

A New-Fangled and Alternative Synthesis of Anticoagulant Drug Substance, Apixaban

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ABSTRACT

A cost effective and technically viable process was for apixaban(anticoagulant drug) developed by using commercially available chlorinating agent sulfurylchloride in the place of phosphorus pentachloride not as everyone using and introduced a new amidation process for ester simply by treating with sodamide and sodium methoxide in methylene dichloride to land up with cost effective and simple process.

KEY WORDS: COMMERCIALLY VIABLE PROCESS, APIXABAN, DI-CHLORINATION, SULFURYL CHLORIDE. AMIDATION, SODAMIDE.

INTRODUCTION

Apixaban (Apixaban. Monograph for Professionals.2019; Raghavan, N., et al., 2009) is an oral anticoagulant used to lower the risk of stroke caused by a blood clot in people with a heart rhythm disorder called atrial fibrillation .It is also used after hip or knee replacement surgery to prevent a type of blood clot called deep vein thrombosis (DVT), which can lead to blood clots in the lungs. There are several routes were available in the literature (Zhou , JC., et al., 2003;Jianan Jiang. and, Yafei, Ji. et al., 2012; Ji, Y., et al., 2012; Huo, SW., et al., 2014;Guo, F., 2014;Dwivedi SD., et al., 2014;Shekar Bhaskar Bhirud., et al., 2014)for its synthesis, but few of were cost effective methods. After a through reveals of the literature of apixaban, the author developed a cost effective and scalable process.

Experimental

MATERIAL AND METHODS

All the raw materials used for the selected route of synthesis are procured from Aldrich and the reagent grade

materials were purchased from Merck synthesis. All the solvents used for its entire apixaban process development were purchased from Merck inc.

RESULTS AND DISCUSSION

Most of the literatures reported for chlorination of 1-(4-iodophenyl) piperidin-2-one is in phosphorous pentachloride (PCl₅) only, but the author in this research invented a new and cheap reagent sulfuryl chloride (SO₂Cl₂) in the place of PCl₅. Which given fruitful results same like regular di-halogenation. In the selected route of synthesis of apixaban was involved a new sequence is that amidation followed by N-alkylation with piperidin-2-one whereas in regular synthesis it is in reverse mode and it has more advantages is that it can be eliminated or minimized the formation of piperidin-2-one ring opening impurity and as well as apixaban acid impurity (Figure 1).

Step-1: Synthesis of 3, 3-Dichloro-1-(4-Iodophenyl)

Piperidin-2-one: In a 500mL round bottom flask 200 mL of sulfuryl chloride was taken at room temperature and cooled the reaction mass temperature to 0-5oC. Added 50gm of 1-(4-iodophenyl) piperidin-2-one portion wise (5 lots) under gentle stirring which lead to the formation of gel type reaction mass and is maintained for 3-4 hours at 0-5 oC. After completion of the TLC (1:9, Ethyl acetate and Hexane) reaction mass was quenched in ice cooled water (300 mL) and the resulting solution was pH adjusted to 7.5-8.0 with sodium carbonate and extracted with

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Ethyl acetate (3 x100 mL), the combined organics were washed with brine solution and dried over anhydrous sodium sulfate. The organic layer further distilled off under reduced pressure and obtained solid was filtered with hexanes slurry to get 3, 3-dichloro-1-(4-iodophenyl) piperidin-2-one as white colored solid material 60 gm. ¹H NMR (CDCl₃, ppm): δ2.07-2.13 (m, 2H), δ2.90-2.93 (m, 2H); 3.72 (t, 2H); δ7.13 (d, 2H); δ7.77 (d, 2H); Mass: 370.7 (M+H), 372(M+2); FT-IR (Cm-1): 3087.93, 2967.07, 2945.89, 1681.72, 1485.27, 1474.87, 685.62, 792.46.

Figure 1: Scheme-I-New route of Synthesis

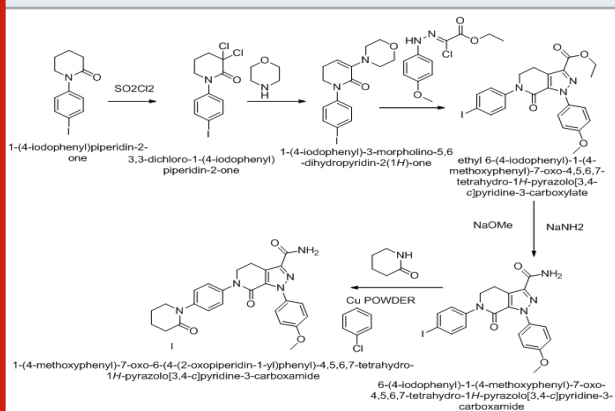
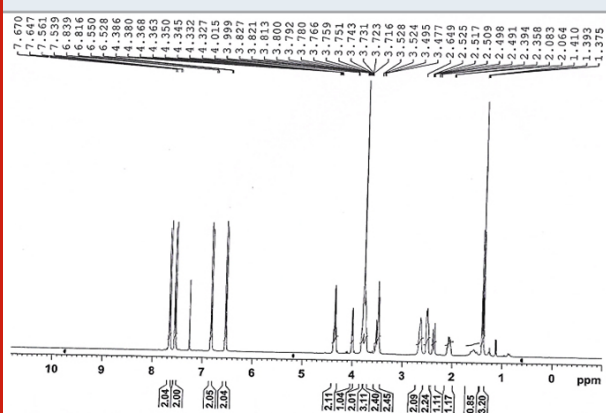
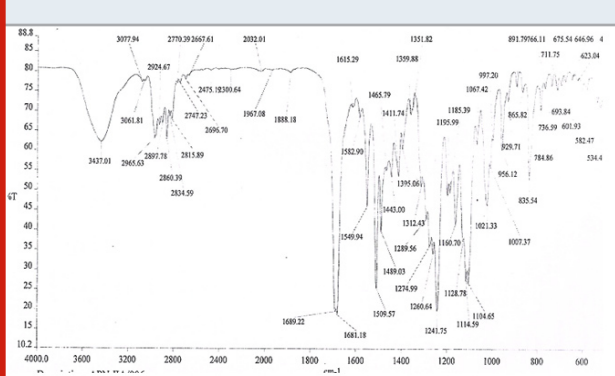
Figure 2: APN-(a) ¹H NMR

Figure 3: APN-(a): FT-IR



Step-2: Synthesis of 1-(4-Iodophenyl)-3-Morpholino-5, 6-Dihydropyridine-2(1h)-One(a): In a dry 250mL round

bottom flask 25gm of 3, 3-dichloro-1-(4-iodophenyl) piperidin-2-one was taken in 100mL of Ethyl acetate and added 10gm of Tri-ethyl amine followed by addition of 15 gm morpholin in 25 mL of Ethyl acetate at room temperature and maintain for another 2 hours. After completion of the reaction mass quenched with Water and separated the organic layer, washed with brine solution and dried over sodium sulfate. The organic layer was distilled under reduced pressure and obtained 1-(4-iodophenyl)-3-morpholino-5, 6-dihydropyridine-2(1H)-one is dried and packed 30gm.

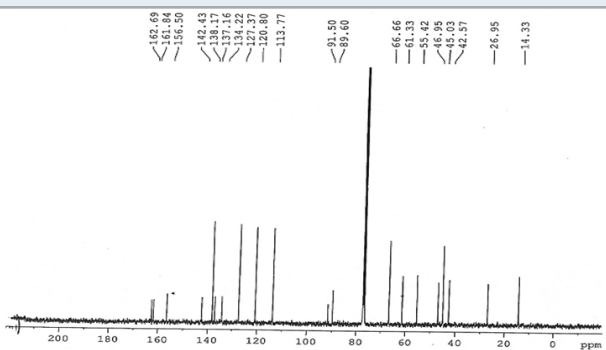
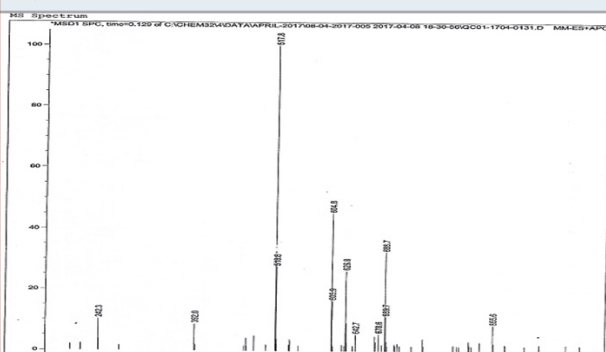
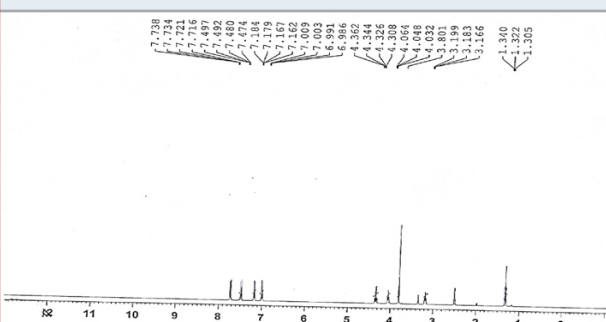
Figure 4: APN-(a): ¹³C NMR

Figure 5: APN-(a): MASS

Figure 6: APN-(b) ¹H NMR

Step-3: Synthesis of Ethyl-6-(4-Iodophenyl)-1-(4-Methoxyphenyl)-7-Oxo-4,5,6,7-Tetrahydro-1h-Pyrazolo[3,4c]Pyridine-3-Carboxylate(b): In a dry 500 mL round bottom flask 50gm of 1-(4-iodophenyl)-3-morpholino-5, 6-dihydropyridine-2(1H)-one and 100mL of methylene dichloride was taken at 0-5o C and added 48 gm of (Z)-Ethyl-2-chloro-2-(2-(4-methoxyphenyl)

hydrazono)acetate dissolved in 50mL of methylene dichloride drop wise and maintain it for 3-4 hours at 0-5°C and then raise the temperature to room temperature, maintain at for another 3 hours. After completion of the reaction 100 mL of water added and separated the organic layer and removed the solvent under reduced pressure. The resulting crude material was taken in 200mL 4N hydrochloride solution and maintained it for 6 hours at room temperature and after completion of TLC; added additional 200 mL water and stirred for 30 minutes at 0-5°C, filtered the resulting precipitated solid, filtered bed was washed with 35 mL water and dried to afford 42 gm of Ethyl-6-(4-iodophenyl)-1-(4-methoxyphenyl)-7-oxo-4, 5, 6, 7-tetrahydro-1H-pyrazolo[3,4c]pyridine-3-carboxylate as off-white solid.

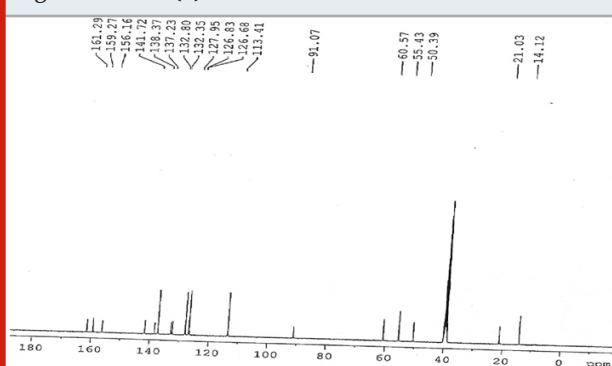
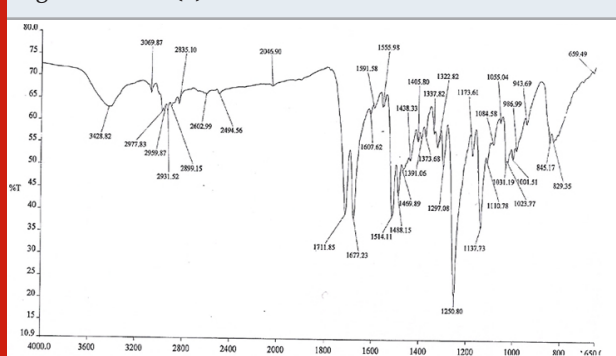
Figure 7: APN-(b) ¹³C NMR

Figure 7: APN-(b) FTIR



Step-4: Ethyl-1-(4-Methoxyphenyl)-7-Oxo-6-(4-(2-Oxopiperidin-1yl)Phenyl)-4, 5, 6, 7-Tetrahydro-1h-Pyrazolo[3,4c]Pyridine-3-Carboxylate(c): 20gm of Ethyl-6-(4-iodo-phenyl)-1-(4-methoxyphenyl)-7-oxo-4, 5, 6, 7-tetrahydro-1H-pyrazolo[3,4c]pyridine-3-carboxylate, 25gm of piperidin-2-one and 5gm of copper(I)iodide taken in a mixture solution of 40gm of anhydrous potassium carbonate and 5.0mL of triethylamine in 200mL of Toluene. The reaction mixture heated for reflux and collected water by maintaining the reaction mixture for 8-9 hours. Once reaction completed over TLC, then filter the reaction mass through celite bed and the resulting filtrate mother liquor was concentrated under reduced pressure to get crude Ethyl-1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1yl)phenyl)-4, 5, 6, 7-tetrahydro-1H-pyrazolo[3,4c]pyridine-

3-carboxylate and which was isolated in ethyl acetate and hexane (1:1 ratio) to yield pure compound 15gm with purity ≤ 99%.

Figure 8: APN-(b) MASS

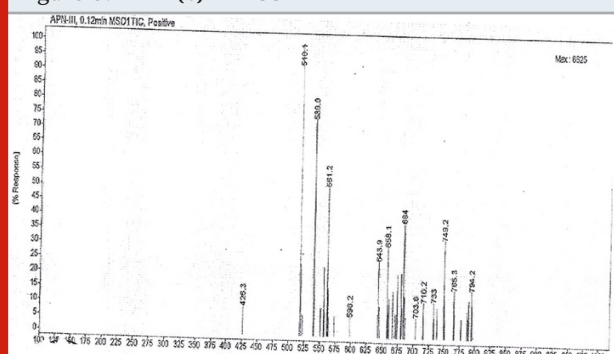
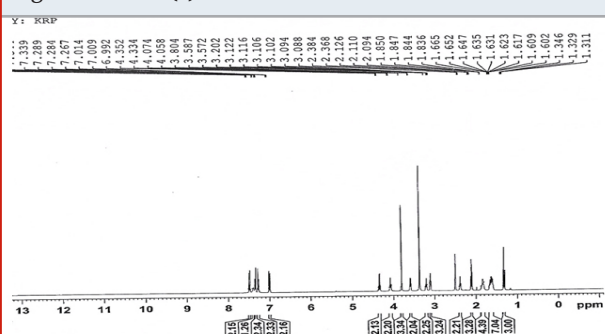
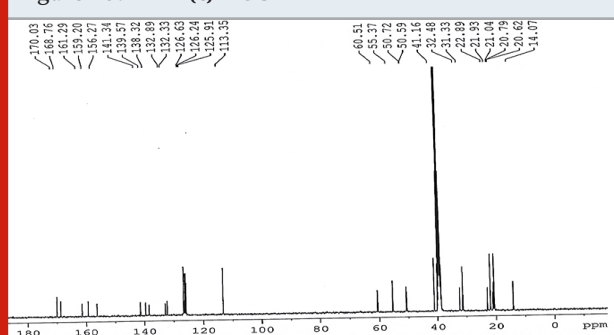
Figure 9: APN-(c) ¹H NMRFigure 10: APN-(c) ¹³C NMR

Figure 11: APN-(c) FT-IR

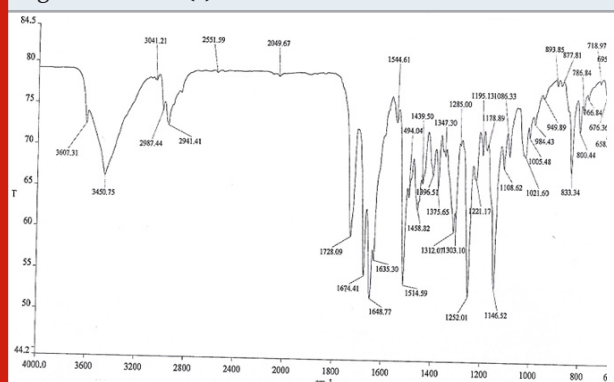


Figure 12: APN-(c) MASS

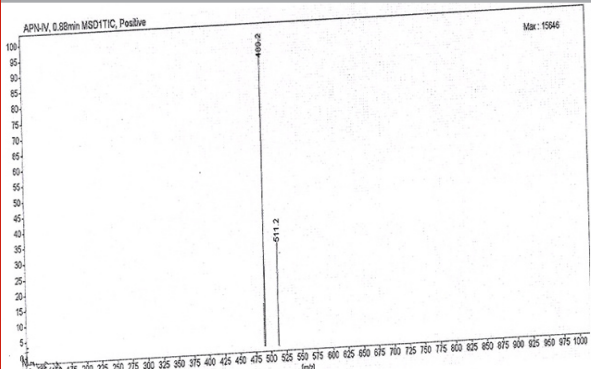


Figure 13: APN-(d) ^1H NMR

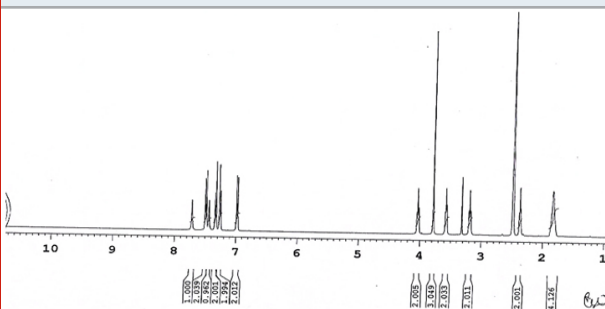
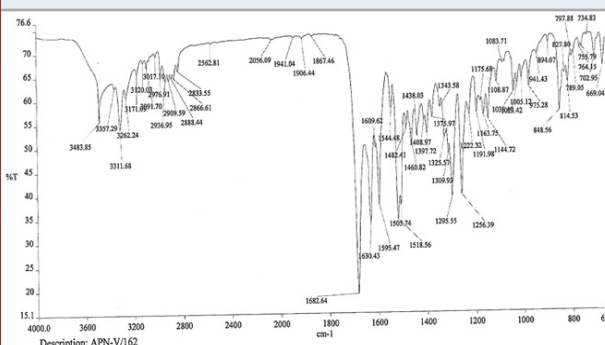
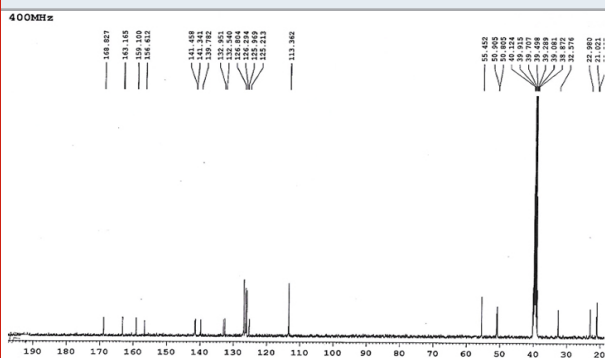


Figure 14: APN-(d) FT-IR

Figure 15: APN-(d) ^{13}C NMR

Step-5: Ethyl-1-(4-Methoxyphenyl)-7-Oxo-6-(4-(2-Oxopiperidin-1yl) Phenyl)-4, 5, 6, 7-Tetrahydro-1h-Pyrazolo[3,4c]Pyridine-3-Carboxamide(d): In a 250 mL round bottom flask taken 12 gm of Sodamide and

Methylene dichloride (MDC)(250 mL) and then added 30 gm Ethyl-1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1yl)phenyl)-4, 5, 6, 7-tetrahydro-1H-pyrazolo[3,4c]pyridine-3-carboxylate. The above reaction mass was cooled to -50C, added 12.1 gm of sodium methoxide powder lot wise in 45 minutes duration. After addition was completed reaction temperature rose to room temperature and maintains for 1-2 hours. After completion of the reaction, the reaction mass was filtered, the filtered cake was washed with MDC (125mL) and the filtrate MLs was washed with Water, the organic layer was concentrated and the resulting solid material was isolated in water by filtration. The crude apixaban (23 gm) was purified in methanol to afford 18gm of pure apixaban with purity of $\leq 99.5\%$ with single maximum impurity $\leq 0.1\%$.

¹H NMR (CDCl₃, ppm): δ 1.83 (t, 4H); δ 2.38 (t, 2H); δ 3.20 (t, 2H); δ 3.58 (t, 2H); δ 3.79 (s, 3H); δ 4.04 (t, 2H); δ 7.00 (d, 2H); δ 7.28 (d, 2H); δ 7.33 (d, 2H); δ 7.44 (s, 1H); δ 7.49 (d, 2H); δ 7.71 (s, 1H); ¹³C NMR (ppm): 21.00, 22.97, 32.56, 50.79, 55.44, 113.35, 125.18, 125.96, 126.79, 132.53, 132.94, 139.77, 141.44, 156.60, 159.09, 163.14, 168.80; Mass: 460.20 (M+H); FT-IR (cm⁻¹): 3311, 3484, 3017, 3071, 2930, 2977, 1595, 1630, 1683, 1144, 1256, 1296.

CONCLUSION

In conclusion, the present paper summarizes the improved synthetic approach utilized for the synthesis of the anticoagulant drug apixaban. The synthetic approach of apixaban was made by using commercially available chlorinating agent sulfurylchloride that a new amidation process for ester simply by treating with sodamide and sodium methoxide in methylene dichloride. The developed process could be used for the industrial production of apixaban in high yield and enantio purity.

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