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Development of Purification Process of Edoxaban Intermediate (Ethyl-2-[(5-Chloropyridine-2-Yl)Amino]-2-Oxoacetate Hydrochloride)

Asim H. Desai, Sanjay N. Patil, Mehul K Patel, Anandkumar B. Jain*, Jignasu T. Desai and Ajit kumar Choubey

Ami Organics Ltd, Sachin, Surat-394230, Gujarat, **INDIA**

Email: rnd@amiorganics.com

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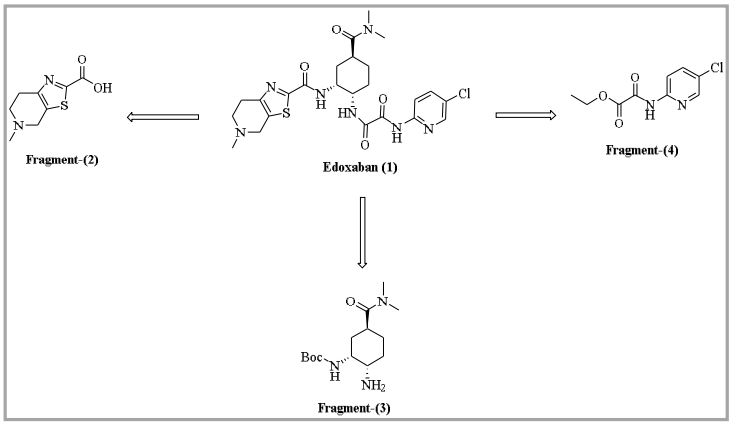
ABSTRACT

Purification method for preparation of edoxaban intermediate, i.e., Ethyl-2-[(5-chloropyridine-2-yl)amino]-2-oxoacetate hydrochloride formula (A) using the alcoholic solvent at reflux condition. The purity of edoxaban intermediate is increased by implementing these manufacturing processes. The process provided in the present invention involves convenient operations and high purity efficiency (<99%). The process is environmental-friendly and suitable for commercial scale.

Graphical abstract



Retrosynthesis of Edoxaban.

Keywords: Direct oral anticoagulant (DOAC), Thromboembolism, Factor Xa inhibitor, Warfarin Edoxaban.

INTRODUCTION

The chemistry of heterocyclic compounds is very important to be an active field in the organic chemistry compounds especially in pharmaceuticals industry. Heterocyclic compounds having the nitrogen and oxygen atoms were the reason for the activity of most of the drugs of natural origin

leads to the discovery of the many synthetic drugs. Significant interest of heterocyclic compounds exists in several natural products exhibiting a broad range of biological and pharmaceutical activities [1].

Several new direct oral anticoagulants (DOACs) have been approved for the prevention of stroke in patients with atrial fibrillation (AF) and for the treatment and prevention of venous thromboembolism (VTE) recurrence [2-5]. DOACs inhibit Factor Xa (FXa) in the coagulation cascade and represent clinical alternatives to traditional vitamin K antagonists such as warfarin, which possess limitations such as risk of bleeding, strong drug−drug interactions, and the requirement of frequent monitoring [6]. Synthetic drug "Edoxaban" (1) is anticoagulant drug and doses take once-daily that has been launched under the trade names Lixiana and Savaysa for the prevention of AF and VTE [7-8].

As shown in figure 1, Edoxaban (1) is synthesized via the combination of three structurally distinct units: thiazole carboxylic acid (2), chiral cyclohexane cis-diamine (3), and oxalate (4). Herein, we are describe the establishment manufacturing procedure of key intermediate 4 using inexpensive and commercially available starting materials with purification to obtained the high purity of the material.

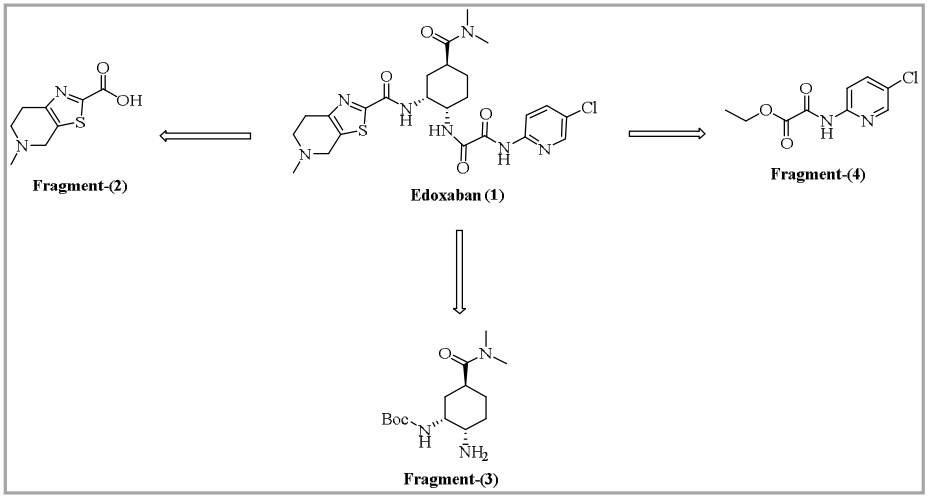
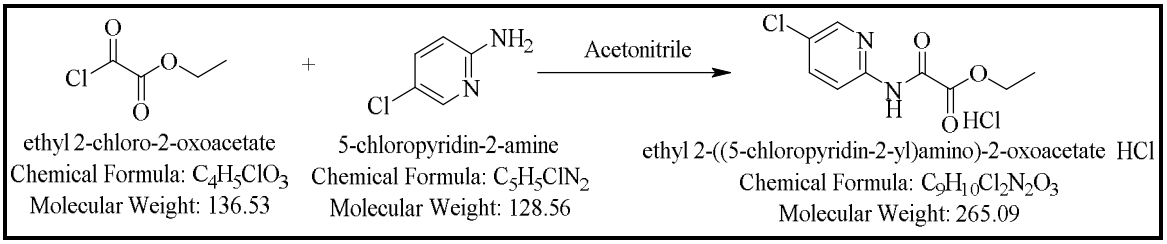


Figure 1. Retrosynthesis of Edoxaban (1)

MATERIALS AND METHODS

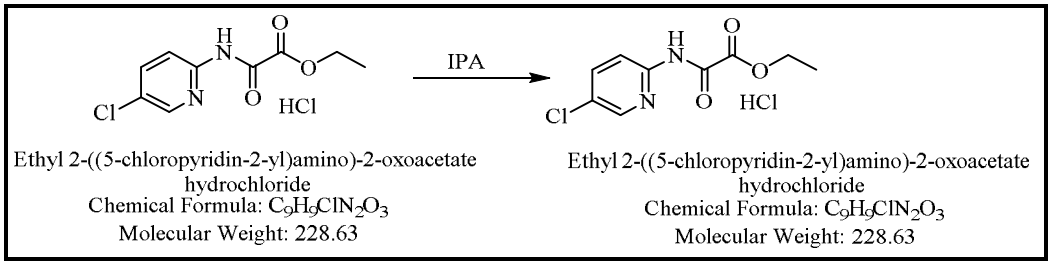
The manufacturing route for the preparation of 4 is that process started with condensation reaction between ethyl oxalyl chloride and 2-amino-5-chloro pyridinein presence of acetonitrile.

Method of Ethyl-2-[(5-chloropyridine-2-yl)amino]-2-oxoacetate Hydrochloride



Synthesis process: Charge acetonitrile 450.0 mL into clean RBF, charge 2-amino-5-chloro pyridine (100.0 g) and flush with the 50.0 mL acetonitrile followed by stir the reaction mass for 10 to 15 min at 20-30°C. Slowly add ethyl oxalyl chloride at 20 to 30°C within 1-2 h. Raise reaction mass temperature 60 to 65°C and maintain for 6 h. After TLC observation, reaction mass cool to 20 to 30°C. Filter the reaction mass. Weight of dry solid = 150.0 g (0.77 w/w), HPLC>95%.

Purification Method of Ethyl-2-[(5-chloropyridine-2-yl) amino]-2-oxoacetate Hydrochloride



Ethyl 2-((5-chloropyridin-2-yl)amino)-2-oxoacetate hydrochloride
Chemical Formula: $C_9H_9ClN_2O_3$
Molecular Weight: 228.63

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A first reactor was charged 150.0 mL Isopropyl alcohol followed by charging of 100.0 g ethyl-2-[(5-chloropyridine-2-yl) amino]-2-oxoacetate hydrochloride and flush with 50.0 mL Isopropyl alcohol under stirring. Raise the reaction mass temperature up to 55°C and maintain for 2 h. After maintaining, cool the reaction mass and maintain for 1 hr at 25-30°C. Filter and get the product.

RESULTS AND DISCUSSION

Ethyl 2-chloro-2-oxoacetate condensed with 5-chloropyridine-2-amine in acetonitrile as solvent as per above mentioned method to obtained ethyl-2-[(5-chloropyridine-2-yl) amino]-2-oxoacetate having >95.0% purity.

To improve the purity of the final product, we established the purification process to get the <99% purity by HPLC. We take trials using the methanol, ethanol, n-butanol solvents which is not helpful to get the maximum purity. Finally, we obtained the superior result by using the isopropyl alcohol as solvent for purification and achieved the higher purity and yield.

APPLICATION

In the United States, edoxaban is approved for treating deep vein thrombosis and pulmonary embolism following five to ten days of initial therapy with a parenteral anticoagulant. It is also approved for reducing the risk of blood clots in people with non-valvular atrial fibrillation.

In the European Union, edoxaban is approved for preventing blood clots in people with non-valvular atrial fibrillation who also have at least one risk factor, such as having had a previous stroke, high blood pressure, diabetes mellitus and heart failure or being 75 years old or over. It is also used to treat deep vein thrombosis and pulmonary embolism and to prevent either of these from reoccurring.

CONCLUSION

After several purification method tried, finally we achieved desired purity of ethyl-2-[(5-chloropyridine-2-yl) amino]-2-oxoacetate hydrochloride more than <99% which is more helpful and environmental friendly to prepare anticoagulant drug.

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Ami Organics Ltd, Plot No: 440/4, 5, 6, 8206-B, 478, 479 & 494, 495, Road No: 82/A & 82/C, G.I.D.C, Sachin, Surat - 394230,Gujarat, INDIA.

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