ONE-POT ENVIRONMENT FRIENDLY SYNTHESIS OF IMINE DERIVATIVE OF FURFURAL AND ASSESSMENT OF ITS ANTIOXIDANT AND ANTIBACTERIAL POTENTIAL

Miss Maria Abdullah Butt[1]*, Prof. Dr. Muhammad Nawaz Chaudhary[2], Prof. Dr. Sajid Rashid Ahmed[3], Dr. Muhammad Zaheer[4], Dr. Muhammad Naeem[5]

ABSTRACT

In this study, an environment friendly, one-pot method is used to synthesize immine derivative (E)-8-((furan-2-ylmethylene)amino)-4-methyl-7-oxo-2-thiabicyclo[4.2.0]oct-4ene-5-carboxylic acid from renewable lignocellulosic biomass furfural and 7-ADCA. Furfural derived from lignocellulosic biomass plays an important role in this environment friendly approach. This process is based on the principles of green chemistry, especially the use of ethanol as a solvent reduces the environmental impacts associated with conventional synthetic methods. The chemicals and processes utilized, highlights a sustainable practice in pharmaceutical research and are aimed at using 7-aminodeacetoxy cephlospornic acid (7ADCA) and furfural for the synthesis of Schiff Base (FA). The synthesized imine derivative (FA) was characterized using various analytical techniques such as melting point, FT-IR, NMR and SEM. The derivative appeared to be a brown coloured fine powder having melting point 170°C and average particle size 450nm with agglomerated form and spherical shape. The yield was calculated to be 64%. Systematic screening of the synthesized imine showed promising antioxidant activity by phosphomolybdenum assay and In-Vitro antibacterial assay exhibited bactericidal activity against a variety of gram-positive and gram-negative bacteria. These studies not only appear to provide strategies for manufacturing sustainable products also promotes sustainable practices in pharmaceutical research and explores the ways in which furfural-derived imines can be used in pharmaceutical and materials science.

Keywords: Schiff base ligand, green synthesis, 7-aminodeacetoxy cephlospornic acid, InVitro Antibacterial activity, Drug Discovery

[1]*College of Earth and Environmental Sciences, University of the Punjab, Lahore-54000, Pakistan, Email: maria.abdullahbutt@gmail.com
[2]Principal of Department of Environmental Sciences and Policy, Lahore School of Economics, Lahore-53200, Pakistan, Email: muhammadnawazchaudhry@yahoo.com
[3]Principal of College of Earth and Environmental Sciences, University of the Punjab, Lahore-54000, Pakistan, Email: sajidpu@yahoo.com
[4]Senior Scientific Officer in Applied Chemistry Research Centre, Pakistan Council of Scientific and Industrial Research Laboratories Complex, Ferozepur Road, Lahore-54570, Pakistan, Email: mzaheerchem@yahoo.com
[5]Principal Scientific Officer in Applied Chemistry Research Centre, Pakistan Council of Scientific and Industrial Research Laboratories Complex, Ferozepur Road, Lahore-54570, Pakistan, Email: chmnaeem08@yahoo.com

***Corresponding Author:** Maria Abdullah Butt
*College of Earth and Environmental Sciences, University of the Punjab, Lahore-54000, Pakistan, Email: maria.abdullahbutt@gmail.com

DOI: 10.53555/ecb/2024.13.01.39

1.0 INTRODUCTION

In recent years, it has become important in pharmaceutical industry to pursue sustainable and environment friendly methods of production[1-5-25]. Producing efficient and green products not only addresses the growing concerns about environmental pollution but is also aligns with chemistry principles.[3-14] Furfural, a novel bio-based chemical derived from lignocellulosic biomass, has received considerable attention as a key building material for the production of a variety of value-added products due to its bulk and sustainability [4-7] Imine derivatives exhibit a wide array of pharmacological activities, including antioxidant and antibacterial properties, making them intriguing candidates for exploration in drug discovery and development.[24]

The continuous exploration of novel and inventive compounds remains of utmost importance. In the initial era of the chemical revolution [28], the discovery of groundbreaking compounds not only revolutionized contemporary life but also raised concerns about escalating environmental pollution. In the present day, there is a growing advocacy for industries to shift towards the initial synthesis of environmentally benign chemicals and materials, as opposed to implementing remedial measures for environmental restoration post-manufacturing to address chemical contaminants.[16] Additionally, Schiff base coordination complexes are of considerable industrial interest due to their easy synthesis, broad chemical versatility, and diverse applications in materials chemistry, biological modelling, and catalytic processes.[20] There is a growing emphasis on green synthesis strategies that optimize drug development, employing efficient and eco-friendly approaches to foster symbiotic relationships.[23] This approach aims to contribute to the production of vital medicines while minimizing environmental impact through improved chemical processes. Currently, substantial efforts are underway to devise new multicomponent reactions (MCRs) and enhance existing reactions, further advancing the field and reducing the ecological footprint of chemical processes.[33]

This study attempts to present one pot, eco-friendly method to synthesize Schiff base derivative of Furfural. This study is practical implication of green chemistry principals and aims to reduce environmental impacts produced by traditional methods and reduce the hazardous effluents produced by pharmaceutical industry.

The imine derivative of furfural synthesized in this study was systematically evaluated for its antioxidant capacity, as oxidative stress plays an important role in various pathological conditions Besides, the antibacterial properties of the compound were also evaluated contributing to growing knowledge in terms of methods Instead, it explores potential applications of furfural-derived imines in the fields of medicine and physical science The results of this study may pave the way for the development of new environment friendly drugs with activity a broad range of types in line with the overarching goals of green and sustainable medicine.

2.0 MATERIALS AND METHODS

2.1 Materials

Chemicals such as ethanol, methanol, furfural, 7-ADCA (7-aminodeacetoxy cephlospornic acid) were obtained from Merck, and are analytical grade locally available commercial organic solvents, distilled following industry standards for consistency 94.9% ethanol concentration before use.

2.2 Schiff Base (FA) Synthesis methodology

The Schiff base ligand (FA) was synthesized (Fig. 1) by dissolving 2g of 7-ADCA (7Aminodeacetoxycephalosporanic acid) in 40mL of ethanol in a round-bottom flask. The solution was stirred at room temperature using a magnetic stirrer, and 0.2mL of triethylamine
(TEA) was added to facilitate the dissolution of 7-ADCA. Once dissolved, the reaction mixture was transferred to a water bath and heated at 80-90°C with continuous stirring. During the reaction, furfural (0.8mL) was added dropwise, and the reaction proceeded for approximately 46 hours.

Upon confirming the completion of the reaction by TLC using a chloroform: methanol (4:1) solvent system, the ethanol was evaporated. Subsequently, 100mL of cold water was added to the residue and stirred. Following that, 0.3mL of sulfuric acid was added dropwise to precipitate the crude product. The resulting product was filtered, washed three times with cold water and dioxane (1:1) and then dried at room temperature, resulting dark brown coloured precipitate.

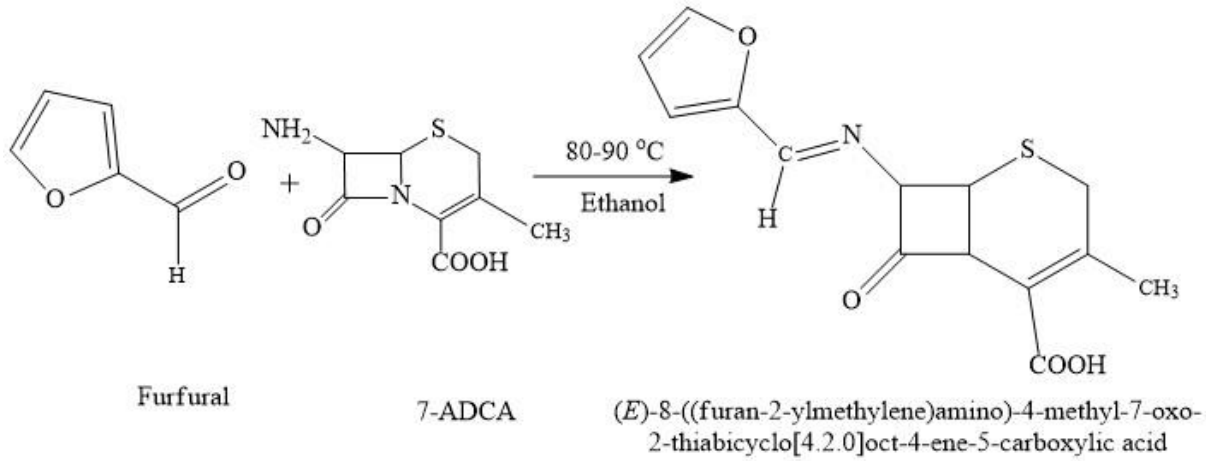

Fig 1. Synthesis of Schiff Base Ligand (E)-8-((furan-2-ylmethylene)amino)-4-methyl-7-oxo2-thiabicyclo[4.2.0]oct-4-ene-5-carboxylic acid

2.3 Antioxidant Activity

The estimation of the total antioxidant activity of the imine derivative (FA) involved measuring the development of a phosphomolybdenum complex by following a method established by Prieto et al.[26] In individual capped vials, both the test material FA and the standard Cefradine were dissolved in methanol at a concentration of 0.25 mg/mL. Later, a newly made phosphomolybdenum reagent solution (2 mL) was added to these solutions. (The reagent solution was created by dissolving half the quantities: ammonium molybdate (1235 mg), sodium phosphate (2660 mg), and concentrated sulfuric acid (8.35 mL) in distilled water (250 mL)). All containers having the test compounds were incubated for 70 minutes in an incubator set at 55 ± 1 °C [11-29] A duplicate blank was accomplished pursuing the same protocol but eliminating the adding of the test compound. Subsequent to the incubation period, all vials were cooled to room temperature, and the absorbance for the test solutions, standard, and blank were measured using a UV-Vis spectrophotometer at 695 nm [12].The total antioxidant potential of the Schiff base was stated relative to half the value of BHT (0.609). To guarantee accuracy, all experiments were conducted in triplicate.

2.4 In-Vitro Antibacterial Activity

In-vitro antibacterial efficiency of the synthesized Schiff Base (FA) was accessed by using four bacterial strains, namely *Staphylococcus aureus* and *Stenotrophomonas maltophilia* (gram-positive), and *Pseudomonas aeruginosa* and *Xanthomonas campestris* (gramnegative), following the methodology outlined by Yousif et al. [34] The ability of the Schiff base complex to impede bacterial growth was compared with the well-known antibacterial drug Cefradine, serving as the positive control, while DMSO was utilized as the negative control.

A well-expansion method was adopted to determine the efficacy and sensitivity of the Schiff Base (FA) against pathogenic microorganisms. These experiments were performed in duplicate for consistency. After 24 hours of incubation, the inhibition zone was measured in millimetres to determine the level of bactericidal activity.[13]

2.5 Characterization Techniques

The characterized Schiff base (FA) involved extensive analysis using analytical, physicochemical, and spectral techniques for NMR analysis using a Bruker Advance III HD 400 MHz NMR instrument equipped with TopSpin 3.5 software for identification and characterization. The surface morphology of the synthesized Schiff base ligand (FA) was studied by SEM analysis using a Nova NanoSEM 450 field emission scanning electron microscope (FE-SEM) The functional groups of the Schiff base (FA) were identified in the range of 4000–2000. Melting Point of FA was determines using electrothermal instrument for measuring temperature. This allowed a better and more detailed characterization of the Schiff basis (FA) synthesized by a multistage approach.

Fig. 2 Schematic diagram showing the (E)-8-((furan-2-ylmethylene)amino)-4-methyl-7-oxo2-thiabicyclo[4.2.0]oct-4-ene-5-carboxylic acid synthesis process.

3.0 RESULTS AND DISCUSSION

3.1 IR Spectra Studies

In this study, we performed FT-IR spectroscopy, as illustrated in Fig. 3, to elucidate the functional groups of imine derivative (FA). The FT-IR spectrum of derivative was attained in the wavenumber range 640-3300 cm^{-1}. The prominent peak observed at 3350cm^{-1} agrees to O-H stretching vibrations, indicating the presence of hydroxyl groups. Especially in the case of furfural and 7-ADCA this peak suggests the presence of hydroxyl groups[10]. A further remarkable peak at 3280cm-1 is attributed to a specific O-H stretching vibration, which can arise from hydroxyl groups.[17] The peak detected at 2850cm-1 is allied with C-H stretching vibrations, suggesting that it is correlated with aliphatic (saturated) hydrocarbon chains [31]. A clear peak at 1725cm^{-1} indicates a C=O broadening vibration, indicating the presence of a carbonyl group. In the case of furfural this probably agrees to the carbonyl group of the aldehyde functional group[22]. The peak at 1636cm^{-1} reveals C=C stretching vibrations, demonstrating the presence of double bonds. This is precisely related to the furan ring in furfural [18]. Furthermore, the point at 1383cm^{-1} is attributed to the C-H bending vibrations generally seen in aliphatic compounds [19]. The peak at 1287cm^{-1} is associated with C-N stretching vibrations, indicating a possible correlation between the amide groups in 7-ADCA [9-35]. A peak for C-O broadening vibration is noticed at 1126cm-1, indicating the existence of ether or ester functional groups [2]. In addition, the peaks at 938cm^{-1} and 751cm^{-1} are allocated to C-H bending vibrations, which can be related to the substituted benzene rings [30]. Together, these data contribute to a broader understanding of the functional groups of the investigated Schiff bases (FA).

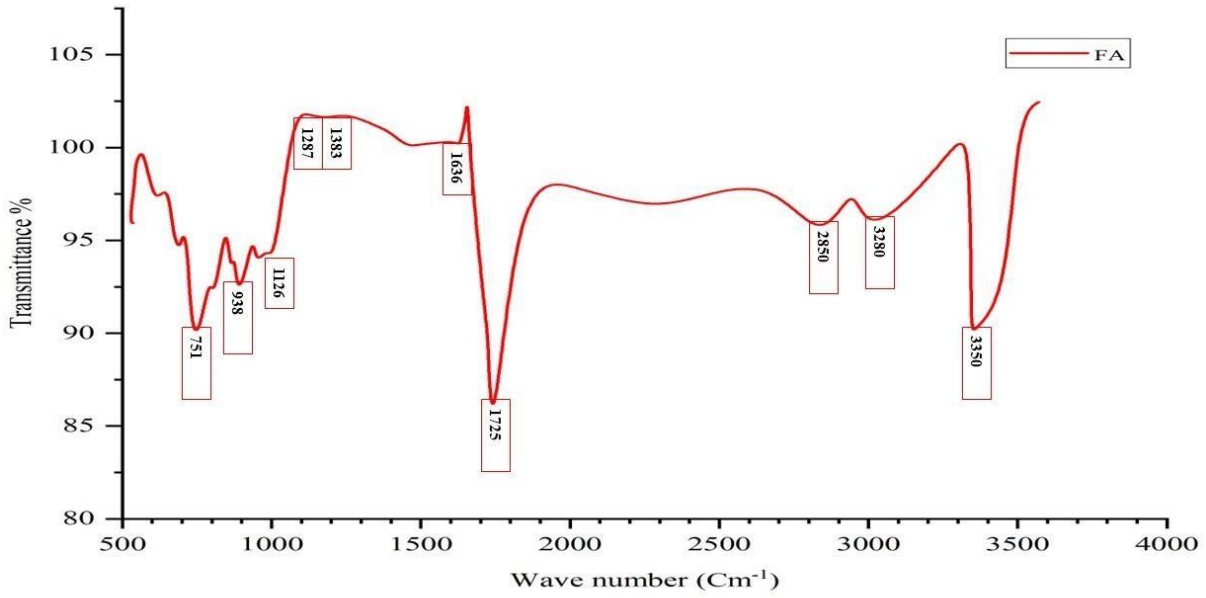

Fig. 3 FTIR Spectra of Imine Derivative (FA) showing prominent peaks.

3.2 NMR Analysis

The aldehyde proton signal shows in the normal low-field place at 9.10ppm[21]. The aromatic protons appear anticipated to the asymmetry as two groups of signals in a region 9.411-and 9.811 ppm shows azomethine proton (–CH=N–) of the compound while aliphatic protons of compounds were found in the range of 1.174-3.339.[6]

Table.1 Analytical data of prepared Schiff Base (FA)

Name	(E)-8-((furan-2-ylmethylene)amino)-4methyl-7-oxo-2-thiabicyclo[4.2.0]oct-4ene-5-carboxylic acid
Chemical Formula	C14H13NO4S
Molecular Weight (g mol^{-1})	291.32
Elemental Analysis (%)	**C**=57.72 **H**= 4.50 **N**= 4.81 **O**= 21.97 **S**= 11.01
Melting Point (°C)	170
Colour	Dark Brown
Yield % **Percentage Yield=** **(Theoretical Yield/Actual Yield) ×100**	64

3.3 Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) is applied to acquire synthesized imine derivative's (FA) images by plane probing with a centered electron beam. In the present study, the ligand FA was inspected through Scanning Electron Microscopy Fig 4 (b) to estimate size of particles and plane of the FA. The plane of Sample FA demonstrates that particles vary in size and have spherical shape. Likewise, SEM analysis determined non-existence of contamination and particles appear in the form of agglomerates. Other than this, size of particles was projected to be in the range of 300-900nm and the average particle size was 450nm Fig 4 (a).

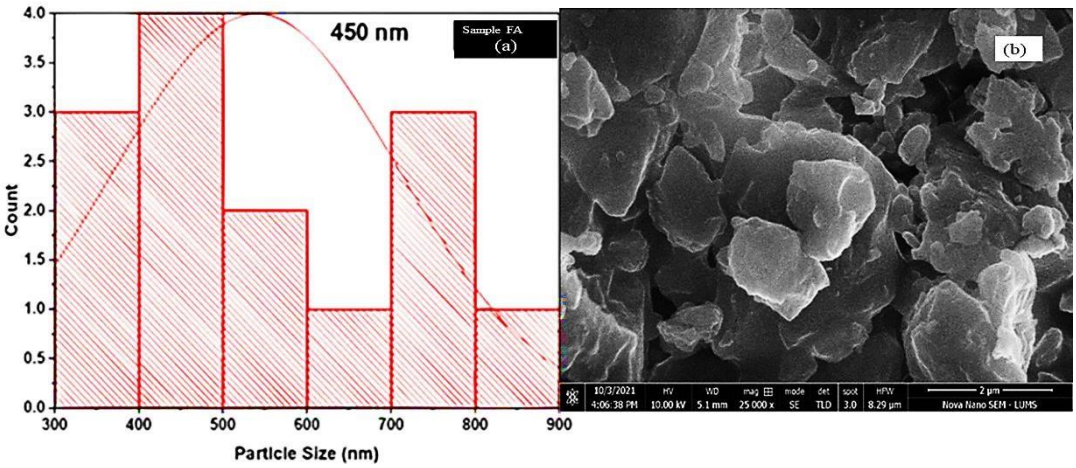

Fig. 4 (a) Histogram plot (b) SEM micrograph of FA

3.4 Total Antioxidant Activity

In the this study, the total antioxidant capacity of Schiff base (FA) complexes was evaluated by phosphomolybdenum assay with BHT (butylated hydroxytoluene) taken as standard[32]. There are few reasons for the employment of this method for this study; BHT is a renowned and widely utilized synthetic antioxidant. Taking it as a standard permitted for the comparative investigate of Schiff base complex' antioxidant capacity against identified reference compound. Through the phosphomolybdenum assay, Mo(VI) reduction into Mo(V) can be measured by the formation of green complex.[12] The Schiff base moiety normally possesses a nitrogen atom from an imine group and an amine group. This structure participates in antioxidant property by delivering electron-donating N atom which are responsible for free radical scavenging[15]. Antioxidant activity of Schiff base (FA) came out to be 0.680 ± 0.03 which is higher than standard drug Cefradine 0.48 ± 0.05 taken BHT as control 0.46 ± 0.09.

3.5 In Vitro Anti-Bacterial study

The *in vitro* experiment concerning organic testing effects of the tested synthesized compound was

performed alongside chosen pathogenic species by using well diffusion method. Complete antibacterial assay showed that synthesized Schiff base (FA) plays efficient role as antibacterial agent[27]. In this search, Schiff base (FA) exhibited its effective function as antibacterial drug and their action was calculated alongside Cefradine, promising bactericidal drug which was used as positive control and DMSO was utilized as negative control. In accumulation to this, DMSO stays inactive against all infective species and displayed no activity. Cefradine showed the utmost anti-bacterial activity against *Stenotrophomonas maltophilia* conc. 25mg/ml and least against *Staphylococcus aureus.* On the other hand, FA demonstrated the utmost antibacterial activity against *Staphylococcus aureus* at conc. 25mg/ml. Consequently, inhibiting bacterial growth capacity of derivative is imperative as because to this specific property this compound can be utilized for the treatment of any of the bacterial disease that arise with these pathogenic species. [8]

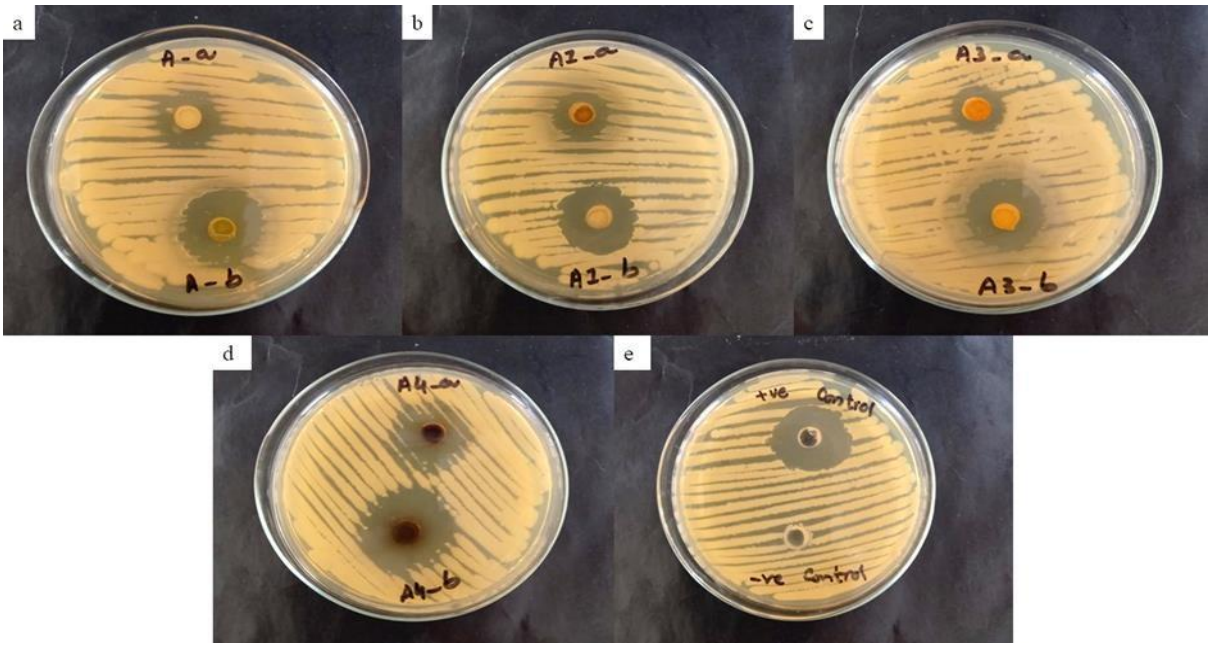

Fig. 5 (a, b, c, d, e) Analysing Microbial Susceptibility: Exploring Inhibition Profiles of FA

Table: 2 Percentage Inhibition of Antibacterial Activity for Compound FA at Two Different Doses Against Four Pathogenic Bacterial Strains. All Values Represent Mean ± RSD.

12.5 mg/ml					**25mg/ml**			
	S. Aureus	***P. Aeruginosa***	***X. Campestris***	***Steno Maltophilia***	***S. Aureus***	***P. Aeruginosa***	***X. Campestris***	***Steno. Maltophilia***
FA	71.4 ±0.3	68.6±0.4	73.1 ±0.6	76.5 ±0.4	92.1 ± 0.8	86.5 ±0.7	93.2±0.3	85.5±0.6
Cefradine	65.5 ±0.5	70.08 ±0.7	69.5 ±0.2	78.5 ±0.7	85.5± 0.3	89.2 ±0.8	86.5 ±0.6	91.6±0.5
DMSO	-	-	-	-	-	-	-	-

4.0 CONCLUSION

This study showcases a one-pot, green synthesis of the imine derivative of furfural, emphasizing the pivotal role of environmentally benign synthetic methodologies. The synthesized Schiff Base Ligand (FA) exhibited significant antioxidant activity, presenting a potential avenue for combating oxidative stress-related pathological conditions. Furthermore, the compound displayed antibacterial efficacy against both gram-positive and gram-negative bacterial strains, addressing the pressing need for novel antimicrobial agents amid escalating antibiotic resistance. The comprehensive characterization employing NMR, SEM and FTIR confirmed the functional groups present and structural integrity of the synthesized ligand (FA). The use of ethanol as a volatile solvent contributes to the environmental aspect of the study, aligning with sustainable and eco-friendly approaches in chemical synthesis. This research, at the intersection of green chemistry and medicinal chemistry, offers insights into the design of environment friendly synthetic routes for valuable compounds with potential applications in medicine and materials science. The outcomes may tile the avenue for the formation of unique therapeutic agents in alignment with the principles of green and sustainable chemistry.

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