Original Research Article

Identification and synthesis of Flecainide acetate impurities and its control to ICH limit.

ABSTRACT

The improved synthesis of Flecainide acetate (I) is conferred in this article. The chief intent to present this article is to identify and synthesis of the process related impurities of Flecainide acetate. The article also provides the complete study and characterization of the process impurities. Most of the impurities are the in-situ generated intermediates which are tend to carryforward to the final step of synthesis. The more interesting part is the formation of 2,5 –bis (2,2,2-trifluoroethoxy)-N-((4-methylpiperidine-2-yl) methyl) benzamide impurity during Flecainide acetate synthesis.
The article confers the synthesis of 2,5 –bis (2,2,2-trifluoroethoxy)-N-((4-methylpiperidine-2-yl) methyl) benzamide and its control in Flecainide acetate.

Keywords: Catalytic hydrogenation, Platinum catalyst, Cardiac depressant, Antiarrhythmic, Boric acid, impurity formation and characterization.

1. INTRODUCTION

Flecainide acetate, chemically known as N-(2-piperidinylmethyl)-2,5-bis(2,2,2-rrifluoroethoxy) benzamide acetate and represented by Formula **I** is an antiarrhythmic agent also known as cardiac dysrhythmia medication. Antiarrhythmic agent used for the prevention of abnormal fast rhythms of the heart. Flecainide acetate works by blocking the sodium channel in the heart, slowing the upstroke of the cardiac action potential. This there by slows conduction of the electrical impulse within the heart. Other medication include in this class are encainide, propafenone and moricizine.

Image.1. Flecainide Acetate (I)

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. Varian 1HNMR spectra (400 MHz) and 13CNMR spectra (100 MHz) instrument were recorded inDMSO-d6, and mass spectra were determined on API-2000LCMS mass spectrometer, Applied Biosciences.IR spectrum was taken in potassium bromide

and recorded on Shimadzu 8400S FTIR instrument. Differential scanning calorimetric (DSC) analysis was carried on Perkin Elmer DSC80000 instrument.

Preparation of 2,5 –bis (2,2,2-trifluoroethoxy)-N-((4-methylpiperidine-2-yl)methyl) benzamide (Impurity A)

2, 5-Bis (2, 2, 2-trifluoroethoxy) benzoic acid (50g, 1mol), 2-aminomethyl-4- methyl pyridine (25.9g, 1.35mol), boric acid (0.145g, 0.1mol) and toluene (450mL) were added to a flask and heated at 110 to 115°C and water was removed as azeaotrop over 12 hours. After monitoring reaction progress by HPLC toluene was distilled off under vacuum, water (150L) was added and stirred for 2 hours at 25 to 30°C. Precipitated solid was filtered and washed with water (100mL), dried under vacuum for 4 hours to give free base. Further Ethyl acetate in (225mL) and solid were added to a flask and added cooled 10% solution of ethyl acetate in HCl (100mL) were added to clear solution. Filtered the precipitated hydrochloride salt. This salt was dissolved in methanol and 3.0 g of Platinum on carbon (50% wet) were taken in pressure reactor and heated to 60-65°C for 4hr at a hydrogen pressure of 12kg/cm2. Further, the mixture was cooled to 25- 30°C and filtered the catalyst. The filtrate was added into solution of sodium carbonate (9g) and Water (90mL) and Precipitated solid was filtered and dried under vacuum to give title Impurity-A.

1H NMR (DMSO-d6) δ 0.85-1.14 (m, 5H), 1.50 (s , 1H), 1.63-1.76 (m, 2H), 2.63-3.12 (m,3H), 3.33 (brs,2H), 4.73-4.81 (m, 4H), 7.17-7.22 (m, 2H), 7.27 (d, 1H), 8.29 (brs,2H), 3.89 (brs,2H).

.ESI-Mass for C18H22F6N2O3.HCOOH :-429 (M+H)+

IR:3335, 2961 & 2916, 1643, 1582 & 1499, 1285

Characterization data of Impurity –B

Impurity B is an intermediate generated during the synthesis of Flecainide acetate. Compound –II is controlled and characterized under the name of Impurity C

1H NMR (DMSO-d6) δ 4.57 (d, 2H), 4.57-4.87 (m , 4H), 7.20-7.30 (m, 3H), 7.34 (d,1H), 7.40 (d,1H), 7.73-7.77 (m, 1H), 8.51 (d, 1H), 8.79 (t, 1H).

.ESI-Mass for C17H14F6N2O3 :-408.9 (M+H)+, 431.2 Sodium Adduct

IR:3325, 2961 & 2916, 1643, 1582 & 1499, 1285

Preparation of 4-hydroxy-N-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide (Impurity C)

Strting with Compound –II / Impurity B , 5.0 g charged in to the round bottom flask and 50 ml of Aq.solution of hydrogen peroxide is added to it. The reaction mass is then heated to 60° for 24 Hrs and the reaction mixture was distilled off , Finally the impurity is isolated and purified by column chromatography.

1H NMR (DMSO-d6) δ 1.02-1.73 (m , 6H), 2.46-2.95 (m , 3H), 3.15-3.26 (m, 2H), 3.88 (brs, 2H), 4.60-4.67 (q,2H), 4.73-4.80 (q, 2H), 6.61 (s, 1H), 7.43 (s, 1H), 7.74 (t, 1H).

.ESI-Mass for C17H14F6N2O4 :-431.3 (M+H)+,

IR:3331, 2941, 1616, 1503,1285

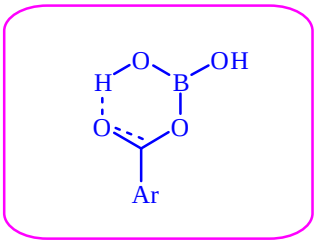
2. RESULTS AND DISCUSSION

Various researchers have attempted to synthesize pharmaceutically acceptable Flecainide Acetate of formula I. However, these methods are tedious, poor selectivity of pyridine ring reduction, lower yield, high loading of catalyst, longer reaction time result in a higher cost of the final API and additional purification render these process unviable on commercial scale [1-3].

Flecainide acetate synthesis starts with the reaction between the 2,5 bis trifluroeythoxy benzoic acid and 2- aminomethyl pyridine. This is the amidation process and various reagents are reported for the synthesis.

The usage of those reagents make the process costlier as they need use on the equimolar basis. Most of the reagents discussed are sensitive towards moisture and make the process stringent on bulk scale (100-200 kg scale)

Boric acid catalyzed amide formation from carboxylic acid is a known synthetic approach. Keeping these aspects in mind boric acid was a preferred catalyst. It was observed that highly facile condensation of 2, 5-bis(2,2,2-trifluoroethoxy) benzoic acid with 2-amino methyl pyridine was possible when the reaction was carried out in presence of catalytic amount (0.1 eq.) of boric acid. Boric acid activates the carboxylic acid moiety by reducing the electron density at the carbonyl function, which makes the intermediate 1 more prone to amine nucleophilic substitution to facilitate the transformation in moderate to good yield.



Intermediate 1

Thus in the first step of the synthesis of compound- III, presence of a catalyst eliminated the need for chemical activation of 2-aminomethyl pyridine and thus use of the hydroxybenzotriazole (HOBt) and N, N′-dicyclohexylcarbodiimide (DCC) reagents was bypassed, since mole to mole ratio is used and lot of solid waste is generated during reaction workup. Therefore, these reagents were not suitable at commercial level. Compound - III was isolated as a hydrochloride salt with impurity profile found as per ICH limit with high purity (99.91 %) and satisfactory yield (85.8 %) (Figure 1)

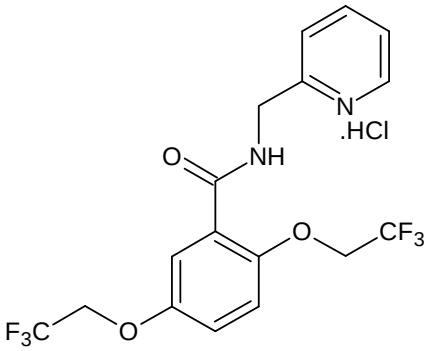
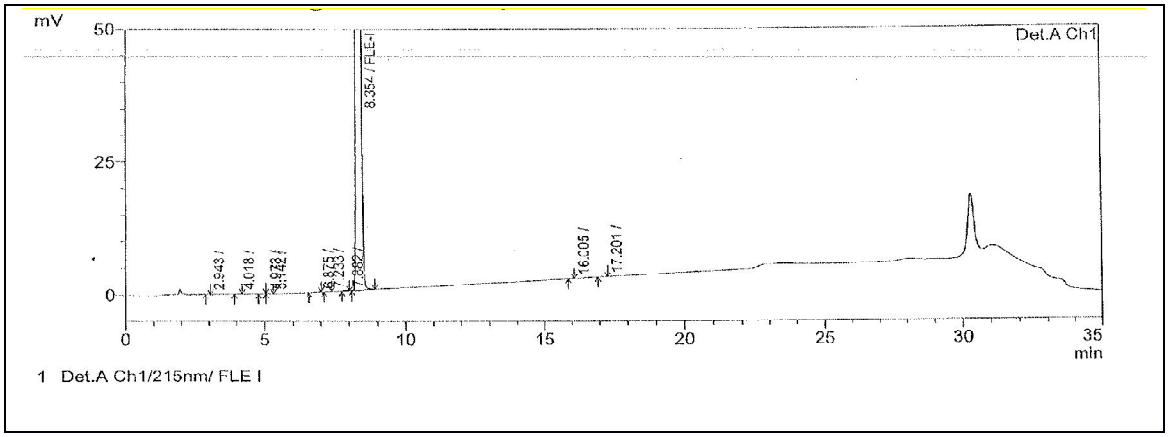


Figure 1. Related substance by HPLC (Compound- III)



Hydrogenation is the second step in synthetic route, it is very important for the efficient synthesis of compound II particularly for the minimization of reaction time with less loading of catalyst and

unwanted side product at commercial level. Though numerous methods of Flecainide acetate are reported, an improved process with detailed impurity profiling is not yet reported.

From the literature, it was evident that there is a need for improvement in the manufacturing process of Flecainide acetate in terms of selectivity, specifically for reduction of pyridine ring of compound III, cost effectiveness, controls the formation of impurities below regulatory limit and which does not require column chromatography or repeated crystallization for getting the desired purity at commercial scale.

An improved process which is free from impurities associated with existing synthetic routes and does not utilize column chromatography or other tedious purification methods and is highly selective towards reduction of pyridine ring with low loading of catalyst with less reaction time is described.

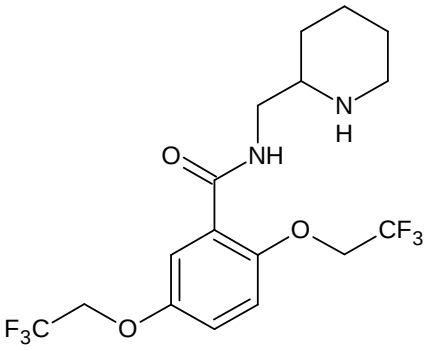
The optimization of catalytic hydrogenations is often a challenging problem due to the difficulty in predicting the changes that will occur from even minor variations in experimental conditions [4]. However, a systematic approach can lead to significant improvements in important processes.

Flecainide Acetate consists of two trifluoroethoxy group which show sensitivity towards reduction. Reactions particularly with high loading of catalyst, longer reaction time, high hydrogen pressure and higher temperature lead to removal of trifluoroethoxy group ended with trans-etherification product [5-6] and other unwanted impurity. In order to avoid loss of trifluoroethoxy group, we focused on reduction of compound III, to reduce reaction time and catalyst with low loading.

If hydrogenation was stopped early too much starting material left unreached, it was difficult to restart the hydrogenation due to catalyst deactivation. On the other hand, loss of trifluoroethoxy group could be suppressed by reducing the contact time of the product with solvent and catalyst.

By keeping these aspects in mind, the catalytic hydrogenation of II was investigated with a wide selection of catalysts, and the results are tabulated in Table 1. Reactions with several other catalysts (PtO2, Rh/C, Ra-Ni, Ru/C, and pd/C) were attempted and it was observed that, even after 30% loading of catalyst under 15-20 kg/cm2 hydrogen pressure rendered the reaction incomplete after prolonged period of times which leads to poisoning of catalyst initiating the formation of undesired product [7-8]. Reduction reaction was monitored by TLC and found that the reaction was contaminated with unknown impurity and it was very difficult to remove this impurity once it formed. The resulting impurity was identified and the structure was confirmed by 1H NMR and mass spectrometry as Dimethoxy impurity, this could be formed by loss of trifluoroethoxy group

(transetherification product A) in presence of methanol at high temperature, high pressure with high loading of catalyst. Anhydrous Hydrochloride salt of pyridine from compound - III was reduced within 2 hours in presence of Pt/C. Compound - II was isolated with excellent purity (99.78%) and satisfactory yield (89.4%)



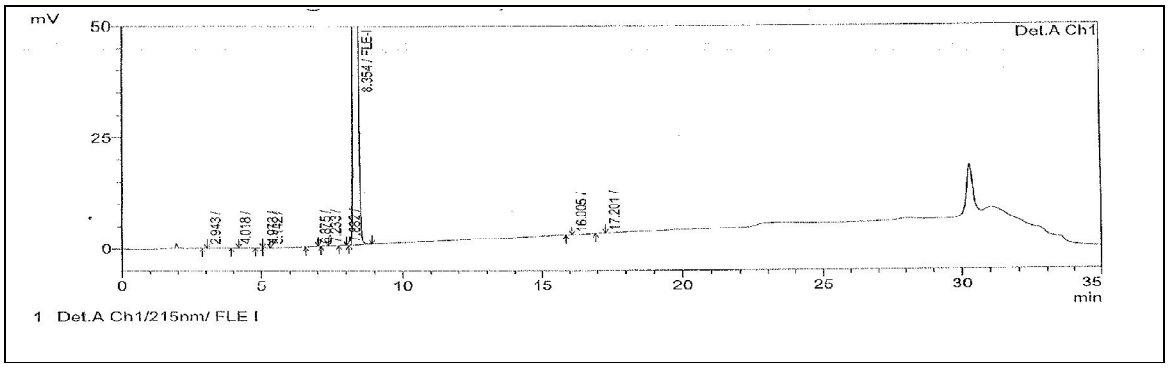
The reduction reaction was carried out at 60 to 65°C and at15 to 20 kg/cm2 hydrogen pressure in auto clave with methanol as a solvent. [b]Reaction progress checked as on TLC. It was a challenging task to keep amount of compound III below 1.0% during reaction itself, if being more than 1.0% it becomes strenuous to remove it during isolation and requires repeated crystallization to achieve impurity profile as per ICH limit in final API [9-10].

The main intent of the article is the identification and characterization of the impurities.

Our earlier work is about the total synthesis of Flecainide acetate, the article gives an idea about amidation process by known known synthetic approach [11]. Boric acid catalyzed amide formation from carboxylic acid and we successfully implemented the concept in the Flecainide acetate synthesis.

The bathes were commercially manufactured with purity of (99.91 %) and satisfactory yield (85.8 %) (Figure 2)

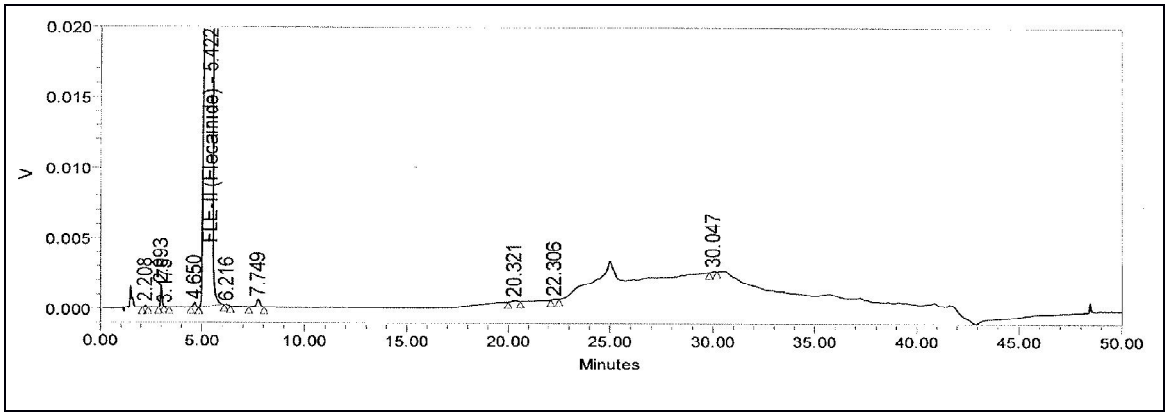
Figure 2. Related substance by HPLC (Compound- III)



The use of boric acid make the synthesis cost effective and plant feasible.

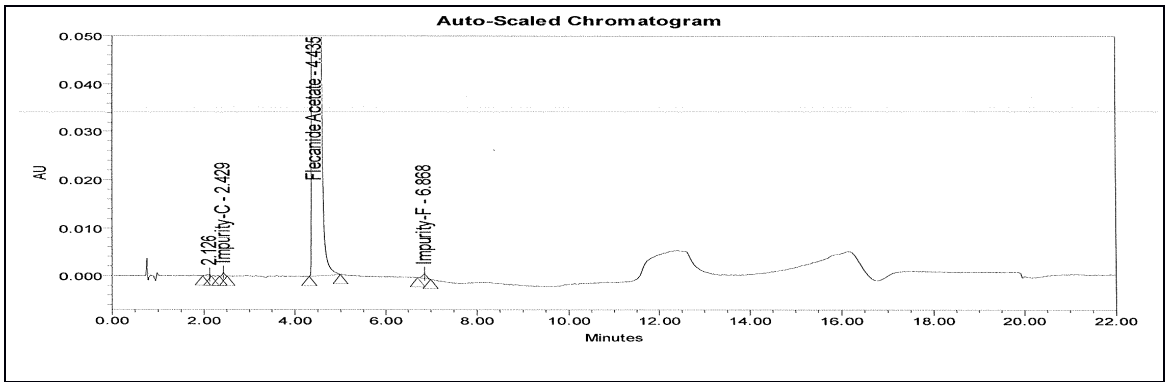
In second the step of synthesis is the reduction of pyridine ring is facilited with the HCl salt formation of pyridine ring. The new process yield in high pure Flecainide free base with the purity of (99.78%) and satisfactory yield (89.4%).

Figure 3. Related substance by HPLC (Compound - II)



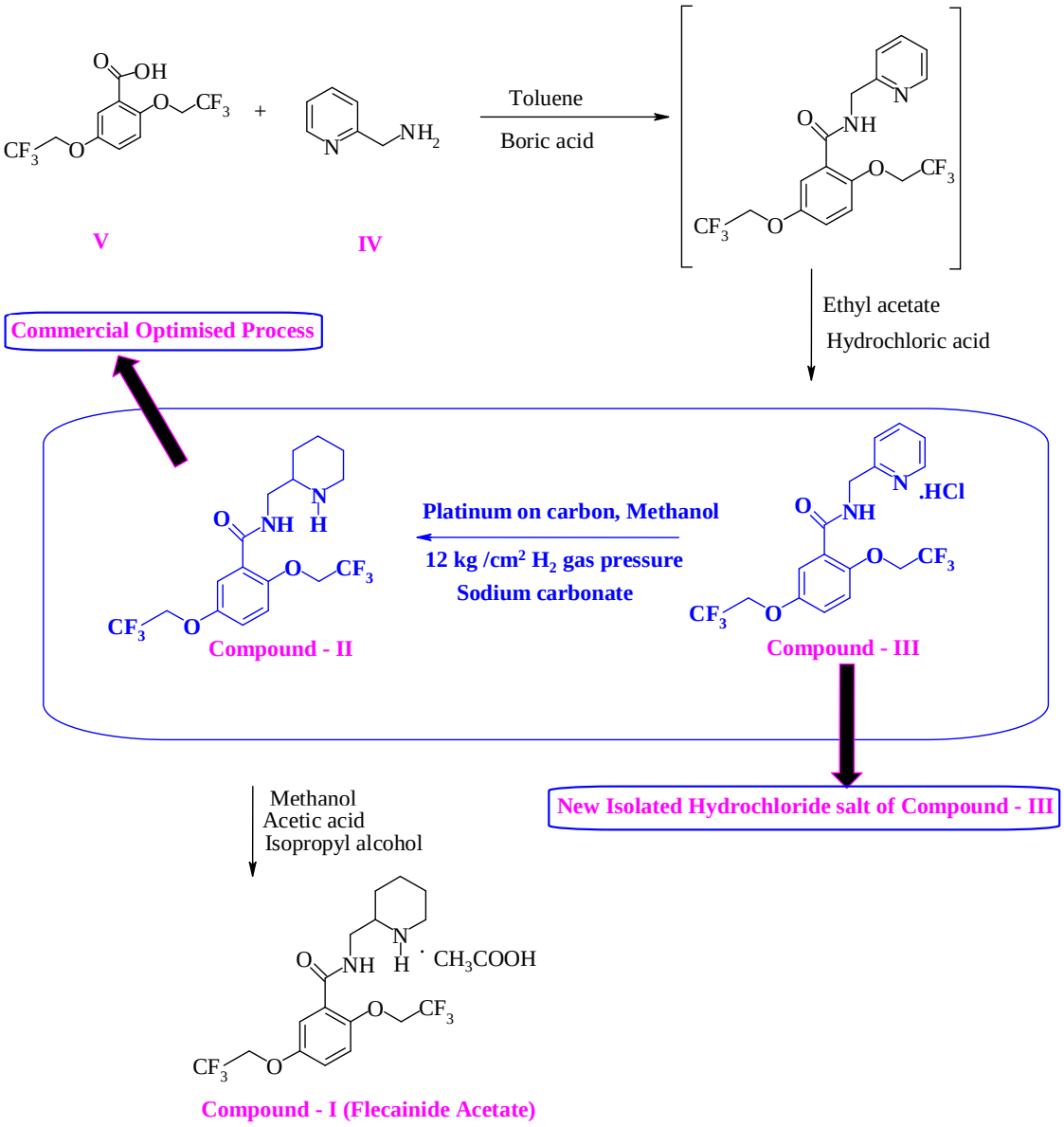
Finally, acetate salt is prepared in methanol and isolated form IPA cyclohexane mixture. Impurity profile found at below regulatory limits, and purifications such as column chromatography or repeated crystallization were not required to attain the desired purity.

Figure 4. Flecainide acetate (Compound- I) Related substance by HPLC



Synthesis of compound I using optimized reaction conditions is depicted in Scheme 1.

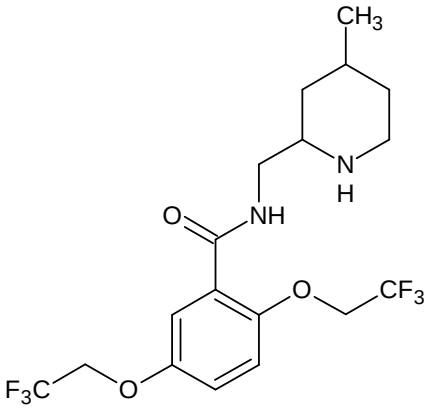
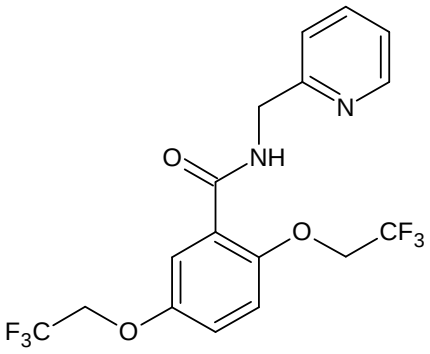
Scheme 1.

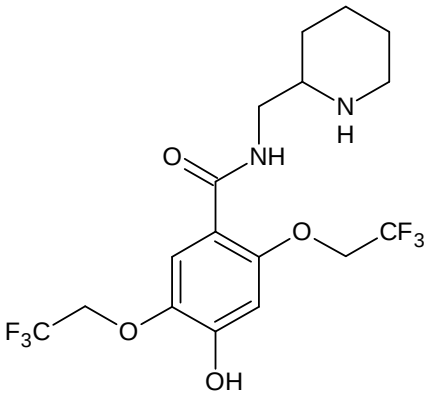


On the basis of the optimized conditions, the batch was carried on 75kg scale and the results were reproduced.

During the synthesis and optimization study the isolated drug substance is contaminated with unknown impurities, which are difficult purge out to extent of ICH limit. To achieve the ICH limit, multiple purification require which has a direct impact on the yield and subsequently cost of the product. Hence we decided to the identify the impurities and to control these impurities in the initial stages of the synthesis.

Table 1: The major impurities which are identified and control in drug substance, these impurities are tabulated below.

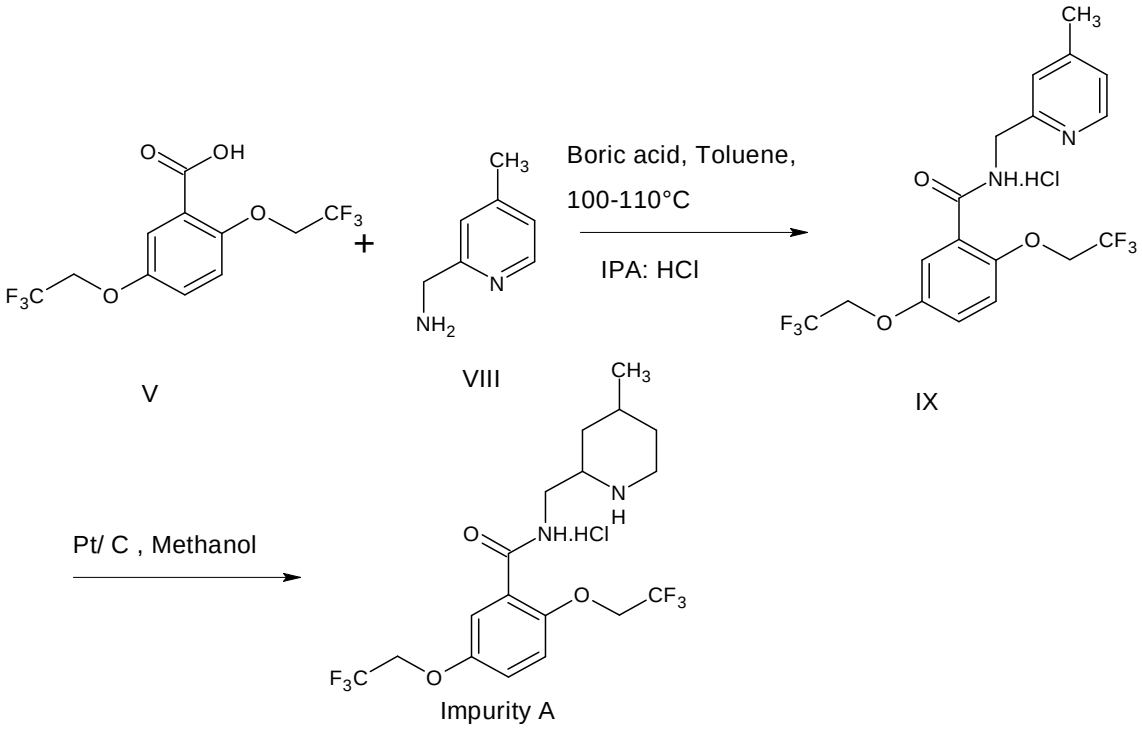
Sr. No.	Impurity name and structure	Type of the impurity
1.	2,5–bis(2,2,2-trifluoroethoxy)-N-((4-methylpiperidine-2-yl) methyl) benzamide  Impurity-A	Process related impurity
2.	N-(pyridin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide  Impurity-B / Compound III	Process related impurity

3.	4-hydroxy-N-(piperidin-2-ylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide  Impurity-C	Degradation impurity

The main concept of the article to introduce the novel impurities and its synthesis. Article also gives an idea about the control of those impurities to the ICH limit. There are three impurities observed in the synthesis Impurity A, impurity B and Impurity C are the newly formed impurities in the synthesis. Hence the synthesis of impurity A, impurity B and impurity C is given in scheme -2, scheme-3 and scheme-4.

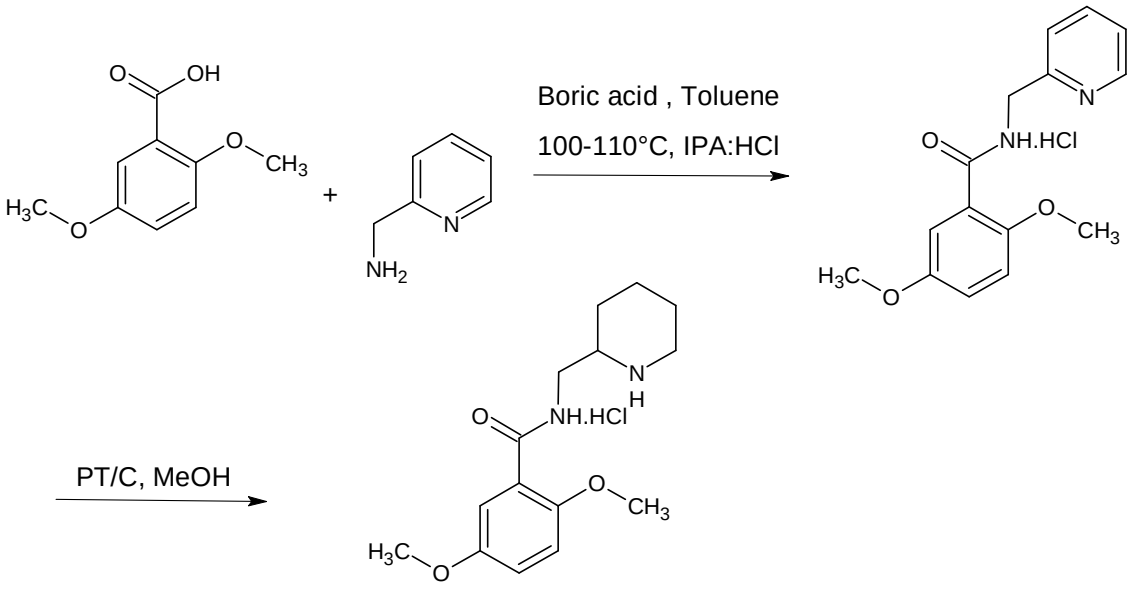
Scheme -2

Synthesis of Impurity A



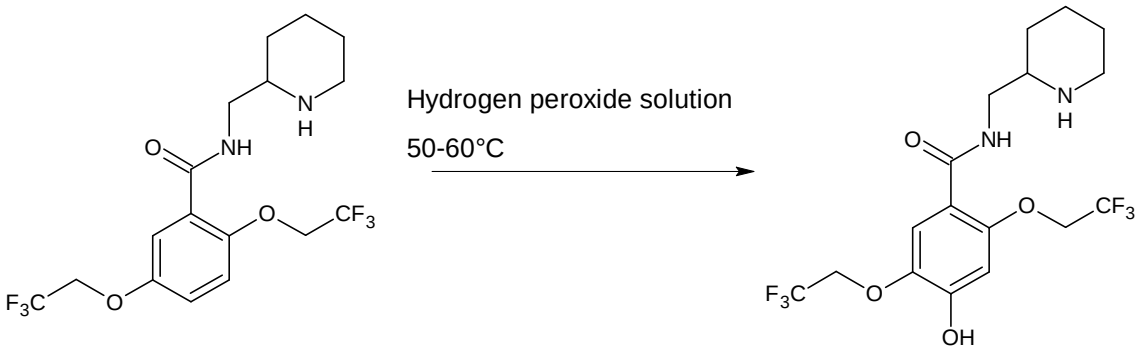
Scheme-3

Synthesis of impurity B



Scheme-4

Synthesis of impurity D



3. CONCLUSION

In conclusion, our efforts resulted in a short efficient improved, cost effective, convenient, environmentally benign, as well user-friendly process for commercial manufacturing of Flecainide Acetate with high purity. Article gives an idea novel impurity generation in the Flecainide acetate synthesis. It also confers the method of synthesis of the novel impurities

ASSOCIATED CONTENT

Supporting Information:

Spectral Copies of IR, ESI-MS, ^{1}H NMR, ^{13}C NMR and Elemental analysis of compound I, II, III and ESI-MS, ^{1}H NMR of Dimethoxy impurity A (PDF). This material is available after reference.

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