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589058

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APPLICATION NUMBER: 61/736,820

FILING DATE: December 13, 2012

RELATED PCT APPLICATION NUMBER: PCT/US13/74522

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS US61/736,820



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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	68011-US-PSP
		Application Number	
Title of Invention	AN IMPROVED PROCESSES FOR THE ISOLATION OF 4-AMINO-3-CHLORO-6-(4-CHLORO-2-FLUORO-3-METHOXYPHENYL)PYRIDINE-2-CARBOXYLIC ACID		
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Application Information:

Title of the Invention	AN IMPROVED PROCESSES FOR THE ISOLATION OF 4-AMINO-3-CHLORO-6-(4-CHLORO-2-FLUORO-3-METHOXYPHENYL)PYRIDINE-2-CARBOXYLIC ACID		
Attorney Docket Number	68011-US-PSP	Small Entity Status Claimed	<input type="checkbox"/>
Application Type	Provisional		
Subject Matter	Utility		
Suggested Class (if any)		Sub Class (if any)	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	68011-US-PSP
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	Application Number	
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Organization Name	Dow AgroSciences LLC
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Signature	/Robert Chang/	Date (YYYY-MM-DD)	2012-12-13
First Name	Robert	Last Name	Chang
		Registration Number	63753

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

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Title of Invention

AN IMPROVED PROCESSES FOR THE ISOLATION OF 4-AMINO-3-CHLORO-6-(4-CHLORO-2-FLUORO-3-METHOXYPHENYL)PYRIDINE-2-CARBOXYLIC ACID

Attorney Docket Number (if applicable)

68011-US-PSP

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

No.

Yes, the name of the U.S. Government agency and the Government contract number are:

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Applicant claims small entity status under 37 CFR 1.27

- Yes, applicant qualifies for small entity status under 37 CFR 1.27
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First Name	Robert	Last Name	Chang	Registration Number (If appropriate)	63753

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AN IMPROVED PROCESSES FOR THE ISOLATION OF 4-AMINO-3-CHLORO-6-(4-CHLORO-2-FLUORO-3-METHOXYPHENYL)PYRIDINE-2-CARBOXYLIC ACID

Background

5 Provide herein are improved processes for the preparation and isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid.

U.S. Patent 7,314,849 (B2) describes *inter alia* the preparation 4-amino-3-chloro-6-(poly-substitutedphenyl)pyridine-2-carboxylic acids and their use as herbicides, including 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid. The
10 parent acids are conveniently prepared by the hydrolysis of either the corresponding esters or the corresponding protected *N*-acetylated esters. However, when the sodium salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid resulting from hydrolysis is neutralized with an inorganic acid such as hydrochloric acid, a very fine precipitate is formed which is difficult to filter. While use of acetic acid improves upon this
15 method, the precipitate is still difficult to process, giving both slurries that are difficult to agitate and crystals that are difficult to filter. In addition, use of acetic acid also can result in product crystals which contain occluded acetic acid, which cannot be removed by reslurrying the product.

It would be advantageous to have a method to neutralize the sodium salt of 4-amino-
20 3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid that would improve the ability to process and handle the resulting 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid.

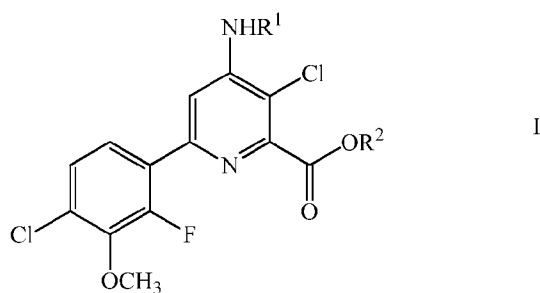
Summary

25 Provided herein are improved processes for the isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid which comprises (a) neutralizing an aqueous solution of an alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid with an excess of 85 – 99 percent formic acid at a temperature from about 45 to about 90 °C to produce an

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aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, (b) cooling the aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid to about 10 to about 25 °C to crystallize the 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, and (c)
5 collecting the crystalline 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid.

Provided herein are also improved processes for the preparation and isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid which comprises (a) contacting an ester of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-
10 methoxyphenyl)pyridine-2-carboxylic acid of Formula I



in which

R¹ represents H or C(O)CH₃, and

R² represents C₁-C₁₂ alkyl or an unsubstituted or substituted C₇-C₁₁ arylalkyl

15 with an aqueous solution of an alkali metal or alkaline earth metal hydroxide in a C₁-C₄ alcohol at a temperature from about 45 to about 100 °C to produce an aqueous alcoholic solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, (b) optionally removing most of the C₁-C₄ alcohol from the aqueous alcoholic solution of the alkali metal or alkaline earth metal salt
20 of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, (c) neutralizing the aqueous solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid with an excess of 85 – 99 percent formic acid at a temperature from about 45 to about 90 °C to produce an
25 aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, (d) cooling the aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-

methoxyphenyl)pyridine-2-carboxylic acid to about 10 to about 25 °C to crystallize the 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, and (e) collecting the crystalline 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid.

5 Detailed Description

The term alkyl and derivative terms such as alcohol, as used herein refer to straight chain or branched chain moieties. Typical C₁-C₄ alkyl groups are methyl, ethyl, propyl, 1-methylethyl, butyl, 1,1-dimethylethyl and 1-methylpropyl. Methyl and ethyl are often preferred.

10 The term "arylalkyl," as used herein, refers to a phenyl substituted alkyl group having a total of 7 to 11 carbon atoms, such as benzyl (–CH₂C₆H₅), 2-methylnaphthyl (–CH₂C₁₀H₇) and 1- or 2-phenethyl (–CH₂CH₂C₆H₅ or –CH(CH₃)C₆H₅). The phenyl group may itself be unsubstituted or substituted with one or more substituents independently selected from halogen, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogenated C₁-C₆ alkyl, halogenated C₁-C₆ alkoxy, C₁-C₆ alkylthio, C(O)OC₁-C₆ alkyl, or where two adjacent substituents are taken
15 together as –O(CH₂)_nO– wherein n=1 or 2, provided that the substituents are sterically compatible and the rules of chemical bonding and strain energy are satisfied.

Alkali metals and alkaline earth metals refer to members of groups 1 and 2 of the periodic table. Preferred alkali metal (group 1) hydroxides are sodium hydroxide and
20 potassium hydroxide. Preferred alkaline earth metal (group 2) hydroxides are magnesium hydroxide and calcium hydroxide.

By neutralizing with formic acid, crystals of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid that are easier to handle are obtained. In the improved process, an aqueous solution of an alkali metal or alkaline earth metal salt of 4-
25 amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid is neutralized with an excess of 85 – 99 percent formic acid at a temperature from about 45 to about 90 °C to produce an aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid. It is often most convenient to add the aqueous solution of an alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-
30 fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid to a preheated large molar excess of formic acid (> 10 times). While concentrations of formic acid from about 85 – 99 percent

are acceptable, better crystallizations occur at higher concentrations of formic acid. Usually, the neutralized mixture is maintained in the temperature range from about 45 to about 90 °C for about 1 hour before cooling. At the lower end of the temperature range, crystal formation may initiate before cooling. After cooling, the crystalline product can be collected by

5 standard procedures such as filtration or centrifugation.

In some embodiments, the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid that is subsequently neutralized is prepared by the hydrolysis / deprotection of esters or protected *N*-acetylated esters of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid. In the initial steps of this process, the ester or protected *N*-acetylated ester of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid is contacted with an aqueous solution of an alkali metal or alkaline earth metal hydroxide in a C₁-C₄ alcohol at a temperature from about 45 to about 100 °C. While only one equivalent of hydroxide is required for each ester and protecting group, it is preferable to employ an excess. Sodium and potassium hydroxide are the preferred alkali metal or alkaline earth metal hydroxides. Methanol is the preferred C₁-C₄ alcohol and the preferred temperature range for this alcohol is from about 45 to about 65 °C.

Once the ester has been hydrolyzed and the protecting group removed, most of the C₁-C₄ alcohol may be removed from the aqueous alcoholic solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid. The C₁-C₄ alcohol is conveniently removed under reduced pressure, leaving a solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid in predominantly water. Depending on the amount of C₁-C₄ alcohol that is employed, this step may be omitted. It is the aqueous solution containing small to negligible amounts of alcohol that is then neutralized and cooled and from which 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid is obtained as crystals as described previously.

The described embodiments and following examples are for illustrative purposes and are not intended to limit the scope of the claims. Other modifications, uses, or combinations with respect to the compositions described herein will be apparent to a person of ordinary skill in the art without departing from the spirit and scope of the claimed subject matter.

EXAMPLES

Example 1.

To a 250 milliliter (mL) flask equipped with a magnetic stirrer, condenser, and N₂ bubbler was added 5.0 gram (g) of methyl 4-(acetylamino)-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate, 16 mL MeOH, and 4 mL of water. A solution of 2.3 g of 50% NaOH in 4 mL of water was added and the mixture was heated to reflux for 2-2.5 hours (hr). The mixture is allowed to cool to 20-25 °C and filtered using Whatman #50 paper. The filtrate was concentrated on the rotovap at about 25 °C to give a crude aqueous solution of 15.2-15.7 g. To a 250 mL flask equipped with a mechanical stirrer, condenser, and N₂ bubbler was added 40 mL of 98% formic acid. The acid was heated to about 50 °C and the aqueous solution was added to the formic acid over 1-2 minutes (min) at 50 °C. After several min, the product began to crystallize from solution. The resulting slurry was maintained at 50 °C for about 1 hr and then allowed to cool to 20-21 °C over 1-1.5 hr. Water (20 mL) was added and the slurry was stirred for 1-2 hr at 20-21 °C. The slurry was filtered using Whatman #50 paper and the wet cake was washed twice with 30 mL of water. After drying, 4.0 g of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid was obtained as a white solid (93.5% yield).

Example 2.

Organically wet methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate solid (253.4 pounds (lb), containing 5.8% toluene and isooctane and 231.7 lb of actual methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate) was loaded into a 300 gallon (gal) metal reaction vessel and the vessel was inerted with nitrogen. Aqueous sodium hydroxide solution (221 lb of 24.4% sodium hydroxide in water) was pumped into the reactor, followed by 199 lb of water. Methanol (52 lb) was pumped into the reactor, and the mixture was stirred and heated to 67-68 °C for 3.25 hr. The reactor contents were then cooled to 25 °C and filtered through a Celite bed (10 lb) on a centrifuge. The filtered solution was transferred as it was filtered into a stirred 500 gal stainless steel reaction vessel containing 98% formic acid (2266 lb) at 50 °C. The neutralized mixture was slowly cooled to 20 °C at a rate of 10 °C /hr to precipitate the product. When the mixture had cooled to 20 °C, additional water (96 gal) was added. The precipitated 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid was collected via

centrifugation and washed with water. A total of 539.0 lb of crude wet product was obtained. This product was loaded into the 500 gal stainless steel reactor and suspended in 450 gal of water. The mixture was stirred for 3 hr and then the solids were collected via centrifugation and washed with water (1000 lb). A total of 513.5 lb of 4-amino-3-chloro-6-(4-chloro-2-
5 fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid wet cake was collected, which contained 176.45 lb of product on a dry basis (87.7% yield, with a dry basis purity of 98.6%). Residual formate levels were < 0.07% by ¹H NMR, calculated as formic acid.

Comparative Example 3 (Acidification with Acetic Acid)

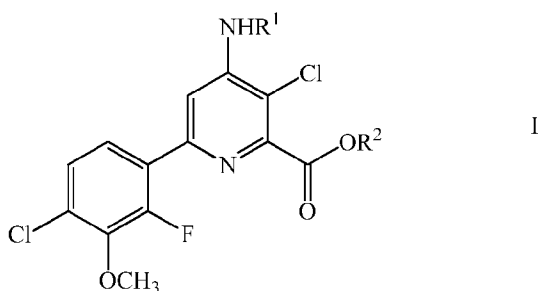
Methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-
10 carboxylate (1.24 kilograms (kg); 3.2 mole) was loaded into a 12-liter (L) three-necked flask equipped with a heating mantle and suspended in a mixture of water (1.00 kg) and methanol (3.14 kg). Diluted aqueous sodium hydroxide (2.2 equivalents; 0.99 kg water + 0.57 kg 50% sodium hydroxide) was then added and the mixture was stirred and heated to reflux (64.7 °C). The reaction was sampled and analyzed by HPLC to ensure complete hydrolysis. The mixture
15 was then filtered hot through an inline filter equipped with a glass frit on which a pad of Celite was laid. The purpose of this filtration was to remove small quantities of insoluble inorganic salts that were present in the methyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate intermediate. The filtered solution of the sodium 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylate was
20 concentrated in a rotary evaporator to remove the methanol. The aqueous solution was then transferred to a 22-L glass reactor. Glacial acetic acid (54.1 eq., 10.42 kg) was added with stirring to precipitate the product. The resulting slurry was warmed to 50 °C for about an hr, and then cooled. The solids were recovered by filtration using a Buchner-type filter crock with Whatman # 50 filter paper. The solids were washed with water, then returned to the 22-
25 L glass reactor. Previous batches had shown residual levels of acetic acid in the solid ranging from 0.3-47.0% at this stage. Water (9.5 kg) was added and the resulting slurry was stirred for 1.5 hr and the solids were again recovered by filtration as described previously. After recovered, the solids were air dried, and then dried in a vacuum oven. The product was analyzed by HPLC and ¹H NMR and was found to contain 1.54% acetic acid. The solids were
30 returned to the 22-L reactor and again reslurried in water, refiltered, and dried. After this treatment, the acetic acid level was reduced to 0.87% by weight. A third reslurry reduced the acetic acid level to 0.84% by weight. The final yield of product was 0.906 kg of with an assay

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of 97.59%, and contained 0.84% acetic acid and 0.34% water. The yield was 83.44% of the theoretical amount. Another subsequent batch run in this manner maintained an acetic acid level of 2.25% after two reslurries.

WHAT IS CLAIMED IS:

1. A process for the isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid which comprises:
- (a) neutralizing an aqueous solution of an alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid with an excess of 85 – 99 percent formic acid at a temperature from about 45 to about 90 °C to produce an aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid;
- (b) cooling the aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid to about 10 to about 25 °C to crystallize the 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, and
- (c) collecting the crystalline 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-pyridine-2-carboxylic acid.
2. A process for the preparation and isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid which comprises:
- (a) contacting an ester of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid of Formula I



in which

R^1 represents H or $C(O)CH_3$, and

R^2 represents C_1 - C_{12} alkyl or an unsubstituted or substituted C_7 - C_{11} arylalkyl

with an aqueous solution of an alkali metal or alkaline earth metal hydroxide in a C_1 - C_4 alcohol at a temperature from about 45 to about 100 °C to produce an aqueous alcoholic

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solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid,

(b) optionally removing most of the C₁-C₄ alcohol from the aqueous alcoholic solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid ,

(c) neutralizing the aqueous solution of the alkali metal or alkaline earth metal salt of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid with an excess of 85 – 99 percent formic acid at a temperature from about 45 to about 90 °C to produce an aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid,

(d) cooling the aqueous mixture of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid to about 10 to about 25 °C to crystallize the 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid, and

(e) collecting the crystalline 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid.

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ABSTRACT

Processes for the preparation and isolation of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)pyridine-2-carboxylic acid.

Electronic Acknowledgement Receipt

EFS ID:	14462434
Application Number:	61736820
International Application Number:	
Confirmation Number:	5935
Title of Invention:	AN IMPROVED PROCESSES FOR THE ISOLATION OF 4-AMINO-3-CHLORO-6-(4-CHLORO-2-FLUORO-3-METHOXYPHENYL)PYRIDINE-2-CARBOXYLIC ACID
First Named Inventor/Applicant Name:	..
Customer Number:	25212
Filer:	Robert Chang/Amanda Vianco
Filer Authorized By:	Robert Chang
Attorney Docket Number:	68011-US-PSP
Receipt Date:	13-DEC-2012
Filing Date:	
Time Stamp:	15:47:20
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$250
RAM confirmation Number	2651
Deposit Account	041529
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	68011_US_PSP_20121213_RC_Application_Data_Sheet_Fillable_PDF.pdf	716478 abd8cbd1b3310b8155b824a0901740535765f39e	no	4

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2	Provisional Cover Sheet (SB16)	68011_US_PSP_20121213_RC_Provisional_Patent_Application_Transmittal_Fillable_PDF.pdf	2064540 4a844262e996bad8e4d9dbe55623a2d3fcd8b27b	no	3
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Information:

3		68011_US_PSP_Provisional_Application.pdf	55110 a5dfe83ee7be09c4bf1d046efd7c9130e66e38b	yes	10
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Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	7
Claims	8	9
Abstract	10	10

Warnings:

Information:

4	Fee Worksheet (SB06)	fee-info.pdf	30128 4a9af93a933e66bc5e5a90b133b7466a47fb8dd	no	2
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