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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF CEFADROXIL-BENZALDEHYDE DERIVED LIGAND, METAL COMPLEXES, AND EVALUATION OF THEIR ANTI-INFLAMMATORY, CYTOTOXIC, AND ANTIMICROBIAL ACTIVITIES

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Abstract

Background: The rise of infectious diseases and drug-resistant strains of bacteria and fungi poses a significant challenge, threatening human health and life expectancy. Researchers are actively working to develop novel antimicrobial therapies to counteract these issues.
Methods: In this study, new derivatives were synthesized from (6R,7R)-7-{[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino}-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid (cefadroxil) by reaction with Benzaldehyde. The primary aim was to enhance the antibacterial efficacy of existing antibiotics and develop therapeutically active compounds. The synthesized ligand was characterized through elemental analysis, various physicochemical tests, and multiple spectroscopic techniques, including infrared (IR), ^{1}H NMR, ^{13}C NMR, and UV spectroscopy. The ligand underwent solubility and chemical tests and was screened for *in vitro* antibacterial activity using the disc diffusion method. Anti-inflammatory and antioxidant properties were also evaluated.
Results: Synthesized compound exhibited superior antibacterial properties compared to cefadroxil alone, with significant zones of inhibition and MIC values. Additionally, anti-inflammatory and cytotoxicity tests yielded promising outcomes, indicating potential for future antibiotic applications.
Conclusion: Study concludes that while metal coordination with structural modifications could lead to the discovery of novel lead compounds with enhanced therapeutic potential.
Keywords: antibacterial, cefadroxil, NMR spectra, schiff base ligand, UV.

INTRODUCTION

The escalating threat of antibiotic-resistant pathogens presents a formidable challenge to global public health, necessitating the continuous pursuit of novel therapeutic strategies[1,2,3]. Although many efforts have been made in medicinal chemistry, comparatively less work has been done on the synthesis of Schiff base derivatives of cephalosporin antibiotics. This is partly because of the structural complexity of the molecules of cephalosporins, which contain multiple reactive functional groups, often resulting in low synthetic yields[4-6].

A promising approach to overcoming this challenge involves the rational modification of existing antibiotics through structure-activity relationship (SAR) studies. It is well known that Schiff base derivatives co-ordinate with metal ions and are known to form mono, di and polynuclear complexes with metal ions. The electronic and steric properties of their donor atoms make these compounds monodentate, bidentate or tridentate ligands[7,8].

In this study, we report the synthesis of Schiff base derivatives of cefadroxil, a first-generation cephalosporin, through condensation with benzalde-hyde, with the objective of enhancing its antimicrobial potency. Cefadroxil exhibits broad-spectrum activity against Gram-positive cocci and select Gram-negative bacteria, alongside notable resistance to β-lactamase degradation and a favorable safety profile. Schiff bases are well-established pharmacophores, displaying diverse biological activities such as antimicrobial, anti-inflammatory, antioxidant, and cytotoxic properties, making them attractive scaffolds for drug development[9,10]. The structural elucidation of the synthesized derivatives was performed using infrared (IR) spectroscopy, proton

nuclear magnetic resonance (1H NMR), carbon-13 nuclear magnetic resonance (13C NMR), and ultraviolet-visible (UV-Vis) spectroscopy, confirming the successful formation of the characteristic azomethine (-CH=N-) functional group, a key determinant of bioactivity. To further enhance their pharmacological potential, these Schiff base derivatives were complexed with transition metals, including silver (Ag), copper (Cu), cobalt (Co), and nickel (Ni). Metal complexation has been shown to improve the stability, bioavailability, and antimicrobial efficacy of ligands by modulating their electronic properties and facilitating interactions with bacterial membranes. The resulting metal complexes exhibited enhanced antibacterial and antifungal activity, likely due to their ability to disrupt microbial cell walls, generate reactive oxygen species (ROS), and inhibit key enzymatic pathways, ultimately leading to microbial cell death[11,12].

In vitro antimicrobial evaluation demonstrated that the Schiff base derivatives exhibited superior efficacy compared to unmodified cefadroxil, particularly against multidrug-resistant strains such as *S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *C. albicans*, and *A. niger*[13,14]. These findings underscore the potential of Schiff base derivatives as promising next-generation antimicrobial agents, offering a viable strategy to mitigate the escalating crisis of antibiotic resistance. Future investigations should focus on *in vivo* pharmacokinetic profiling, toxicity assessments, and mechanistic studies to further optimize these derivatives for clinical applications. Given the urgent need for innovative antibiotics, the structural modification of cephalosporins through Schiff base derivatization represents a compelling avenue in the development of novel antimicrobial therapeutics.

MATERIALS AND METHODS

The synthesis of ligands involved condensation reactions between β-lactam antibiotics and aromatic aldehydes under reflux. Cefadroxil and benzaldehyde (1:1 molar ratio) were dissolved in methanol and refluxed at 80 °C for 8 hours with continuous stirring. After cooling in ice bath, standing for 24 hours, the precipitate thus obtained was filtered, washed with distilled water and dried in a vacuum. For ligand LI, cefotaxime sodium (2 mmol) was reacted with isatin (2 mmol) in methanol under reflux for 6 hours in the presence of glacial acetic acid, forming a brown precipitate. Ligand LII was synthesized by refluxing cefotaxime sodium with 4-dimethylaminobenzaldehyde (2 mmol each) in methanol and acetic acid for 3 hours, yielding an olive-green solid. All products were purified by sequential washing with hot methanol–water, cold methanol, and ether, followed by vacuum drying and storage under desiccation to ensure structural integrity and stability.

Synthesis of metal complex of ligand

The synthesized ligand of the cefadroxil and benzaldehyde was reacted with $AgNO_3 \cdot 7H_2O$ in the 1:1 molar ratio in Methanol solvent. The reaction mixture was transferred into a round bottom flask, equipped with a magnetic stir bar and heated with stirring on a hot plate at 80°C for 8 hours. After the reaction was completed, the reaction mixture was heated and stirred and was then cooled in an ice-water bath. It was then allowed to stand for 24 hours undisturbed for precipitation of the product. The solid formed was filtered off, dried in the desiccator and weighed to calculate the yield of the reaction. The dried product was finally placed in a sample vial and stored in a desiccator for further use.

The ligands (0.2 g, 0.33 mmol) were dissolved in 3 mL of an ethanol-water mixture (80:20)% under continuous stirring and heated to boiling for the preparation of metal complexes. These ligand solutions were then reacted with individual alcoholic solutions of the metal salts of $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$, $CdCl_2 \cdot 2H_2O$, $[PdCl_2(PhCN)_2]$ and K_2PtCl_6. The corresponding quantities of the metal salts were 0.039, 0.039, 0.028, 0.036, 0.029, and 0.0804 g, respectively, equivalent to 0.16 mmol each. The reaction mixtures were kept stirred constantly and precipitates were immediately formed. The synthesized metal complexes were named as C1–C6 for the L1 series and C7–C12 for the LII series, respectively. The heating was continued for an additional hour to assure complete precipitation[13,14].

Next, the precipitated complexes were filtered, washed with hot ethanol-water solution (EtOH:H_2O), washed with ether and dried under vacuum.

The significance of Ag metal complex with cefadroxil

The metal (Ag-II) complex of cefadroxil play a significant role by prolonging antibacterial efficacy, improving stability and help in reducing resistance.

Moreover, it shows the synergistic effect of cefadroxil with Ag (II) supplements rather it broaden the antimicrobial spectrum. Over and above, if someone needs to have antibiotic (cefadroxil) along with Ag supplement for improving their immune system, they just can have only silver (Ag) complex of cefadroxil.

Consequently, it helps to make promising for therapeutic and biomedical applications[15].

Anti-inflammatory effect

This study employs the human red blood cell (HRBC) membrane stabilization assay to assess *in vitro* protein denaturation, comparing the effects across control, positive, and experimental groups. The degree of protein denaturation is directly proportional to the extent of inflammatory action, which, in turn, enhances the anti-inflammatory activity of the ligand under investigation. Human blood, phosphate buffer and iso-saline, hypo-saline and test compounds were used to perform the assay. In the experiment, a pH meter, test tubes, centrifuge, incubator and UV spectrophotometer were used. Diclofenac sodium was used as the standard reference drug. To prepare the sample solutions, 5 mL of the mother solution was combined with 5 mL of DMSO to achieve a concentration of 1000 µg/mL (test tube 1). Subsequently, 5 mL of test tube 1 was diluted with an additional 5 mL of DMSO to obtain a 500 µg/mL concentration, resulting in four final concentrations: 1000 µg/mL, 500 µg/mL, 250 µg/mL, and 125 µg/mL. The experimental setup included four test tubes

for the standard, four for the control, and four for the ligand, all of which were appropriately labeled. In the assay, 1 mL of phosphate buffer, 2 mL of hypo-saline was added to each test-tube and 0.5 mL of HRBC suspension was added. Later, 1 mL acetyl-salicylic acid was added to the standard group, while 1 mL of the corresponding ligand solution was added to the test groups. The developed mixtures were allowed to incubate at 37°C for 30 minutes. After incubation the samples were centrifuged and the absorbance measured at 560 nm on a UV spectrophotometer.

Cytotoxic activity

The cytotoxicity activity of the ligand was evaluated using the brine shrimp lethality bioassay with *Artemia salina* leach as the test organism, sourced from an aquarium shop in Chittagong, Bangladesh. Essential equipment included a desiccator, air pump, test tubes, test tube stand, valve, petri dish, magnifying glass, and dropper. Chemicals such as iodine-free sea salt, Dimethyl Sulfoxide (DMSO), and distilled water were utilized, with the ligand derived from cefadroxil and benzaldehyde. For the assay, 10 living nauplii were introduced into each vial containing 5 mL of simulated sea water using a Pasteur pipette, and the nauplii were counted under a magnifying glass. After 24 hours, the number of dead nauplii was recorded, and the LC50 values for the test compounds were determined. This assay is advantageous as it is a rapid, inexpensive method that requires no specialized equipment and uses a small sample size, making it suitable for statistical validation. A control vial containing 50 µL of DMSO diluted to 5 mL was prepared, and vincristine sulfate was used as a positive control. After 24 hours of incubation, the number of surviving nauplii in each vial was counted, and the mortality percentage was estimated.

Antimicrobial activities

The antimicrobial activity of nitrogen and sulfur-containing heterocyclic compounds, such as imidazole and nitroimidazole, has been shown to exhibit significant microbial effects, particularly when attached to carbohydrates, which enhances their ability to inhibit bacterial growth. In this study, the ligand N-benzal cefadroxil (L) was synthesized, isolated, and characterized at the Inorganic Research Laboratory of the Department of Pharmacy, USTC. The antimicrobial susceptibility of this ligand was evaluated using the disc diffusion method, as outlined by Bauer *et al*. (1966). The test organisms used were *S. aureus* (Gram-positive) and *E. coli* (Gram-negative). A bacterial culture was adjusted to the 0.5 McFarland standard and inoculated onto Muller Hinton agar plates by evenly swabbing with a sterile applicator. Inoculated agar plates were dried for 15 minutes and then the sterile discs containing the different solutions of the ligands were laid onto the plate surface. Six discs were placed on each plate, with one disc being the positive control, one was the negative control, and the others contained varying concentrations of the test ligand. The positive controls used were standard antibiotics, such as Vancomycin (30 µg) against *S. aureus*, Ampicillin (10 µg) against *E. coli*, and Oxacillin (1 µg) against methicillin-resistant *S. aureus*. The negative control used was a 100% dimethyl sulfoxide (DMSO) solution. The inoculated plates were allowed to grow for 18-24 hours at 37°C. The diameters of the bacterial growth inhibition zones were measured with the help of calipers after the incubation and the observation was recorded. Each experiment was repeated thrice to verify the repeatability and reliability of the results.

The Minimum Inhibitory Concentration (MIC) was determined by the inhibitory concentration in diffusion (ICD) procedure according to Guerin-Faublee *et al*. (1996). Assay was carried out with diffusion method with 12 sterile discs with different concentration of plant extract. The method was applied against the five bacterial strains which were previously determined for their antibacterial susceptibility. After incubation, the growth inhibition of the bacteria was measured around each disc. The minimum concentration of the extract that caused noticeable inhibition of bacterial growth was considered as the minimum inhibitory concentration (MIC) for the tested bacterial strain[16].

RESULTS AND DISCUSSION

Solubility test: The solubility profile of the Schiff base ligand and its metal(II) complexes was systematically evaluated using a range of organic solvents and water. The findings reveal that both the ligand and its metal(II) complexes exhibit high solubility in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF), while demonstrating complete solubility in chloroform. Moderate solubility was observed in methanol, acetone, and carbon tetrachloride (CCl_4), whereas negligible solubility was noted in n-hexane, distilled water, and ethanol. These solubility assessments were meticulously conducted at the USTC laboratory, providing critical insights into the solvent compatibility of the synthesized compounds[15].

Identification test: The phenolic group test was initially negative, because no violet colour was seen. When ethanol and $FeCl_3$ solution were added to the ligand, however, it turned violet, which suggests the presence of a phenolic functional group, so it was analyzed in the USTC laboratory. The carboxylic acid group was detected by the production of bubbles after the addition of sodium bicarbonate ($NaHCO_3$) which indicated the presence of a carboxyl group. The primary amine test was carried out using dilute hydrochloric acid (HCl), 2-3 drops of β-naphthol and $NaNO_2$ solution with alkali, but the red coloration was not observed; therefore, it did not contain a primary aromatic amine group. Likewise, the aldehyde identification test was negative, which means there will be no red coloration. These findings highlight structural variations between the synthesized ligand and its parent compound, cefadroxil, providing crucial insights into its chemical composition and functional properties[16,17].

UV spectral analysis: The absorption spectra of the synthesized Schiff base ligand and its metal complexes were recorded in UV–Visible spectrophotometer in ethanol at 1×10^{-4} M. The free Schiff base ligand exhibited intense absorption bands at 245 nm and 327 nm, which were attributed to $\pi \rightarrow \pi^*$ electronic

transitions within the aromatic system and n→π* transitions associated with the azomethine (-HC=N-) moiety, respectively.

Notably, the π→π* transitions remained largely unaffected upon metal coordination. The electronic spectra of the metal complexes revealed two broad, intense absorption bands in the 400–700 nm region, characteristic of d–d transitions, indicative of an octahedral coordination environment, consistent with prior studies. Besides, the spectra of the free ligand and cefadroxil were recorded in the methanol solvent at room temperature. The free ligand and its metal complexes did not show any specific d–d electronic transition beyond 400 nm, indicating the absence of any noticeable d–d transition in the recorded spectral range. The absorption bands detected at <400 nm were mostly assigned to the intraligand π→π* and n→π* electronic transitions. Moreover, the absorption lines in the near 400 nm were tentatively attributed to the charge-transfer transitions from the ultraviolet region. These spectral findings provide crucial insights into the stereo electronic characteristics of the ligand and its metal complexes, offering a complementary perspective to other spectroscopic analyses in elucidating coordination geometry and electronic structure[18-22].

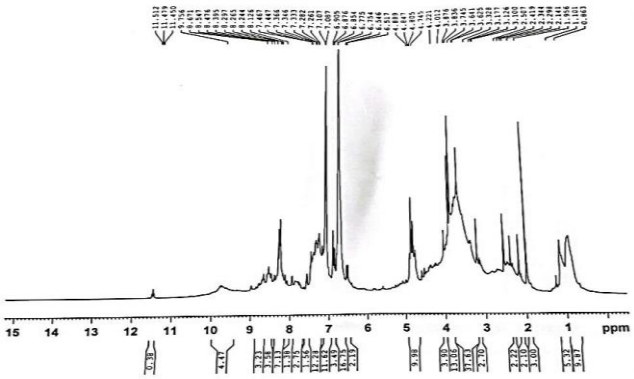


Figure 1: ^{1}H NMR spectrum of the synthesized schiff base ligand derived from cefadroxil.

^{1}H NMR analysis: The ^{1}H NMR spectrum of the Schiff base ligand was recorded at the Analytical Laboratory, Jahangirnagar University, Dhaka, providing critical insights into its structural characteristics. A broad singlet resonance was observed at 8.3 ppm, corresponding to the azomethine (-N=CH-) proton, aligning well with literature reports indicating a characteristic chemical shift within the 8.1–8.4 ppm range. Additionally, a sharp singlet at 9.75 ppm was attributed to the phenolic (-OH) proton, while the carboxylic (-COOH) proton exhibited a distinct downfield shift, appearing at 11.5 ppm, indicative of strong hydrogen bonding or deshielding effects. The presence of a C=O proton signal at 9.8 ppm further corroborates the ligand's structural integrity. Moreover, the multiplet signal observed at 8.2 ppm corresponds to the C=C protons, reflecting the conjugated electronic environment within the aromatic framework. These spectral observations affirm the electronic influence of the azomethine moiety and other functional groups, offering a robust spectral fingerprint that substantiates the ligand's structural identity and its coordination potential in complex formation[23-26].

^{13}C NMR analysis: The ^{13}C NMR spectrum of the Schiff base ligand was recorded at the Analytical Laboratory, Jahangirnagar University, Dhaka, providing key insights into its molecular framework. A broad singlet at 147 ppm was assigned to the azomethine (-CH=N-) carbon, consistent with characteristic shifts reported in the literature. The C=C carbon resonance appeared at 150 ppm, indicative of the conjugated electronic environment within the aromatic system. Furthermore, the carboxyl (-COOH) carbon exhibited a significant downfield shift at 180 ppm, reflecting the strong deshielding effects associated with its electron-withdrawing nature.

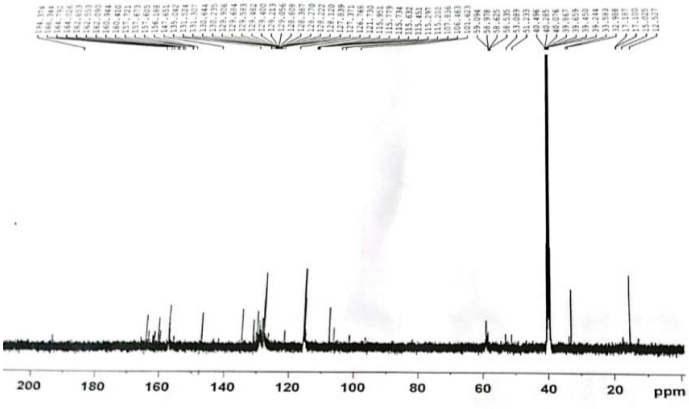


Figure 2: 13C NMR Spectrum.

The hydroxyl (-OH) carbon signal at 50 ppm further substantiates the ligand's structural integrity. These spectral findings confirm the expected chemical shifts of the azomethine functionality and other key carbon environments, reinforcing the molecular identity of the ligand and its potential coordination behavior in metal complexation[27-29].

Infrared spectra: The infrared (IR) spectrum of the Schiff base ligand was recorded at the Analytical Laboratory, Albion, Chittagong, utilizing KBr disc methodology within the spectral range of 4000–500 cm^{-1}. The IR spectral analysis revealed characteristic vibrational bands, providing key insights into the ligand's functional groups. A distinct absorption at 1625 cm^{-1} was attributed to the azomethine (-CH=N-) stretching vibration, consistent with its characteristic imine functionality. The carbonyl (C=O) stretching mode appeared prominently at 1750 cm^{-1}, while the C=C stretching vibration was observed at 1550 cm^{-1}, reflecting the presence of conjugated π-electron systems within the ligand's backbone. Additionally, the carboxyl (-COOH) functional group exhibited a strong absorption at 1700 cm^{-1}, indicative of its protonated state. In comparison, the IR spectrum of cefadroxil displayed similar characteristic bands, including C=O stretching at 1700 cm^{-1}, C=C stretching at 1500.21 cm^{-1}, and carboxyl (-COOH) stretching at 1750 cm^{-1}. These spectral observations confirm the structural integrity of the Schiff base ligand and its functional moieties, reinforcing its potential coordination behavior in complex formation[30-33].

Anti-inflammatory Activity Analysis: The anti-inflammatory activity of the Ni(II) and Cd(II) complexes was evaluated by the BSA denaturation method at four concentrations (125, 250, 500 and 1000 µg/mL) and compared with the standard drug Diclofenac sodium. The anti-inflammatory activity of the synthesized complexes was assessed by calculating the percentage inhibition of protein denaturation, which was compared with the anti-inflammatory drug used as a standard, as presented in Table 1. The study was conducted in triplicate, and IC_{50} values were calculated to assess the inhibitory potential of the compounds. The results revealed that diclofenac sodium showed the strongest anti inflammatory activity (92 %) along with 1000µg/mL IC_{50} value. Among the metal complexes, the ligand complex demonstrated superior inhibition (56 %) with an IC_{50} value of 125µg/mL whereas the ligand complex exhibited lower activity (22 5 %) with an IC_{50} value of 1000µg/mL. Although the metal complexes showed lower anti-inflammatory efficacy compared to diclofenac sodium, their activity was attributed to the presence of donor sites ('N' and 'O') from DNPH and DMG within their structures, which contribute to their biological potential. The trend for anti-inflammatory potency is: Diclofenac Sodium >Nickel(II) complex >Cadmium(II) complex.

Considering the negative control absorbance value of 0.146, the percentage inhibition of protein denaturation was calculated by measuring the absorbance of the treatment groups and converting it into inhibition percentages for both diclofenac sodium and the ligand[34].

Cytotoxic activity analysis: The finding revealed that the activity of all the Schiff base ligands was depend on concentration. The LC50 values of all the Schiff base ligands were below 1000 µg/mL that confirm the existence of bioactive secondary metabolites in yield compounds. Eleusine indica ligand (LC_{50} = 647.6 µg/ mLµg/mL) show the greatest cytotoxicity on the brine shrimps in comparison to cyclophosphamide (LC50 =38 µg/mL µg/mL)[35,36]. The findings of the BSLA are given bellow in Table 2.

Antibacterial activity analysis: The minimum inhibitory concentration (MIC) values for *E. coli* and *S. aureus* using the Schiff base ligand and its Ag complex are presented in Table 3. The results indicate that the Ag complex exhibited higher antibacterial activity compared to the ligand. For *E. coli*, the MIC value of the Schiff base ligand was 26 µg/mL, whereas the Ag complex showed an improved MIC value of 28 µg/mL. For *S. aureus*, the Schiff base ligand had an MIC value of 21 µg/mL, while the Ag complex demonstrated a stronger antibacterial effect with an MIC value of 18 µg/mL.

Table 1: Anti-Inflammatory activity of diclofenac sodium and the synthesized ligand.

Test group	Concentration			
	125 µg/mL	250 µg/mL	500 µg/mL	1000 µg/mL
Standard absorbance	0.018	0.017	0.012	0.011
% Inhibition of Standard	92%	88 %	92 %	92 %
Ligand absorbance	0.064	0.087	0.097	0.113
% Inhibition of ligand	56 %	40 %	33 %	22. 5 %

Table 2: Mortality of *Artemia salina* Nauplii following treatment with the synthesized schiff base ligand at different concentrations.

Concentration (µg/mL)	Total nauplii (n)	Dead nauplii	Live nauplii	Mortality (%)	Viability (%)
200	10	0	10	0	100
100	10	1	9	10	90
50	10	2	8	20	80
25	10	3	7	30	70
12.5	10	5	5	50	50

Table 3: Antibacterial activity of Schiff base ligand and its silver (Ag) complex against *E. coli* and *S. aureus*.

Test Organism	Standard (5 mg/ml)	Ligand	Ag-Complex
E. Coli (-ve)	35	26	28
Staphylococcus aureus(+ve)	24	21	18

The enhanced antibacterial activity of the Ag complex compared to the ligand is likely due to metal coordination, which improves lipophilicity[37,38].

Limitations of the study: This study was a preliminary *in vitro* evaluation with a few microbial strains. The mechanisms of the biological activity has not been explored, and structural studies of the metal complex are recommended. Additional mechanistic, toxicity, and *in vivo* studies are needed to establish the therapeutic potential of the synthesized compounds.

CONCLUSIONS

The Schiff base ligand was synthesized using a simple and efficient synthetic route by condensation reaction between the cefadroxil and benzaldehyde. Structural elucidation of the ligand was carried out using infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), and ultraviolet (UV) spectroscopy. The final product was purified through recrystallization to ensure high purity and yield. Notably, the ligand exhibited lower anti-inflammatory activity compared to the standard reference drug. Antimicrobial studies against *E. coli* and *S. aureus* demonstrated that the free ligand exhibited significant antibacterial activity. These findings suggest that while metal coordination influences bioactivity, further structural modifications and in-depth investigations could lead to the discovery of novel lead compounds with enhanced therapeutic potential.

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AUTHOR'S CONTRIBUTION

Islam MS: conceptualization, study design, protocol development. **Nishat SS:** experimental investigation, laboratory work, data interpretation. **Hossain MR:** Data analysis, critical review. **Mysha RY:** literature survey, editing. **Israt RJ:** data interpretation. **Ahmed MA:** writing original draft. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY

The related author can provide the empirical data supporting the study's conclusions upon request.

CONFLICT OF INTEREST

There are no conflicts of interest in regard to this project.

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