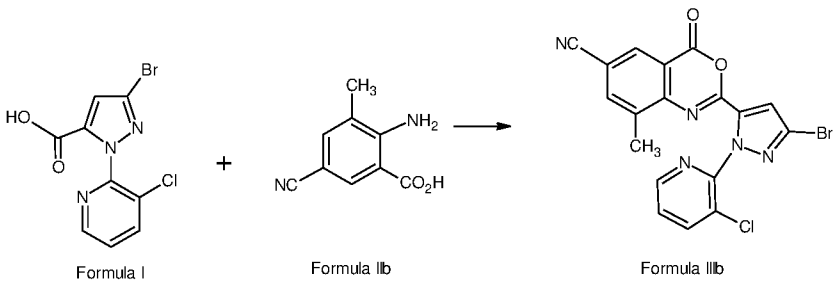


Formula I Formula II Formula III

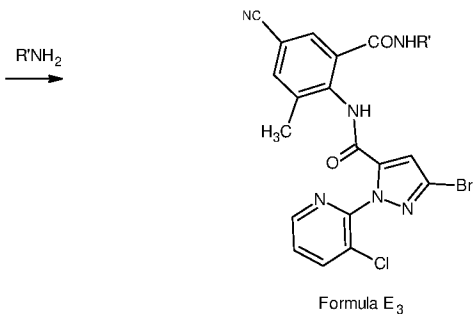


Formula E_1

Scheme 1



Formula I Formula IIb Formula IIIb

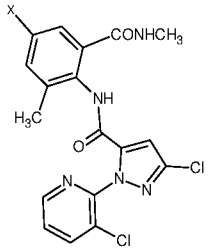


Formula E_3

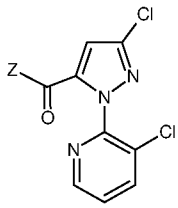
Scheme 2

US8217179 discloses a process for preparation of anthranilamides. Inventors of the present invention noted that the reactions are carried out in hazardous solvents such benzene and toluene and using large volumes of solvent.

It has been observed that preparation of anthranilamides by known processes leads to formation of an undesired compound of Formula E_2 wherein X is chlorine or CN. It has been further noted that the formation compound of Formula B_2 (wherein Z is -OH or chlorine) in the previous steps of the synthesis leads to formation of compound of Formula E_2. Presence of compound of Formula E_2 and /or compound of Formula B_2 lead to the final product of poor quality which do not satisfy the regulatory requirements. Due to the structural similarity of the desired compounds of formula E_1/E_3 with compounds of Formula E_2, it is very difficult to separate those compounds.



Formula E_2



Formula B_2

There is still a need for cost effective and improved production process for anthranilamide compounds that overcomes the above-mentioned drawbacks. Inventors of the present invention noted that carrying out the reactions in one pot using specific solvent system that minimizes side reactions, reduces environmental pollution and increases the process efficiency.

Objects of the Invention

It is an object of the present invention to provide a one pot process for preparation of anthranilamide compounds.

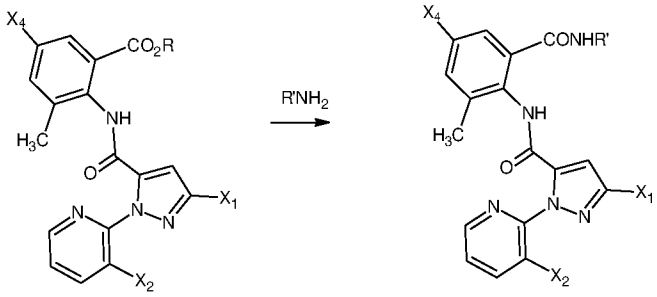
It is another object of the present invention to provide a convenient one pot process for the preparation of anthranilamide compound free from certain impurities.

It is another object of the present invention to provide an environmentally friendly and cost-effective process for the preparation of chlorantraniliprole free of certain impurities.

Summary of the Invention

In one aspect the present invention provides a process for the preparation of an anthranilamide compound of Formula E comprising reacting compound of Formula

D with $R'NH_2$ wherein R' = a lower alkyl group or cycloalkyl to form anthranilamide compound of Formula E; wherein the reaction is carried out in a halogenated hydrocarbon solvent (Scheme 3).



Formula D Formula E

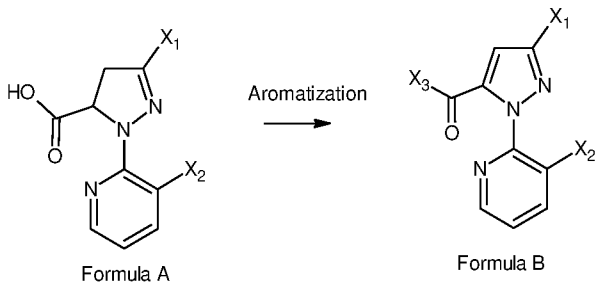
In another aspect, the present invention provides a one pot process for the preparation of an anthranilamide compound of Formula E comprising the steps of:

i) subjecting a compound of Formula A (3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a halogenating agent to form a compound of Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) wherein X_1, X_2 and X_3 are halogens which are same or different;

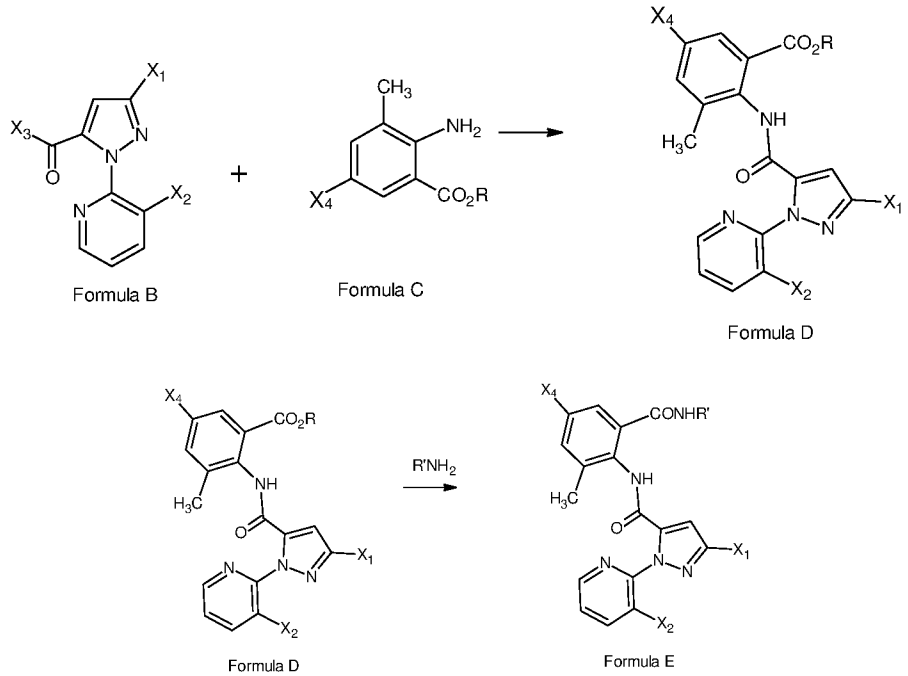
ii) reacting the compound of Formula B with a compound of Formula C wherein X_4= halogen or CN and R = a lower alkyl group to form a compound of Formula D and

iii) reacting the compound of Formula D with a compound of formula $R'NH_2$ wherein R' = a lower alkyl group or cycloalkyl to form compound of Formula E

wherein the process is carried out in a halogenated hydrocarbon solvent (Scheme 3).

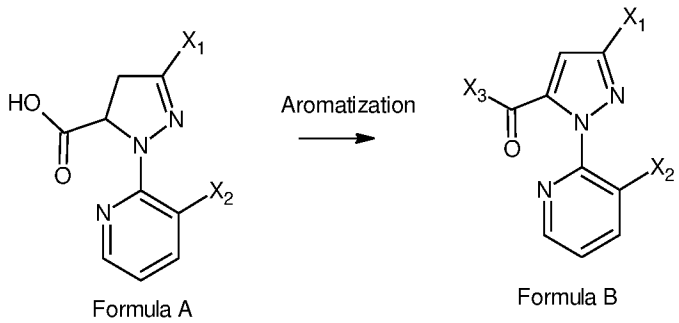


Formula A Formula B



Scheme 3

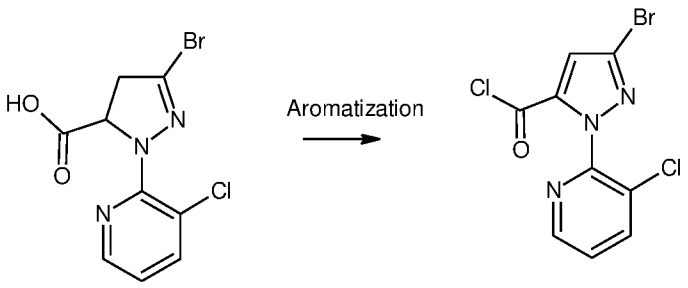
In another aspect the present invention provides a process for the preparation of a compound of Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) said process comprising subjecting compound of Formula A (3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a halogenating agent in a halogenated hydrocarbon solvent wherein X_1, X_2 and X_3 are halogens which are same or different (Scheme 4).



Scheme 4

The present invention further provides a process for preparation of a compound of Formula B_1 (3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride) said process comprising subjecting compound of

Formula A_1 (3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro—1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a halogenating agent in a halogenated hydrocarbon solvent (Scheme 5).



Formula A_1 Formula B_1

Scheme 5

In another aspect the present invention provides chlorantraniliprole substantially free of a compound of formula E_2 wherein X is Cl.

In another aspect the present invention provides cyantraniliprole substantially free of a compound of formula E_2 wherein X is -CN.

A compound of Formula B_1 that is substantially free of a compound of formula B_2 wherein Z is -OH or chlorine.

Brief Description of Drawing

Fig. 1 represents

Chromatogram of 3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride prepared using halogenated hydrocarbon solvent.

Fig. 2 represents Chromatogram of chlorantraniliprole prepared using halogenated hydrocarbon solvent.

Fig. 3 represents Chromatogram of 3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride prepared using toluene solvent

Detailed Description

Those skilled in art will be aware that invention described herein is subject to variations and modifications other than those specifically described. It is to be understood that the invention described herein includes all such variations and modifications. The invention also includes all such steps, features and methods

referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more said steps or features.

Definitions:

For convenience, before further description of the present invention, certain terms employed in the specification, examples are described here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. The terms used throughout this specification are defined as follows, unless otherwise limited in specific instances.

The terms used herein are defined as follows.

As used in the specification and the claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise.

The present disclosure is not to be limited in scope by the specific embodiments described herein, which are intended for the purposes of exemplification only.

As used herein in this context, the expression “substantially free” will be understood to mean that 20% or less, 10% or less, 5% or less, 2% or less, or 1% or less or 0.5% or less of any known or unknown impurity as measured, for example, by HPLC.

The term "purity" means purity as determined by HPLC ("High Pressure Liquid Chromatography").

The term "about" shall be interpreted to mean "approximately" or "reasonably close to" and any statistically insignificant variations therefrom.

As used herein, the terms “comprising” “including,” “having,” “containing,” “involving,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to.

The terms “preferred” and “preferably” refer to embodiments of the invention that may afford certain benefits, under certain circumstances. In an embodiment, the aspects and embodiments described herein shall also be interpreted to replace the

clause "comprising" with either "consisting of" or with "consisting essentially of" or with "consisting substantially of".

As used herein, the term 'lower alkyl' refers to "(C_1-C_6) alkyl" which refers to the radical of saturated aliphatic groups, including straight or branched-chain alkyl groups. A straight-chain or branched chain alkyl has six or fewer carbon atoms in its backbone, for instance, C_1-C_6 for straight chain and C_3-C_6 for branched chain. As used herein, (C_1-C_6) alkyl refers to an alkyl group having from 1 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, 2-methylbutyl and 3-methylbutyl.

As used herein, the term "halogen" refers to chlorine, fluorine, bromine or iodine.

The present invention provides a one pot process for preparation of anthranilamide compound of Formula E. The process avoids isolation of intermediates and each of the steps is carried out in a common solvent system. Using the present invention, it is possible to obtain anthranilamides compound of desired quality in good yield enabling the industrial operation of the process with a solvent selected from halogenated hydrocarbon solvents. It has been noted that the inventive process avoids the formation of undesired compound of Formula E_2 and /or compound of Formula B_2.

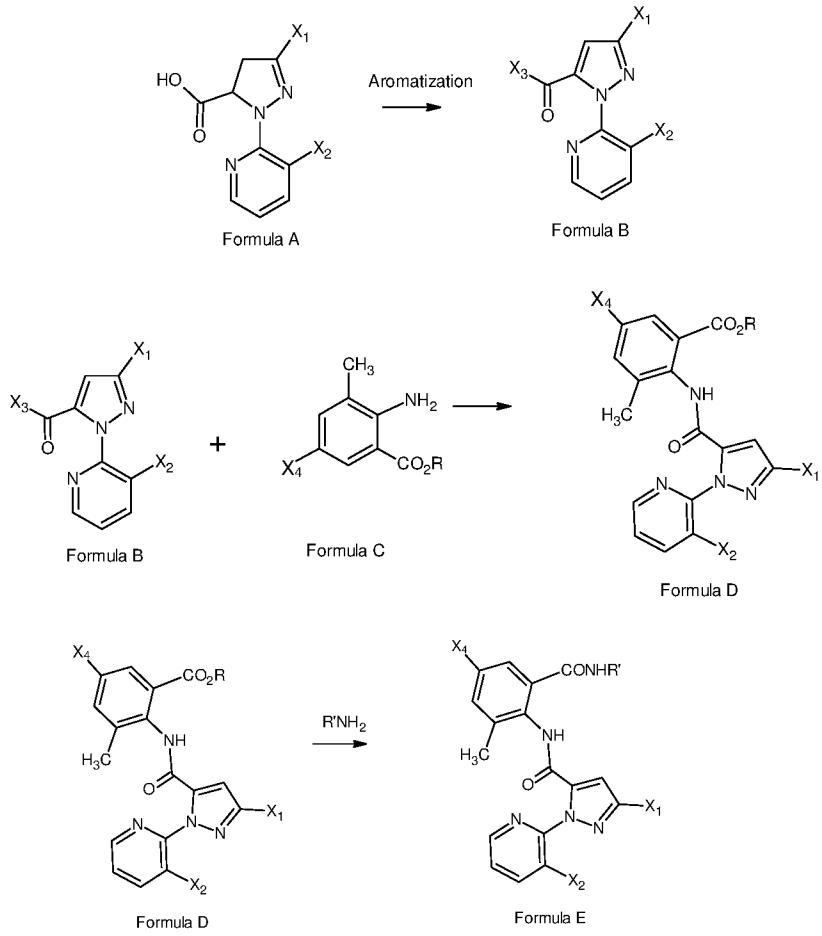
The present invention provides a one pot process for the preparation of an anthranilamide compound of Formula E comprising the steps of:

i) subjecting a compound of Formula A (3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a reagent system comprising a halogenating agent to form compound of Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) wherein X_1, X_2 and X_3 are halogens which are same or different;

ii) reacting compound of Formula B with a compound of Formula C wherein X_4= halogen or CN and R = a lower alkyl group to form a compound of Formula D; and

iii) reacting compound of Formula D with a compound of formula $R'NH_2$ wherein R' = a lower alkyl group or cycloalkyl to form anthranilamide compound of Formula E.

In an embodiment each step of the process is carried out in a halogenated hydrocarbon solvent. In an embodiment the process for preparation of compound E is represented in below Scheme 3.



Scheme 3

The product from each step may be isolated at the end of the step or, more =preferably, the reaction may be proceeded without isolation or purification until the last step.

In an embodiment the compound of Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) is prepared by subjecting the compound of Formula A (3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) to

pyrazoline aromatization using a halogenating agent to form a compound of Formula B wherein X_1, X_2 and X_3 is independently a halogen which is same or different.

With respect to the present invention, pyrazoline aromatization refers to reaction in which 3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid is converted to the corresponding 3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide.

In one preferred embodiment the compound of Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) is prepared by subjecting the compound of Formula A (3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a halogenating agent to form a compound of Formula B wherein X_1, X_2 and X_3 is selected from bromine and chlorine.

In an embodiment the halogenating agent is selected from thionyl chloride, phosgene, oxalyl chloride, phosphorus oxychloride, phosphorus trichloride or phosphorus pentachloride.

In a preferred embodiment the halogenating agent is thionyl chloride.

In an embodiment the molar ratio of pyrazoline to the halogenating agent is from about 1:2 to about 1: 5.

In an embodiment the pyrazoline aromatization is carried out optionally in the presence of a catalyst.

In an embodiment the catalyst is an organic base.

In an embodiment the catalyst is triethylamine or dimethylformamide.

In an embodiment the reaction is carried out at a temperature of 30°-70°C, preferably at a temperature of 30°-65°C.

In an embodiment the halogenated hydrocarbon solvent is selected from dichloromethane, dichloroethane, trichloromethane, chloroform, carbon tetrachloride and halogenated aromatic hydrocarbons.

In an embodiment Formula A (3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) represents a compound wherein X_1 is bromine and X_2 is chlorine.

In an embodiment Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) represents a compound wherein X_1 is bromine and X_2 and X_3 are chlorine.

In an embodiment the compound of Formula B is not isolated or purified.

In an embodiment the present process provides a compound of Formula B substantially free of a compound of Formula B_2.

In the present process the compound of Formula B is reacted with a compound of Formula C wherein X_4= halogen and R = a lower alkyl group to form a compound of Formula D.

In an embodiment the compound of Formula B is reacted with a compound of Formula C wherein X_4=- CN and R = a lower alkyl group to form a compound of Formula D.

In an embodiment the compound of Formula B is reacted with a compound of Formula C in a halogenated hydrocarbon solvent.

In an embodiment the halogenated hydrocarbon solvent is selected from dichloromethane, dichloroethane, trichloromethane, chloroform, carbon tetrachloride and halogenated aromatic hydrocarbons.

In an embodiment the compound of Formula B is reacted with a compound of Formula C optionally in the presence of a base.

In an embodiment the base used is a weak inorganic base.

In an embodiment the base used can be alkali or alkaline earth metal salts.

In an embodiment the base such as sodium carbonate or potassium carbonate can be used in the process.

In an embodiment Formula C represents a compound wherein X_4= Chlorine and R = Methyl group.

In an embodiment Formula C represents a compound wherein X_4= Chlorine and R = Ethyl group.

In an embodiment Formula C represents a compound wherein X_4= -CN and R = Methyl group.

In an embodiment Formula C represents a compound wherein X_4= -CN and R = Ethyl group.

In an embodiment Formula D represents a compound wherein X_1=Bromine, X_2, X_4=Chlorine and R = Methyl group.

In an embodiment Formula D represents a compound wherein X_1=Bromine, X_2, X_4=Chlorine and R = Ethyl group.

In an embodiment Formula D represents a compound wherein X_1=Bromine, X_2=Chlorine, X_4=-CN and R = Methyl group.

In an embodiment Formula D represents a compound wherein X_1=Bromine, X_2=Chlorine, X_4=-CN and R = Ethyl group.

In further embodiment the compound of Formula D is reacted with compound of formula R'NH_2 wherein R' = a lower alkyl group to form anthranilamide compound of Formula E.

In an embodiment Formula E represent a compound wherein X_1=Bromine, X_2, X_4=Chlorine and R' =Methyl.

In an embodiment Formula E represent a compound wherein X_1=Bromine, X_2=Chlorine, X_4=-CN and R' =-Methyl.

In an embodiment, the reaction of compound of Formula D with a compound of formula R'NH_2 is carried out by purging methyl amine gas.

In an embodiment, the reaction is carried out by using methyl amine aqueous solution.

In an embodiment the present invention provides a one pot process for the preparation of chlorantraniliprole of Formula E_1 said process comprising:

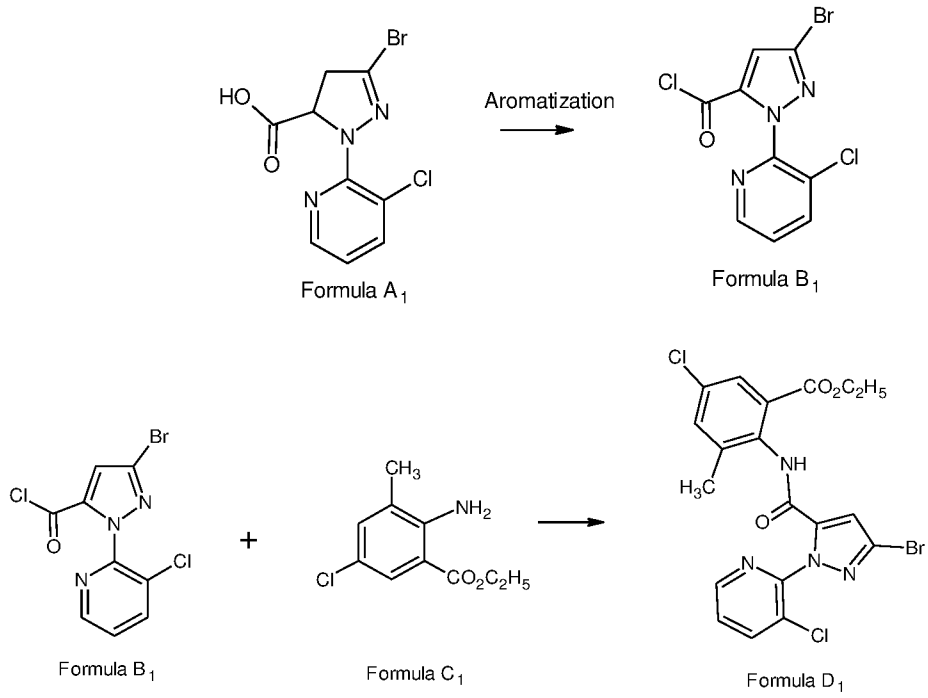
reacting compound of Formula D_1 with methyl amine in a halogenated hydrocarbon solvent to form chlorantraniliprole of Formula E_1.

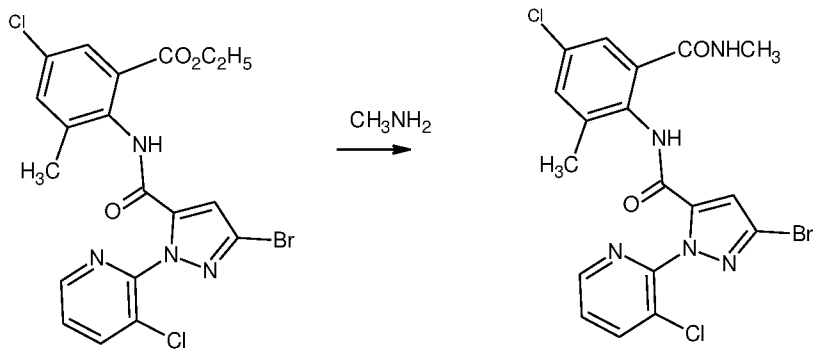
In an embodiment the present invention provides a one pot process for the preparation of chlorantraniliprole of Formula E_1 said process comprising the steps of:

i) subjecting compound of Formula A_1 to pyrazoline aromatization using a halogenating agent to form compound of Formula B_1;

ii) reacting compound of Formula B_1 with a compound of Formula C_1 to form a compound of Formula D_1; and

iii) reacting compound of Formula D_1 with methyl amine to form chlorantraniliprole of Formula E_1 wherein each of the steps is carried out in a halogenated hydrocarbon solvent (Scheme 6).



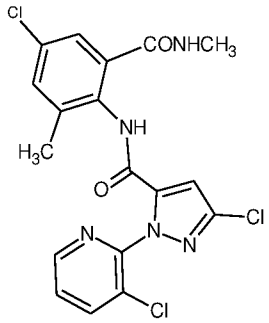


Formula D_1 Formula E_1

Scheme 6

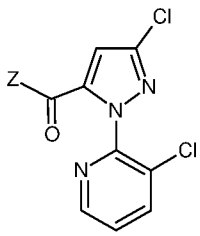
In an embodiment the present invention provides chlorantraniliprole substantially free of a compound of formula E_2.

In an embodiment the present invention provides chlorantraniliprole that contains less than 1.0 % by weight of a compound of formula E_2.



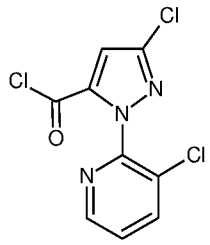
Formula E_2

In an embodiment the present invention provides chlorantraniliprole substantially free of a compound of formula B_2 wherein Z is -OH or chlorine.



Formula B_2

In an embodiment the present invention provides chlorantraniliprole substantially free of a compound of formula B_3 ((3-chloro-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride).



Formula B_3

In an embodiment the present invention provides chlorantraniliprole that contains less than 1.0% by weight of a compound of formula B_3.

In an embodiment the present invention provides cyantraniliprole that contains less than 1.0% by weight of a compound of formula B_3.

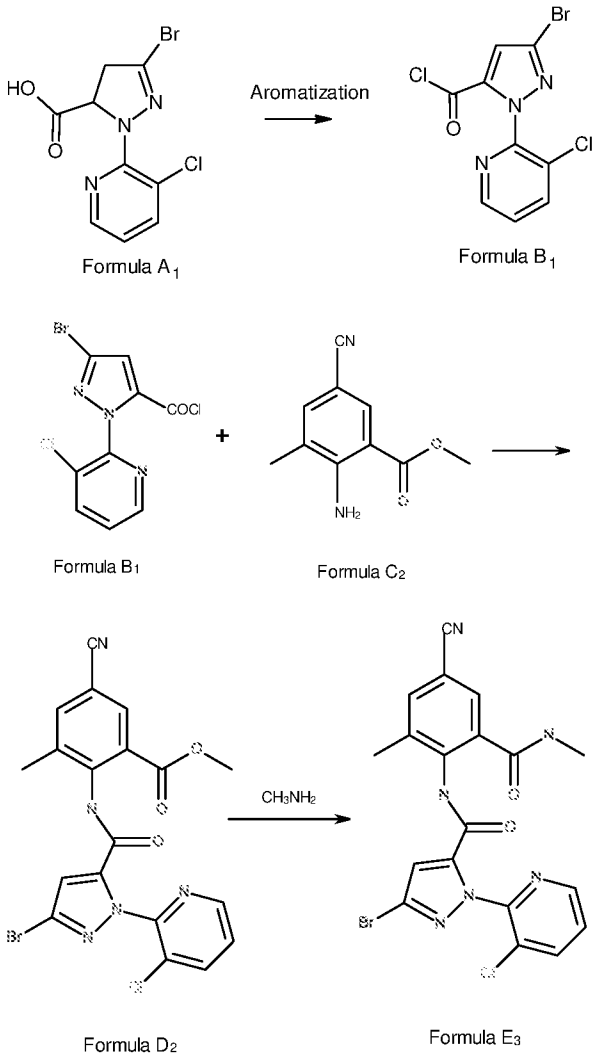
In an embodiment the present invention provides a one pot process for the preparation of cyantraniliprole of Formula E_3 said process comprising:
reacting compound of Formula D_2 with methyl amine in a halogenated hydrocarbon solvent to form cyantraniliprole of Formula E_3.

In an embodiment the present invention provides a one pot process for the preparation of cyantraniliprole of Formula E_3 said process comprising the steps of:

i) subjecting compound of Formula A_1 to pyrazoline aromatization using a halogenating agent to form compound of Formula B_1;

ii) reacting compound of Formula B_1 with a compound of Formula C_2 to form a compound of Formula D_2; and

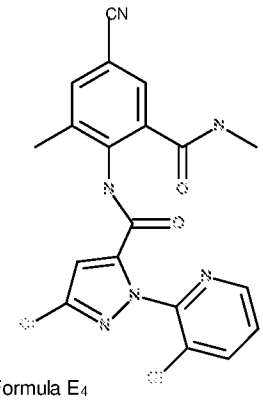
iii) reacting compound of Formula D_2 with methyl amine to form cyantraniliprole of Formula E_3 wherein each of the steps is carried out in a halogenated hydrocarbon solvent (Scheme 7).



Scheme 7

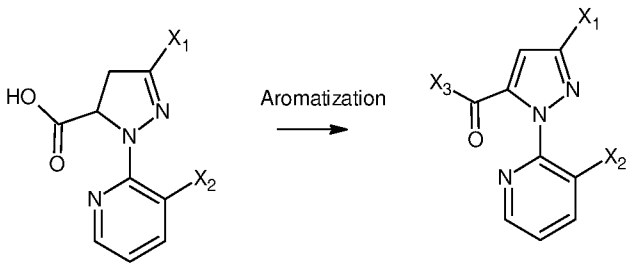
In an embodiment the present invention provides cyantraniliprole substantially free of a compound of formula E_4.

In an embodiment the present invention provides cyantraniliprole that contains less than 1.0 % by weight of a compound of formula E_4.



Formula E4

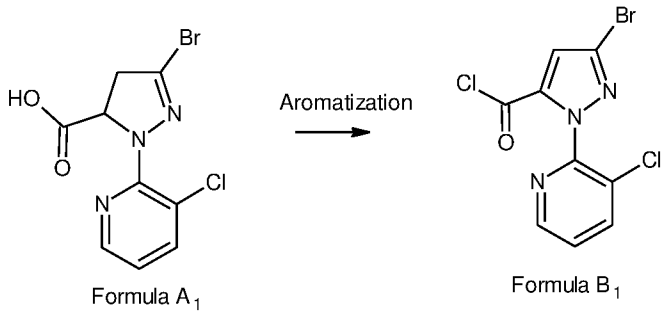
The present invention provides a process for the preparation of a compound of Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) said process comprising subjecting compound of Formula A (3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a halogenating agent in a halogenated hydrocarbon solvent wherein X_1, X_2 and X_3 are halogens which are same or different (Scheme 4).



Formula A Formula B

Scheme 4

The present invention further provides a process for preparation a compound of Formula B_1 (3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride) said process comprising subjecting compound of Formula A_1 (3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a halogenating agent in a halogenated hydrocarbon solvent (Scheme 5).



Scheme 5

In an embodiment the present invention provides a compound of Formula B_1 that is substantially free of a compound of formula B_2.

In an embodiment the present invention provides a compound of Formula B_1 that contains less than 1.0% by weight of a compound of formula B_3.

In an embodiment the present invention provides a process for preparation of compound of Formula B_1 in conditions that are not favourable for the formation of a compound of formula B_2.

In an embodiment the halogenating agent is selected from thionyl chloride, phosgene, oxalyl chloride, phosphorus oxychloride, phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride.

In a preferred embodiment the halogenating agent is thionyl chloride.

In an embodiment the molar ratio of pyrazoline to halogenating agent is from about 1:2 to about 1: 5.

In an embodiment the pyrazoline aromatization is carried out optionally in the presence of a catalyst.

In an embodiment the catalyst is an organic base.

In an embodiment the catalyst is triethylamine or dimethylformamide.

In an embodiment the reaction is carried out at a temperature of 30°-70°C, preferably at a temperature of 30°-65°C.

In an embodiment halogenated hydrocarbon solvent is selected from dichloromethane, dichloroethane, trichloromethane, chloroform, carbon tetrachloride and halogenated aromatic hydrocarbons.

In an embodiment the halogenated hydrocarbon solvent is dichloromethane.

In an embodiment Formula B (3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide) according to the present invention that is substantially free of a compound of formula B2 may be used for preparing high purity insecticidal anthranilamides.

In an embodiment compound of Formula A_1 (3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro—1H-pyrazole-5-carboxylic acid) is prepared by processes known in the art.

In an embodiment 3 compound of Formula A_1 is prepared by treating ethyl 2-(3-chloro-2-pyridinyl)-5-oxo-3-pyrazolidinecarboxylate with phosphorous oxybromide to obtain ethyl 3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate followed by hydrolysis.

In an embodiment hydrolysis of ethyl 3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate is performed by an alkali optionally in presence of a solvent.

In an embodiment the present invention provides an insecticidal composition comprising chlorantraniliprole or cyantraniliprole produced according to present inventive process as described herein and agrochemically acceptable excipients.

In an embodiment the present invention provides a method of controlling insects comprising applying to the pests or to their locus an insecticidally effective amount of chlorantraniliprole or cyantraniliprole produced according to present inventive process as described herein.

Advantages of the present invention:

a) the reaction is carried out in one pot without isolation of intermediates;
b) the reaction is carried out in a halogenated hydrocarbon solvent system;

c) the reaction condition allows the preparation of anthranilamides that are free of certain impurities which are difficult to eliminate from the final reaction mass;
d) the reaction leads to the formation of anthranilamides with high purity required to meet regulatory standards; and
e) one pot process and single solvent system makes the process cost effective and has reduction in effluent.

Further advantages and other parameters of the present invention is illustrated by the below given examples. However, the scope of the present invention is not limited by the examples in any manner. It will be appreciated by any person skilled in this art that the present invention includes aforesaid examples and further can be modified and altered within the technical scope of the present invention.

EXAMPLES:

Example 1

Preparation of 3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride (B_1)

Ethyl 2-(3-chloro-2-pyridinyl)-5-oxo-3-pyrazolidinecarboxylate (1.27 Kg) and acetonitrile (4.45 Kg) were charged in a reaction kettle. Phosphorus oxybromide (0.941 Kg) was added to the mixture dropwise at 25-30°C. After the complete addition, the reaction mass was stirred at 68-70°C for 2 to 3 hours for completion of the reaction. Acetonitrile was then recovered, and the reaction mass was cooled to 30°C. Water (6.2 Kg) was added to the mass and the pH was adjusted between 7.5 to 8 using 20% sodium carbonate solution (3.1 Kg). Dichloromethane (7.2 Kg) was then added and stirred, and the layers were separated. The organic layer was washed with water, dried and solvent was evaporated to get ethyl 3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (1.544 Kg; Purity 97% by HPLC).

Ethyl 3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (1.544 Kg) was charged in a reaction kettle. A solution of dilute caustic lye (water 4.64 Kg, caustic lye 0.467 Kg) was added at 35-40°C. The reaction mass was then stirred for 3 hours. After completion of the reaction, ethanol was recovered from the reaction mass and dichloromethane (7.416 Kg) and water (0.620 Kg) were

added at 25-30°C and the mixture was stirred for 1 hour at the same temperature. pH of reaction mass was then adjusted to 2.0 to 2.5 using 10% hydrochloric acid (1.730 Kg). Organic layer was separated, washed and dried to get the solution of 3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid (8.598 Kg -1.300Kg in 7.384 Kg of dichloromethane). Dichloromethane (0.86 Kg) and DMF (0.0040 Kg) were added to the solution at 25-30°C under nitrogen atmosphere. A solution of thionyl chloride (1.17 Kg) in dichloromethane (1.17 Kg) was added dropwise to the reaction mass at 35-40°C and then maintained for 2-3 hours at 38-40°C. After completion of the reaction, thionyl chloride and dichloromethane were recovered completely. A 25% solution of 3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride was prepared by addition of dichloroethane (4.800 Kg) (HPLC analysis: B_1 : 92%; compound of formula B_3: 0.30%; Figure 1).

Example 2

Preparation of 2-[(3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl] amino]-5-chloro-3-methyl-, Benzoic acid, methyl ester

A reaction kettle was charged with 21% solution of methyl 2-amino-5-chloro-3-methylbenzoate in dichloroethane (2.538 Kg). The reaction mass was heated to 65-70°C within 1 hr. A 25% solution of 3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride in dichloroethane (4.7 Kg) was added to the mixture in 5-6 hours under nitrogen atmosphere and stirred until completion of the reaction. The reaction mass was cooled to 40-50°C. Water (1.32 Kg) was then added to the reaction mass and organic layer was separated from the aqueous layer. The organic layer was washed with dilute caustic solution (1.32 Kg of 1% solution) and finally with water (1.32 Kg). Solvent was evaporated from the organic layer partially until a 15% solution of 2-[(3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl] carbonyl]amino]-5-chloro-3-methyl-, Benzoic acid, methyl ester (8.530 Kg) was obtained (yield = 96% and purity = 94%).

Example 3 Preparation of chlorantraniliprole (E_1):

A reaction kettle was charged with a 15% solution of 2-[(3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-chloro-3-methyl-, Benzoic acid, methyl ester in dichloroethane (8.530 Kg). The reaction mass was cooled to 15-

20°C and then purged with methyl amine gas (0.700 Kg) for about 5-7 hours (at a rate of 0.100 to 0.150 Kg/Hr). The mass was then purged with nitrogen for 1-2 hours and the solvent was evaporated partially. The product was then filtered and washed with acetonitrile (1.27 Kg). A slurry of the wet cake was prepared in water (4.57 Kg) at 45-50°C and stirred for 1hour. The product was filtered and washed with water (1.5 Kg) to get Chlorantraniliprole (E_1: 1.00 Kg; purity: 96.8%; compound of formula B_3 :0.053; compound of formula E_2: 0.295 %; Figure 2).

Example 4

Comparative Example: Preparation of 3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride (B_1) using toluene as solvent

A reaction kettle was charged with a solution of 3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro—1H-pyrazole-5-carboxylic acid in toluene (8.5 Kg -1.300Kg in 7.24 Kg of toluene). Toluene (0.86 Kg) and DMF (0.0040 Kg) were further added to the solution at 25-30°C under nitrogen atmosphere. A solution of thionyl chloride (1.17 Kg) in toluene (1.17 Kg) was added dropwise to the reaction mass at 25-30°C and the reaction mass was then heated to reflux for 2-3 hours. After the completion of the reaction, the reaction mass was concentrated under vacuum to get the product (4.800 Kg; Purity: 88.7%; compound of formula B_3: 1.13%, Figure 3).

Example 5

Preparation of 3-Bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride (B_1)

Ethyl 2-(3-chloro-2-pyridinyl)-5-oxo-3-pyrazolidinecarboxylate (100g) and acetonitrile (350g) were charged in a reaction kettle. Phosphorus oxybromide (74.1g) was added to the mixture dropwise at 25-30°C. After the addition was complete, the reaction mass was stirred at 68-70°C for 2 to 3 hours for completion of the reaction. Acetonitrile was then recovered, and the reaction mass was cooled to 30°. Water (488 g) was added to the mass and the pH was adjusted to 8.5 to 8.9 using 20% sodium carbonate solution (244 g). Dichloromethane was then added and stirred and layers were separated. The organic layer was washed with water, dried and solvent evaporated to get ethyl 3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (121.6g; Purity 98.1% by HPLC).

Ethyl3-bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (121.6g) and 365.5 gm Water were charged in a reaction kettle. A solution of dilute caustic lye (36.8 g) was added at 35-40°C. The reaction mass was then stirred for 3 hours. After completion of the reaction, ethanol was recovered from the reaction mass and dichloromethane (584 g) and water were added at 25-30°C and the mixture was stirred for 1 hour at the same temperature. pH of reaction mass was then adjusted to 2.0 to 2.5 using 10% hydrochloric acid (136g). Organic layer was separated, washed and dried to get the solution of 3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro—1H-pyrazole-5-carboxylic acid (677g) DMF (0.315g) was added to the solution at 25-30°C under nitrogen atmosphere. A solution of thionyl chloride (92g) in dichloromethane (92g) was added dropwise to the reaction mass at 35-40°C and then maintained for 2-3 hours at 38-40°C. After completion of the reaction, thionyl chloride and dichloromethane were recovered completely. A 25% solution of 3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride (115 g) was prepared by addition of dichloroethane (263g) (HPLC analysis: B_1 : 91.9%; compound of formula B_3: 0.29%).

Example 6: Preparation of Chlorantraniliprole (E_1)

A reaction kettle was charged with a solution of methyl 2-amino-5-chloro-3-methylbenzoate in dichloroethane (140g). The reaction mass was heated to 65-70°C within 1 hr. A solution of 3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride in dichloroethane (212 g) was added to the mixture in 3-4 hours under nitrogen atmosphere and stirred until completion of the reaction. The reaction mass was cooled to 40-50°C. Water (91 g) was then added to the reaction mass and organic layer was separated from the aqueous layer. The organic layer was washed with dilute caustic solution (1% solution) and finally with water (91 g). Solvent was evaporated from the organic layer partially until a 15% solution of 2-[(3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-chloro-3-methyl-, Benzoic acid, methyl ester (464 g, 15% solution) was obtained (yield = 96%). The reaction mass was cooled to 15-20°C and then purged with methyl amine gas (38g) for about 4-5 hours (at a rate of 0.100 to 0.150 Kg/Hr). The mass was then purged with nitrogen for 1-2 hours and the solvent was evaporated partially. The product was then filtered and washed with acetonitrile (70g). A slurry of the wet cake was prepared in water (242g) at 45-50°C and stirred for 1hour. The

product was filtered and washed with water (90g) to get Chlorantraniliprole (E_1: 54.3g; purity: 96.6%; compound of formula B_3 :0.11%; compound of formula E_2: 0.28 %)

Example 7: Preparation of 2-[(3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl] carbonyl]amino]-5-cyano-3-methyl-, Benzoic acid, methyl ester

Dichloroethane (870 gm) and methyl 2-amino-5-cyano-3-methylbenzoate (85.9 g) were charged into a reaction kettle. The reaction mass was heated to 65-70°C within 1 hr. A 25% solution of 3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride in dichloroethane (390 g in 191 gm of dichloroethane) was added to the mixture in 5-6 hours under nitrogen atmosphere and stirred until completion of the reaction. Dichloroethane was recovered from the reaction mass and acetonitrile (260g) was added at 40-50°C and the mixture was stirred for 1 hour at the same temperature then cooled to 25-30°C. The product was filtered and washed with acetonitrile. A slurry of the wet cake was prepared in 5% Sodium carbonate solution (261 g) at 25-30°C and stirred for 1hour then filtered and washed with water (174 g) to get 2-[(3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-cyano-3-methyl-, Benzoic acid, methyl ester (160g).

Example 8: Preparation of Cyantraniliprole (E_3)

Dichloroethane (1072 gm) and 2-[(3-bromo-1-(3-chloro-2-pyridinyl)-1*H*-pyrazol-5-yl]carbonyl]amino]-5-cyano-3-methyl-, Benzoic acid, methyl ester (160 g) were charged into a reaction kettle. The reaction mass was cooled to 15-20°C and then purged with methyl amine gas (66 g) for about 5-7 hours (at a rate of 0.100 to 0.150 Kg/Hr). The mass was then purged with nitrogen for 1-2 hours and dichloroethane was recovered from the reaction mass and acetonitrile (400 g) was added at 40-50°C and the mixture was stirred for 1 hour at the same temperature. The reaction mass was cooled to 25-30°C. The product was then filtered and washed with acetonitrile and water to get Cyantraniliprole (102 g; purity: 97.56% compound of formula E_4: 0.45%).

CLAIMS:

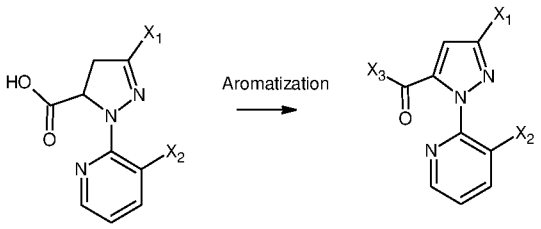
1. A process for the preparation of an anthranilamide compound of Formula E, said process comprising:

i) subjecting a compound of Formula A to pyrazoline aromatization using a halogenating agent to form a compound of Formula B (wherein X_1, X_2 and X_3 are halogens which are same or different);

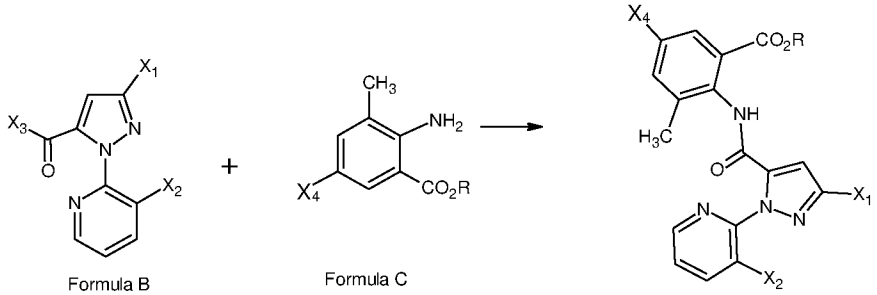
ii) reacting the compound of Formula B with a compound of Formula C wherein X_4 is halogen or CN and R is a lower alkyl group to form a compound of Formula D; and

iii) reacting a compound of Formula D with a compound of formula $R'NH_2$ wherein R' is a lower alkyl group or cycloalkyl to form the anthranilamide compound of Formula E;

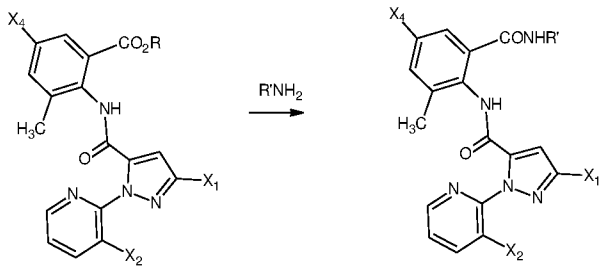
wherein each step of the process is carried out in a halogenated hydrocarbon solvent.



Formula A Formula B

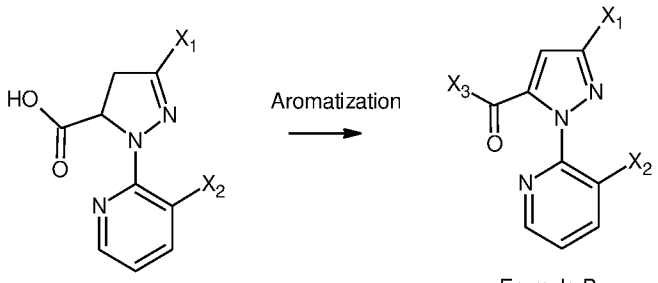


Formula B Formula C Formula D



Formula D Formula E

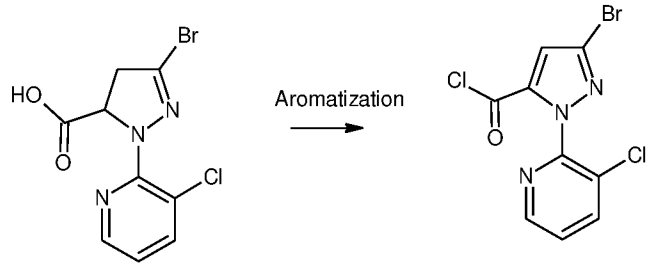
2. The process according to claim 1, wherein Formula E represent a compound wherein X_1=Bromine, X_2, X_4=Chlorine and R' =Methyl.
3. The process according to claim 1, wherein Formula E represent a compound wherein X_1=Bromine, X_2=Chlorine, X_4=-CN and R' = -Methyl.
4. The process according to claim 1 wherein said halogenating agent is selected from thionyl chloride, phosgene, oxalyl chloride, phosphorus oxychloride, phosphorus trichloride and phosphorus pentachloride.
5. The process according to claim 1 wherein said halogenated hydrocarbon solvent is selected from dichloromethane, dichloroethane, trichloromethane, chloroform, carbon tetrachloride and halogenated aromatic hydrocarbons.
6. The process as claimed in claim 1 is carried out at temperature in the range from 30 to 70°C.
7. The process according to claim 1 wherein the compound of Formula A is 3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid and compound of formula of B is 3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide.
8. The process according to claim 1 wherein the compound of Formula C represents a compound wherein X_4= Chlorine and R = Methyl.
9. The process according to claim 1 wherein the compound of Formula C represents a compound wherein X_4= -CN and R = Methyl.
10. A process for preparation of a compound of Formula B comprising subjecting a compound of Formula A to pyrazoline aromatization using a halogenating agent in a halogenated hydrocarbon solvent wherein X_1, X_2 and X_3 is halogen selected from bromine and chlorine.



Formula A Formula B

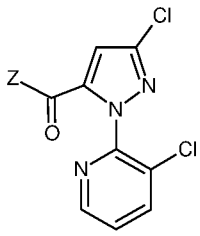
11. The process according to claim 10 wherein the compound of formula A is 3-Halo-1-(3-halo-2-pyridinyl)-4,5-dihydro-1H-pyrazole-5-carboxylic acid and the compound of formula B is 3-Halo-1-(3-halo-2-pyridinyl)-1H-pyrazole-5-carbonyl halide.

12. The process according to claim 10 wherein said process comprises preparation of a compound of Formula B_1 (3-bromo-1-(3-chloro-2-pyridinyl)-1H-pyrazole-5-carbonyl chloride) by subjecting a compound of Formula A_1 (3-Bromo-1-(3-chloro-2-pyridinyl)-4,5-dihydro—1H-pyrazole-5-carboxylic acid) to pyrazoline aromatization using a halogenating agent in a halogenated hydrocarbon solvent.



Formula A_1 Formula B_1

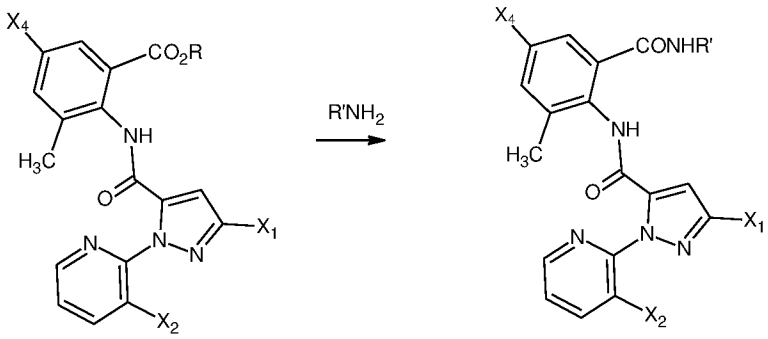
13. A compound of Formula B_1 substantially free of a compound of formula B_2 wherein Z is -OH or chlorine.



Formula B_2

14. A compound of Formula B_1 according to claim 13, containing less than 1.0 % by weight of a compound of formula B_2 wherein Z is chlorine.

15. An anthranilamide compound of Formula E substantially free from compound of formula B_2 wherein Z is -OH or chlorine.
16. An anthranilamide compound of Formula E according to claim 15, containing less than 1.0 % by weight of a compound of formula B_2 wherein Z is chlorine.
17. An anthranilamide of Formula E according to claim 15 is chlorantraniliprole or cyantraniliprole that is substantially free from compound of formula B_2.
18. Chlorantraniliprole containing less than 1.0 % by weight a compound of formula E_2.
19. Cyantraniliprole containing less than 1.0 % by weight a compound of formula E_4.
20. A process for the preparation of an anthranilamide compound of Formula E comprising reacting a compound of Formula D with a compound of formula $R'NH_2$ wherein R' = a lower alkyl group or cycloalkyl to form anthranilamide compound of Formula E; wherein the reaction is carried out in a halogenated hydrocarbon solvent.



Formula D Formula E

21. A process for the preparation of an anthranilamide compound of Formula E according to claim 20, wherein said halogenated hydrocarbon solvent is selected from dichloromethane, dichloroethane, trichloromethane, chloroform, carbon tetrachloride and halogenated aromatic hydrocarbons.
22. An insecticidal composition comprising chlorantraniliprole or cyantraniliprole produced according to process of claim 1 and agrochemically acceptable excipients.
23. A method of controlling insects comprising applying to the pests or to their locus an insecticidally effective amount of chlorantraniliprole or cyantraniliprole produced according to process of claim 1.

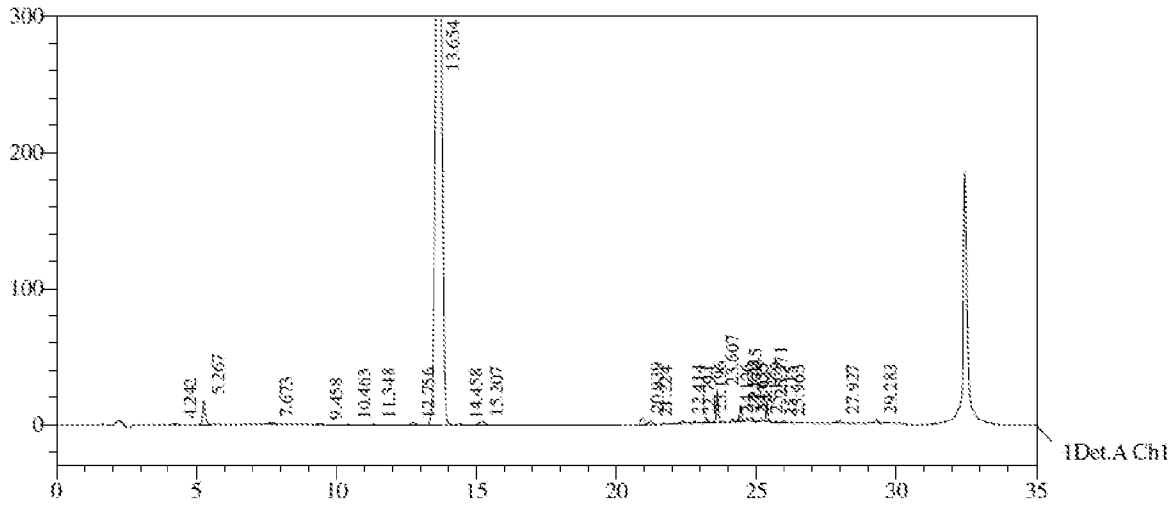


Figure 1

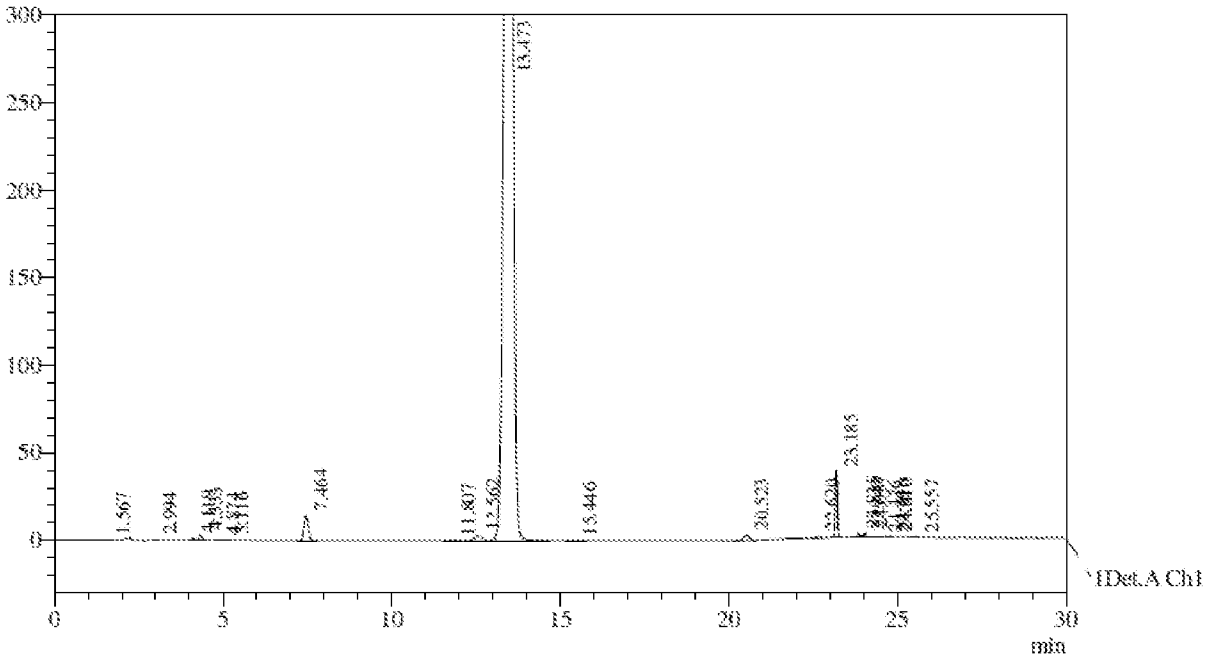


Figure 2

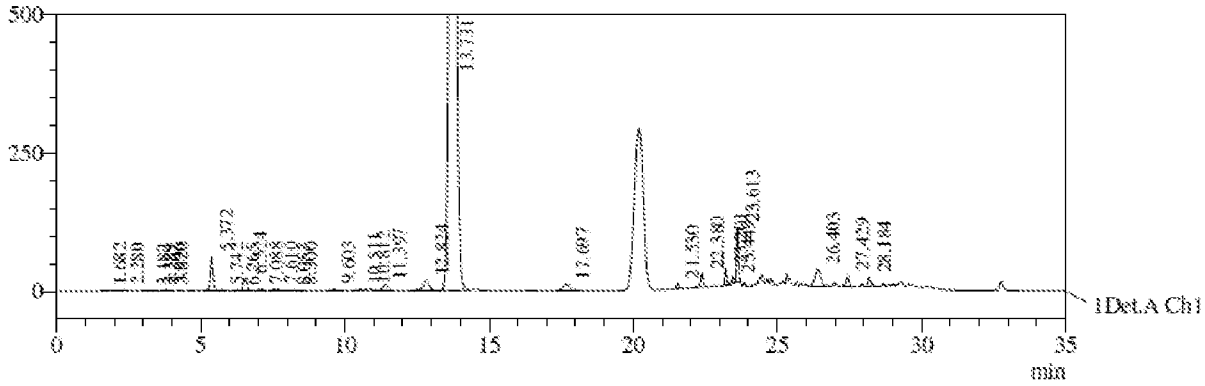

500
250
0
0
5
10
15
20
25
30
35
min
13.731
17.697
23.613
26.403
27.429
28.184
1 Det.A Ch1

Figure 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2022/050124

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/04 (2006.01) C07B 43/06 (2006.01) C07B 39/00 (2006.01) A01P 7/04 (2006.01) A01N 43/56 (2006.01)

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)

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)

STN Registry & Caplus: Searched structures Formula B and D and/or Keywords: ?pur?

Applicant(s)/Inventor(s) name searched in internal databases provided by IP Australia.

Google & EspaceNet keyword search: Applicant/Inventor and/or Keywords: insecticides, anthranilamide, chlorantraniliprole, cyantraniliprole, process, method, aromatization

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] 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
22 March 2022	22 March 2022

Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Aidan Smyth AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262832625

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/IB2022/050124**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 8217179 B2 (SINOCHEM CORP. and SHENYANG RESEARCH INSTITUTE OF CHEMICAL INDUSTRY) 10 July 2012 Abstract, column 1, column 8, column 11, Example 1, Example 2	13, 15, 17, 22, 23
A	CN 105037324 A (JIANGSU FLAG CHEMICAL INDUSTRY Co Ltd) 07 December 2018 Abstract of translated document, para. [0025] pg. 10	1-23
X	US 7232836 B2 (E. I. DU PONT DE NEMOURS AND COMPANY) 19 June 2007 Abstract, Scheme 1, Scheme 2, Test A-L	13-19, 22, 23
X	US 7247647 B2 (E. I. DU PONT DE NEMOURS AND COMPANY) 24 July 2007 Abstract, Scheme 1, Scheme 4, Example A-E, para. 1 column 46	13-19, 22, 23
P,X	WO 2021033172 A1 (EUROFINS ADVINUS LIMITED) 25 February 2021 Abstract, Scheme 4, Scheme 7.2, Scheme 8; steps 4 and 5	1-23

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2022/050124**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 8217179 B2	10 July 2012	US 2010317864 A1	16 Dec 2010
		US 8217179 B2	10 Jul 2012
		CN 101550130 A	07 Oct 2009
		CN 101550130 B	07 Nov 2012
		CN 101945861 A	12 Jan 2011
		CN 101945861 B	21 Nov 2012
		WO 2009121288 A1	08 Oct 2009
CN 105037324 A	07 December 2018	CN 105037324 A	11 Nov 2015
		CN 105037324 B	07 Dec 2018
US 7232836 B2	19 June 2007	None	
US 7247647 B2	24 July 2007	None	
WO 2021033172 A1	25 February 2021	WO 2021033172 A1	25 Feb 2021

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.