Synthesis And Pharmacological Studies of Alcl3 Mediated Synthesis Of 7-Sulfonyl Indoles as Chorismate Mutase Inhibitors

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***Abstract*—Indole derivatives constitute an important class of heterocyclic compounds known for their diverse biological and pharmacological activities. In the present study, a series of 7-sulfonyl indole derivatives were synthesized via an efficient $AlCl_3$-mediated sulfonylation reaction. The synthetic protocol offers mild reaction conditions, good yields, and operational simplicity. Structural elucidation of the synthesized compounds was carried out using IR, ^1H NMR, ^{13}C NMR, and mass spectral analysis.**

The pharmacological potential of the synthesized compounds was evaluated by assessing their inhibitory activity against chorismate mutase, a key enzyme involved in the shikimate pathway essential for microbial survival and absent in humans. Several derivatives exhibited significant inhibitory activity, indicating a strong structure–activity relationship influenced by the nature and position of sulfonyl substitution on the indole nucleus. The findings suggest that 7-sulfonyl indoles synthesized through $AlCl_3$ mediation may serve as promising lead molecules for the development of novel antimicrobial agents targeting chorismate mutase.

***Index Terms*—Indole derivatives; $AlCl_3$-mediated synthesis; 7-sulfonyl indoles; Chorismate mutase inhibitors; Shikimate pathway; Antimicrobial activity**

I. INTRODUCTION

Heterocyclic compounds play a vital role in medicinal chemistry due to their wide spectrum of biological activities. Among them, indole and its derivatives represent a privileged structural scaffold found in numerous natural products, pharmaceuticals, and biologically active molecules. Indole-based compounds exhibit a broad range of pharmacological properties such as antimicrobial, anti-inflammatory, anticancer, antioxidant, and enzyme inhibitory activities. The versatility of the indole nucleus has made it an attractive target for the development of novel therapeutic agents.

Sulfonyl-containing compounds have gained considerable attention in drug discovery because the sulfonyl group ($–SO_2–$) enhances metabolic stability, binding affinity, and overall pharmacokinetic properties of bioactive molecules. The introduction of sulfonyl moieties into heterocyclic frameworks often leads to improved biological efficacy. In particular, 7-sulfonyl indole derivatives have emerged as promising candidates in medicinal chemistry due to their ability to interact effectively with enzyme active sites through hydrogen bonding and electrostatic interactions.

Chorismate mutase is a key regulatory enzyme in the shikimate pathway, catalyzing the conversion of chorismate to prephenate, a crucial step in the biosynthesis of aromatic amino acids in plants, fungi, and microorganisms. Since this pathway is absent in humans, chorismate mutase represents an attractive and selective molecular target for the development of novel antimicrobial agents. Inhibition of this enzyme disrupts microbial growth and survival, making chorismate mutase inhibitors valuable in combating drug-resistant infections.

Conventional synthetic approaches for sulfonyl indole derivatives often suffer from limitations such as harsh reaction conditions, low yields, and poor regioselectivity. In this context, $AlCl_3$-mediated synthesis has emerged as an efficient and regioselective method for introducing sulfonyl groups onto the indole nucleus. Aluminum chloride acts as a Lewis acid catalyst, facilitating electrophilic sulfonylation specifically at the 7-position of indole under controlled conditions. This method offers

advantages including operational simplicity, shorter reaction time, and improved yields.

In view of the pharmacological significance of indole derivatives, the biological importance of sulfonyl groups, and the therapeutic potential of chorismate mutase inhibition, the present study aims to synthesize a series of 7-sulfonyl indole derivatives using $AlCl_3$-mediated methodology and to evaluate their pharmacological activity as chorismate mutase inhibitors. The study further seeks to establish a structure–activity relationship to identify promising lead compounds for future antimicrobial drug development.

II. MATERIALS AND METHODS

Cu- catalyzed synthesis of 2, 2′-spiroindole derivatives

. Materials

All chemicals were purchased from commercial suppliers and used as received without further purification unless otherwise stated. Oxindole and indole derivatives, isatin analogues, and other coupling partners were of analytical grade. Copper salts, including CuI, CuCl, or $Cu(OAc)_2$, were used as catalysts. Bases such as potassium carbonate (K_2CO_3), cesium carbonate (Cs_2CO_3), or triethylamine (Et_3N) were employed as required. Solvents including acetonitrile, dimethylformamide (DMF), ethanol, methanol, and dichloromethane were dried and purified according to standard procedures when necessary.

Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates and visualized under UV light. Column chromatography was carried out using silica gel (60–120 mesh).

Procedure for the Cu-Catalyzed Synthesis of 2,2′-Spiroindole Derivatives

In a typical experiment, the appropriate oxindole or indole-based substrate (1.0 equiv) and the corresponding reaction partner (1.0–1.2 equiv) were placed in a dry round-bottom flask equipped with a magnetic stir bar. To this mixture, the copper catalyst (5–10 mol%) and base (1.5–2.0 equiv) were added, followed by the selected solvent (5–10 mL).

The reaction mixture was stirred at room temperature or heated at 60–80 °C for the specified time until completion, as monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature and quenched with water. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.

The crude residue was purified by silica gel column chromatography using an appropriate gradient of petroleum ether/ethyl acetate to afford the desired 2,2′-spiroindole derivatives in moderate to excellent yields.

Characterization of Products

The synthesized compounds were characterized by melting point determination, infrared (IR) spectroscopy, and nuclear magnetic resonance (^1H and ^{13}C NMR) spectroscopy. High-resolution mass spectrometry (HRMS) was used to confirm the molecular weights of selected compounds. Spectral data were consistent with the proposed structures.

III. RESULTS AND DISCUSSION

Synthesis of Cyclopenta [*b*] indoles

Reaction Optimisation

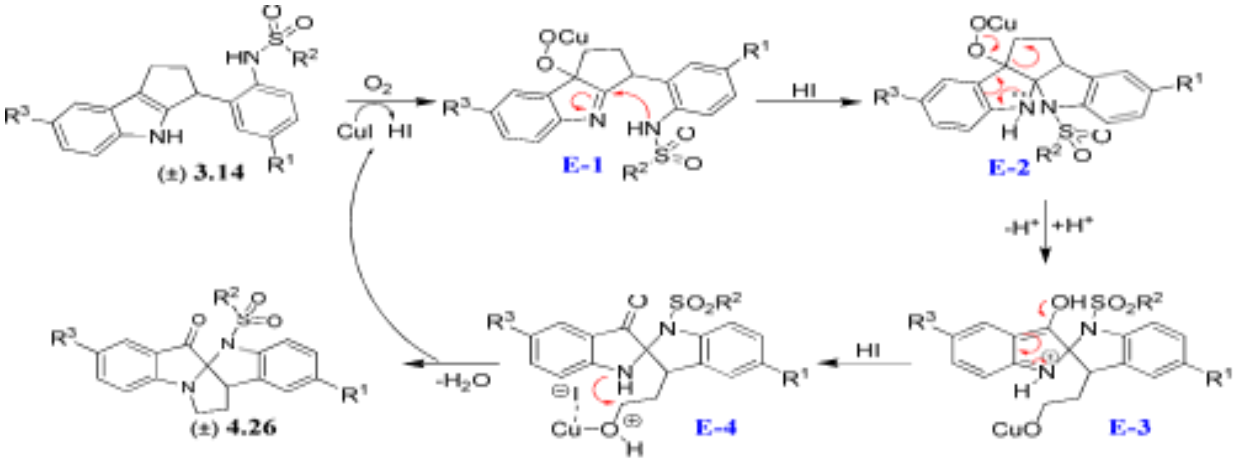
We initiated our study by examining the anticipated cascade reaction of 3.14aa under various reaction conditions, including different catalysts, bases, and solvents. The results are summarized in Table 4.1. Initially, the reaction was carried out using 3.14aa, $Cu(OAc)_2$ (1 equiv), and Et_3N in DMF at 120 °C under air. Under these conditions, the desired product 4.26a was obtained in 25% yield after 3 h (entry 1, Table 1.1).

Replacement of $Cu(OAc)_2$ with other copper catalysts, such as $Cu(OTf)_2$, resulted in a slight improvement, affording 4.26a in 30% yield (entry 2, Table 1.1). Screening of bases revealed that the use of Cs_2CO_3 significantly enhanced the reaction efficiency, providing the desired product in 56% yield (entry 3, Table 4.1). Further optimization showed that the combination of $Cu(OTf)_2$ and Cs_2CO_3 led to an improved yield of 60% (entry 4, Table 1.1).

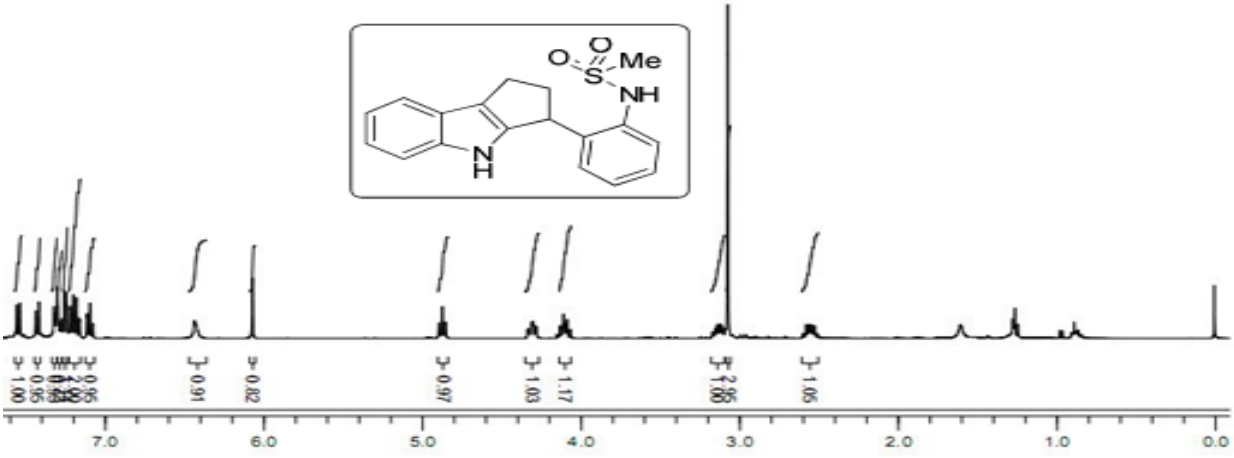
In contrast, the presence of benzoquinone almost completely suppressed product formation, and an unidentified polar material was observed as a side product (entry 5, Table 1.1). At this stage, the precise role of the base in the cascade reaction was not fully

understood. Interestingly, we found that the reaction proceeded efficiently even in the absence of base when $Cu(OTf)_2$ was employed as the catalyst, delivering the desired product in comparable yield (entry 6, Table 1.1).

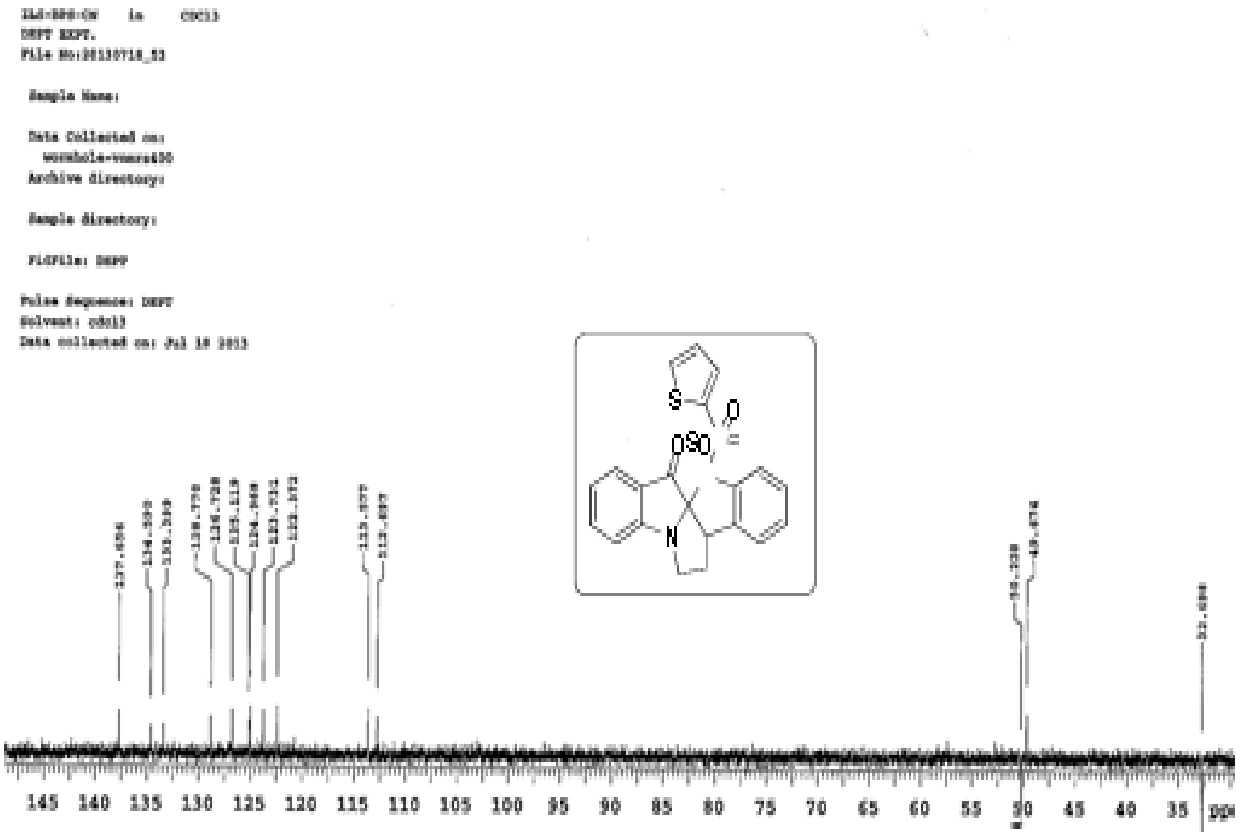
Entry	Catalyst	Solvent/base	Time(h)	Yield[b](%)
1	1eq.$Cu(OAc)_2$	DMF/Et_3N	3	25
2	1eq.$Cu(OTf)_2$	DMF/Et_3N	3	30
3	1eq.$Cu(OAc)_2$	DMF/Cs_2CO_3	2	56
4	1eq.$Cu(OTf)_2$	DMF/Cs_2CO_3	2	60
5	1eq.$Cu(OTf)_2$	DMF/Cs_2CO_3	3	10[c]
6	1eq.$Cu(OTf)_2$	DMF	3	60
7	20mol%$Cu(OTf)_2$	DMF	6	58
8	20mol%$Cu(OTf)_2$	DMF+H_2O(7:3)	1.5	70
9	10mol%$Cu(OAc)_2.H_2O$	DMF+H_2O(7:3)	1.5	65
10	5mol%CuI	DMF+H_2O(7:3)	4	56
11	5mol%CuI	DMF+H_2O(1:1)	4	50
12	10mol%CuI	DMF+H_2O(7:3)	2	66
13	Nocatalyst	DMF/Cs_2CO_3	6	0



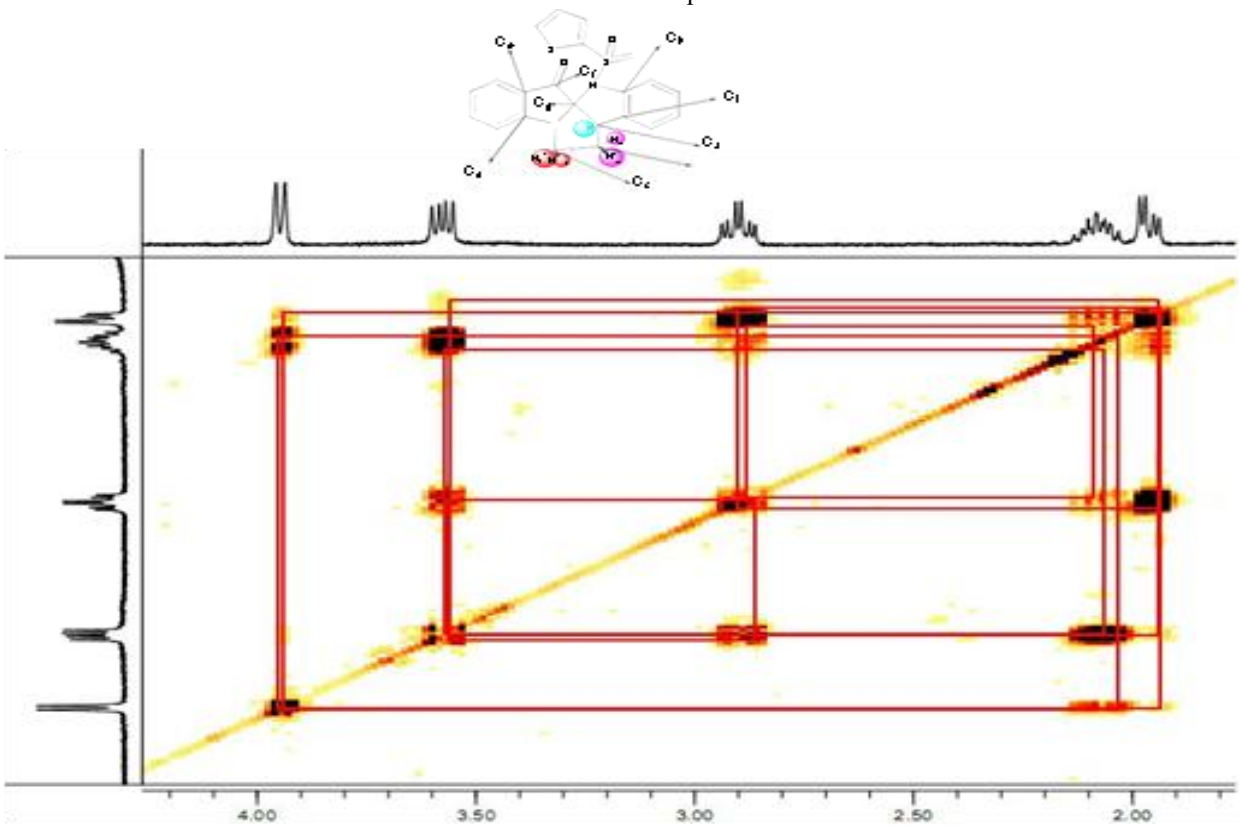
Scheme 1.1 reaction mechanism.



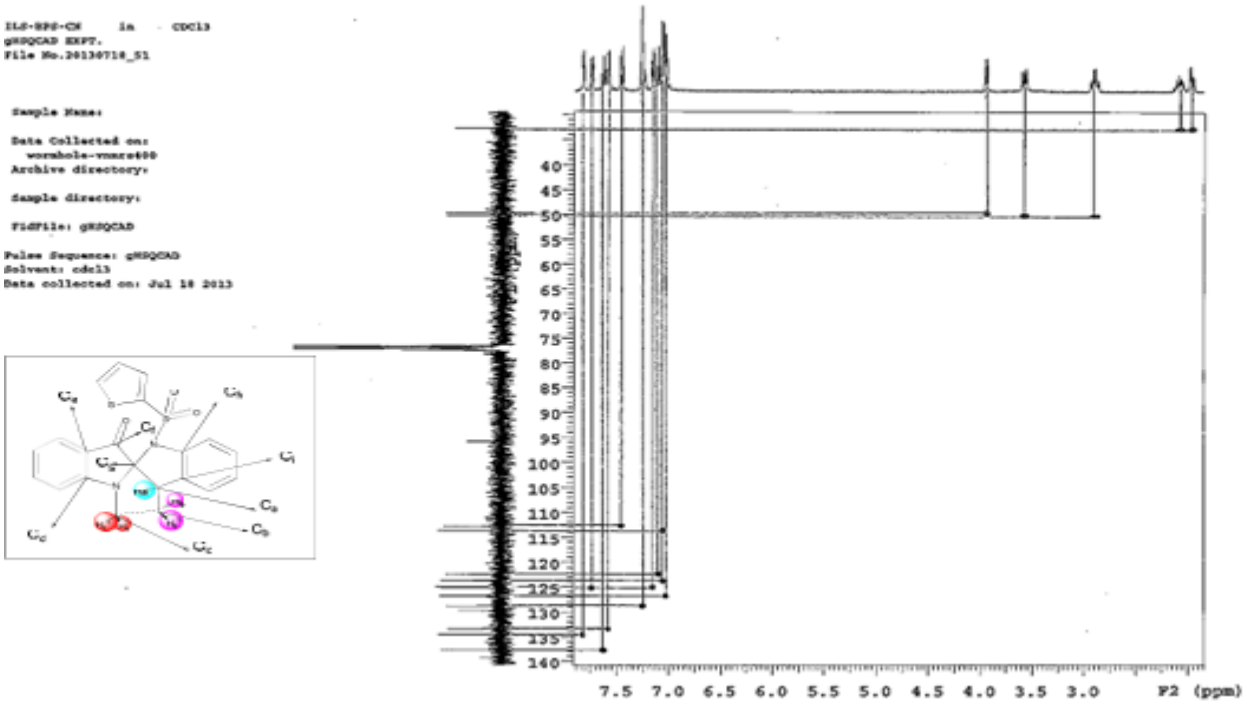
^{13}CNMRspectrum (Varian,100MHz) of compound **1.2 aa**in$CDCl_3$



1.3 DEPT of compound



1.4 ^{1}H-^{1}HCOSY of compound



1.5 HSQC of compound

IV. CONCLUSION

we have developed an efficient copper-catalyzed strategy for the synthesis of structurally diverse 2,2′-spiroindole derivatives via a cascade reaction under mild conditions. Systematic optimization of the reaction parameters revealed that $Cu(OTf)_2$ is the most effective catalyst, enabling smooth product formation with good to excellent yields. Notably, the reaction proceeds efficiently even in the absence of an external base, highlighting the unique catalytic role of copper in promoting the cascade process.

The protocol exhibits broad substrate scope and good functional-group tolerance, allowing the construction of complex spiroindole frameworks from readily available starting materials. The operational simplicity, avoidance of stoichiometric additives, and use of an inexpensive and environmentally benign copper catalyst make this method both practical and sustainable. Given the significance of spiroindole motifs in medicinal chemistry and natural product synthesis, this methodology is expected to find wide applicability in the synthesis of biologically relevant molecules and advanced synthetic intermediates**.**

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