Improved Process for Anti-Coagulant Drug Substance Rivaroxaban

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ABSTRACT

An anti-coagulant drug substance rivaroxaban is developed with improved process by introducing a new oxazolidine ring formation with commercially available carbamide in presence of strong base like potassium hydroxide in toluene as solvent and the developed process is scalable, economic than innovator process, which is mentioned in scheme 1.

KEY WORDS: IMPROVED SYNTHESIS, ALTERNATIVE REAGENTS, RIVAROXABAN.

INTRODUCTION

Rivaroxaban is an orally bioavailable member of a new class of potent and novel factor Xa inhibitors (oxazolidinone derivatives) is used for the treatment and prevention of various thromboembolic ailments, especially deep venous thrombosis, pulmonary embolism, angina pectoris, myocardial infarction, cerebral stroke, restenosis after angioplasty or aortocoronary bypass, transitory ischemic attacks and the peripheral arterial occlusive diseases. It has also been used in the treatment of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and for the prevention of deep vein thrombosis. It has also been approved for the treatment of atherothrombotic events in patients who have high cardiac biomarkers.

In this accord great attention has been focused on the synthesis of rivaroxaban and as such many reviews have been published on the rivaroxaban. Whereas, the

Author in his improved route of synthesis he developed with commercially viable and available reagents used for cyclization and as well as peptide bond formation This current paper describes an insight into the improved route synthesis of rivaroxaban that is commercially viable.

Experimental: Chemical & Solvents: All the chemicals for the synthesis of rivaroxaban were supplied from Merck and Aldrich Chemicals & Co. And used as received. All reactions were carried out with dry, freshly distilled solvents under anhydrous conditions.

The UV-Visible absorption spectra were recorded in DMSO with a SHIMADZU UV-1800 spectrometer at concentration range of 10–4 M. IR spectra were recorded in the region of 4000 cm⁻¹ to 400 cm⁻¹ on an FT-IR-Alpha Bruker IR spectrometer in KBr pellets. The ¹H- and ¹³C-NMR spectra were recorded in DMSO-d₆ at 500MHz using AV500-High Resolution Multinuclear FT-NMR Spectrometer with tetramethylsilane as internal standard.

RESULTS AND DISCUSSION

Improved process of synthesis of rivaroxaban was made by introducing a new oxazolidine ring formation with commercially available carbamide in presence of strong base like potassium hydroxide in toluene as solvent. The synthesized compound was analyzed and characterized by melting point, UV-Vis, IR, ¹H-NMR, ¹³C NMR, and elemental analysis.

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Process for the preparation of 2-(2-Hydroxy-3-((4-(3-Oxomorpholino) Phenyl) Amino) Propyl) Isoindoline-1, 3-Dione (3): In a 500 ML round bottom flask 50gm of 4-(4-aminophenyl) morpholin-3-one(1) and 45 gm of 2-(oxiran-2-ylmethyl) isoindoline-1, 3-dione(2) was taken in a 300ml of Toluene at room temperature. Slowly rose the temperature up to 80-85°C and maintained the reaction mass for 4-5 hours. After completion of the reaction, cooled the reaction mass temperature to room temperature and filtered through Buckner funnel. The obtained off-white solid was again purified in water and dried.

Process for the preparation of 2-((2-Oxo-3-(4-(3-Oxomorpholino) Phenyl) Oxazolidin-5-Yl) Methyl) Isoindoline-1, 3-Dione (4): 34.5 gm of 2-(2-hydroxy-3-((4-(3-oxomorpholino) phenyl) amino) propyl) isoindoline-1, 3-dione (3) in 250 mL of Toluene was taken in a 500 ML round bottom flask and added 50gm of carbamide, 22 gm of potassium hydroxide. The reaction mass was refluxed for 10-11 hours. After completion of the reaction in thin layer chromatography monitoring cooled the reaction mass to room temperature and filtered the precipitated reaction mass to obtain a half white solid, which was further purified in water to get pure ring closed materials(4).

Process for the preparation of 4-(4-(5-(Aminomethyl)-2-Oxooxazolidin-3-Yl) Phenyl) Morpholin-3-One (5): 15gm of 2-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) isoindoline-1, 3-dione (4) was subjected to de-phthalation in 100mL of 10% Ammonia in Isopropyl alcohol under reflux condition for 5-6 hours. Once reaction completed reaction mass was cooled to room temperature and filtered the light brown colored targeted product 5 good quality and yield.

round bottom flask 75 gm of 4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one (5), 82gm of 5-chlorothiophene-2-carbonyl chloride (6) taken in 200 mL of N,N-Dimethyl amine (DMF) and 45gm of Potassium tertiary butoxide at room temperature and maintained it for 2-3 hours for completion of the reaction. After completion of the reaction 350 mL of Water was added to quench the reaction and the obtained white colored material was purified in ethyl acetate to get high pure material with any other impurity NMT 0.10%.

Scheme 1: Route of Synthesis of rivaroxaban (Improved process route of synthesis)

Figure 1: Structure of rivaroxaban

Process for the preparation of 5-Chloro-N-((2-Oxo-3-(4-(3-Oxomorpholino) Phenyl) Oxazolidin-5-Yl) Methyl) Thiophene-2-Carboxamide (7): In a 1000mL

Figure 2: 1H NMR 2-(2-hydroxy-3-((4-(3-oxomorpholino) phenyl) amino) propyl) isoindoline-1, 3-dione

Figure 3: ^{13}C NMR 2-((2-hydroxy-3-((4-(3-oxomorpholino phenyl) amino) propyl) isoindoline-1, 3-dione

Figure 4: Mass 2-((2-hydroxy-3-((4-(3-oxomorpholino phenyl) amino) propyl) isoindoline-3-dione

Figure 5: FT-IR 2-((2-hydroxy-3-((4-(3-oxomorpholino phenyl) amino) propyl) isoindoline-1, 3-dione

Figure 6: ^1H NMR 2-((2-oxo-3-(4-(3-oxomorpholino phenyl) oxazolidin-5-yl) methyl) isoindoline-1, 3-dione

Figure 7: ^{13}C NMR 2-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) isoindoline-1, 3-dione

Figure 8: Mass 2-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) isoindoline-1, 3-dione

Figure 9: FT-IR 2-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) isoindoline-1, 3-dione

Figure 10: ^1H NMR 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl) phenyl) morpholin-3-one

Figure 11: ^{13}C NMR 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl) phenyl) morpholin-3-one

Figure 12: Mass 4-(4-(5-(amino methyl)-2-oxooxazolidin-3-yl) phenyl) morpholin-3-one

Figure 13: ^1H NMR 5-chloro-n-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) thiophene-2-carboxamide

Figure 14: 5-chloro-n-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) thiophene-2-carboxamide

Figure 15: Mass 5-chloro-n-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) thiophene-2-carboxamide

Figure 16: FT-IR 5-chloro-n-((2-oxo-3-(4-(3-oxomorpholino) phenyl) oxazolidin-5-yl) methyl) thiophene-2-carboxamide

CONCLUSION

In conclusion, the present paper summarizes the improved synthetic approach utilized for the synthesis of the anticoagulant drug rivaroxaban. The synthetic approach of rivaroxaban was made by introducing a new oxazolidine ring formation with commercially available carbamide in presence of strong base like potassium hydroxide in toluene as solvent that could be used for the industrial production of rivaroxaban in high yield and enantiopurity.

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