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"Synthesis of the Key Intermediate of the Direct Factor Xa* Inhibitor: Apixaban"

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Abstract

Ethyl-2-Chloro-2-(2-(4-methoxyphenyl) hydrazinylidene) acetate is an important intermediate in the synthesis of Apixaban, a widely used anticoagulant that works by inhibiting Factor Xa. Its structure, featuring a chloroacetate group and a methoxyphenyl-substituted hydrazone, is crucial in building the pyrazole ring—a key part of Apixaban's active core. It plays a vital role in the scalable production of Apixaban, supporting the global supply of this critical antithrombotic therapy. The synthesis uses a diazocoupling reaction, where 4-methoxyaniline is diazotized with sodium nitrite under acidic conditions to form a diazonium salt. This salt is then coupled with ethyl 2-chloroacetoacetate in a polar solvent like ethanol or methanol to efficiently form the target product. The chromatographic data confirms that the product is of high purity, with a single peak at 36.234 minutes and 100% area, indicating no detectable impurities. The tailing factor of 1.05 and high plate count of 233,711 further demonstrate excellent peak symmetry and column efficiency, confirming the product meets pharmaceutical quality standards required for Apixaban synthesis. The conclusion is that the reaction shows better efficiency and yield (74.32%) in a single-pot process using a polar solvent compared to a lower yield (43.83%) in a double-pot process with a non-polar solvent, confirming the single-pot method as the preferred route for higher yield and process efficiency.

Key words : Apixaban,Anticoagulant,Diazocoupling reaction, Diazonium salt,One pot,Double pot,Antithrombic therapy.

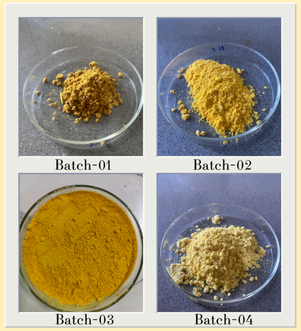
Raw Material

1. P-Anisidine
2. Sodium Nitrite
3. Con Hydrochloric Acid
4. Ethy 2 Chloro AcetoAcetate
5. EhylAcetate
6. Sodium Acetate

Process Data

Batch No.	Type	Solvent	% yield
1	Double pot	Toluene	43.83 %
2	Double pot	Methanol	71.46 %
3	Single pot	Methanol	65.65 %
4	Single pot	Methanol	74.32 %

Product

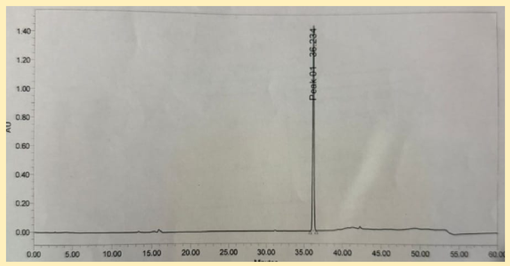


Process

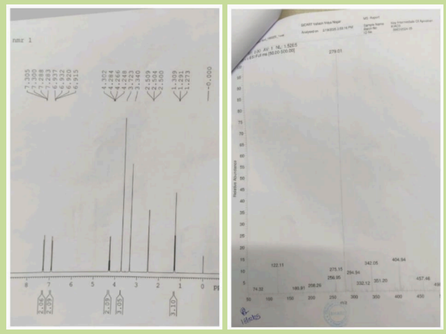
The process begins by dissolving p-Anisidine in water, adding concentrated HCl, and stirring. A separate sodium nitrite solution is prepared and mixed at -10 to 0°C to form the diazonium salt. Sodium acetate is dissolved in water at a low temperature. Ethyl 2-chloro acetoacetate is then mixed with acetone and other reagents, stirred, and allowed to react completely. The reaction mixture undergoes layer separation using a separating funnel, followed by washing with water to remove impurities. The ethyl layer is distilled, stripped with methanol, filtered, and washed with cold methanol before drying to obtain the final product.

For product recovery, the mother liquor is evaporated, mixed with methanol while chilling for an hour, and filtered to obtain the product crystals. The recovered slurry is then dried to yield purified powder. This ensures maximum yield and purity of the final product while removing unwanted residues.

Characterization



Parameter	Observed Value	Standard Limit	Conclusion
Retention Time (RT)	36,234 min	Matches Standard	Acceptable
Peak Time	16,702,342	Within expected range	Acceptable
USP Tailing Factor	1.05	<= 2.0 (Good Peak Symmetry)	Acceptable
USP Plate Count	233,711	>= 2000 (High Column efficiency)	Excellent
Peak Purity (% Area)	100.00 %	No impurities detected	High Purity



The NMR spectrum exhibits characteristic chemical shifts that align well with the expected values from standard references. The aromatic proton signals appear in the 7.0–7.5 ppm range, while the methoxy (-OCH_3) proton resonates at ~3.8 ppm, confirming the presence of the para-methoxyphenyl moiety. The ethyl (-CH_2CH_3) protons are evident in the 1.2–4.5 ppm range, with a distinct triplet and quartet pattern confirming the presence of the ethyl ester functional group. No extraneous peaks suggest a high level of purity.

The Mass Spectra (MS) analysis further supports the molecular composition, with a molecular ion peak (M^+) at 270.01, which corresponds precisely to the theoretical molecular weight of the target compound. Fragmentation patterns align with expected cleavage pathways, with significant peaks at 122.11, 273.15, 342.05, and 457.46, further validating the proposed structure.

Conclusion

Among the tested batches for synthesizing the key intermediate of apixaban from p-anisidine, Batch 4 achieved the highest yield (74.32%) and superior purity using a single-pot process with methanol. TLC confirmed the product's purity, while batches using toluene had lower yields and poorer quality. The double-pot process also resulted in reduced yield, highlighting the efficiency of the single-pot method and the critical role of solvent selection in optimizing synthesis.

Acknowledgment

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Pinto, Orwat, Koch, Donald J.P. Michael J. Stephanie (2007). "Discovery of 1-(4-Methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (Apixaban, BMS-562247), a Highly Potent,Selective, Efficacious, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa". Journal of Medicinal Chemistry. 50 (22): 5339–56.