ORIGINAL RESEARCH ARTICLE

Synthesis of New Salicylaldehyde-based Schiff Base Copper (II) Complexes and Evaluation of their Antimicrobial/Antioxidant Activities

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Abstract

Drug resistance has become a major healthcare threat, necessitating the development of new therapeutics. Oxidative stress has also been linked to various illnesses and disorders, increasing the need for potent antioxidant agents. Schiff base compounds have been utilized to develop new drugs due to their potential biological properties. In this study, two new salicylaldehyde – based copper (II) Schiff base complexes were synthesized, characterized and evaluated for their antimicrobial and antioxidant properties. The ligands 2-{[(4-fluorophenyl) imino] methyl} phenol, **(L1)** and 4-Bromo-2-{[(4-Fluorophenyl) imino] methyl} phenol, **(L2)** were prepared from 4-fluoroaniline with salicylaldehyde and 5-bromosalicylaldehyde, respectively. They were reacted with copper (II) chloride dihydrate to form $[Cu(L1)_2]2H_2O$ **(C1)** and $[Cu(L2)_2]2H_2O$ **(C2),** respectively. Characterization was performed using FT-IR, UV-Vis, ^1H NMR, elemental analysis, molar conductance and melting points. Antibacterial activity was assessed *in vitro* against *E. coli, P. aeruginosa, B. subtilis* and *S. aureus* using the disc diffusion method, while the antifungal activity was tested against *C. albicans*. The antioxidant activity was determined using the DPPH scavenging method. Statistical analysis was conducted using one-way analysis of variance with Tukey's post hoc test ($p < 0.05$). Spectroscopic data confirmed coordination of the ligands to the copper (II) ions via their oxygen & nitrogen donor atoms, thereby supporting a square-planar geometry. Molar conductance studies revealed that the complexes are non-electrolytes. Biological assays showed that the Cu (II) complexes exhibited significantly higher antimicrobial and antioxidant activities than their free ligands. The brominated Schiff base compounds, **L2** and **C2**, showed significantly higher antimicrobial activity than their non-brominated analogs, **L1** and **C1**, whereas no significant differences were observed in antioxidant activities. All synthesized compounds showed good antioxidant properties with IC_{50} values below 10 µg/mL. Among the synthesized compounds, **C2** demonstrated the highest potency and is hence a promising candidate for future clinical applications.

Keywords: Drug resistance, antimicrobial, Schiff base ligands, and copper (II) complexes.

1.0 Introduction

Various synthetic drugs have been used in disease treatment over the years, but their misuse and overuse have led to the development of drug-resistant microbes (Uddin et al., 2021). This occurs when various pathogens undergo evolutionary processes that equip them with defense

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mechanisms against medications that were previously efficacious in treating diseases caused by them (Arip et al., 2022). Consequently, standard antibiotics have become less effective, necessitating the need for novel therapeutic agents (Dragojević et al., 2025a; Onunkwo et al., 2025)

The pathogenesis and pathophysiology of many illnesses and disorders, including neurological disorders (Alzheimer's, Parkinson's, Huntington's disease, and amyotrophic lateral sclerosis), diabetes, cataracts, autism, cardiovascular diseases, inflammatory diseases, cancer, and aging, are significantly influenced by oxidative stress (Fadaka et al., 2019). This has led to the increased demand for potent antioxidant agents. In biological systems, antioxidants play a crucial role in protecting cells from oxidative damage caused by reactive oxygen/nitrogen species (ROS/RNS) and free radicals (Gulcin, 2025; Kisoi et al., 2025) They achieve this by directly scavenging free radicals, thereby preventing damage to DNA, RNA, proteins, and lipids (Chouikh et al., 2025). Moreover, antioxidants inhibit free radical-generating enzymes and enhance the activity of intracellular antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), which neutralize harmful free radicals (Ohiagu et al., 2024).

Schiff base ligands have been referred to as privileged ligands in organic chemistry due to their ease of synthesis by condensation and ability to form stable metal complexes with pharmacological properties (Abbas et al., 2025; Gosu et al., 2025). Schiff bases are synthesized through the condensation reaction of a primary amine with an aldehyde or ketone (Marinova & Tamahkyarova, 2025). The azomethine group (-C=N-) in the Schiff base ligands is responsible for their diverse biological properties, such as antibacterial (Caviglia et al., 2025; Karmokar et al., 2025; Saravanaselvam et al., 2025), antiproliferative (Gungor et al., 2025; Marinova & Tamahkyarova, 2025), anti-inflammatory (Dhanya, et al., 2025; Maddikayala et al., 2025), antifungal (Malav et al., 2025; Murugan et al., 2025), antioxidant (Bursal et al., 2021; Rana et al., 2024a), antiviral (Kaushik et al., 2023; Khaldoune et al., 2024), antitubercular (Bufarwa et al., 2025; Taxak et al., 2025), antidiabetic (Ajaz et al., 2025; Almehizia et al., 2025), and anticancer properties (Raju et al., 2025; Shaaban et al., 2025). The sp^2-hybridized azomethine nitrogen of the Schiff base ligands forms stable hydrogen bonds with the active sites of cellular components through its lone pair of electrons, disrupting the normal cellular functions (El-Sonbati et al., 2025).

Schiff base ligands have proved to be good chelating ligands with excellent binding affinity towards transition metal ions (Venkatesh et al., 2024). Coordinating Schiff base ligands to transition metal (II) ions has proved to lower the polarity of the metal center and increase π-electron delocalization across the chelate ring (Abduljawad et al., 2025). As a result, Schiff base metal complexes with significant physiological and pharmacological properties are formed due to increased lipophilicity, stability, specific molecule recognition and interaction (Khan et al., 2022; Tsacheva et al., 2023).

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Salicylaldehyde-based Schiff bases have received a lot of research interest due to their varied pharmacological potential (Rana et al., 2025a). Their biological properties have been reported to increase upon coordination to transition metal (II) ions (Rana et al., 2025b). Research studies have shown that copper (II) complexes possess excellent binding affinity to microbial targets, and hence potential therapeutic agents (Behzad et al., 2025; Lawan et al., 2025). Their antimicrobial and antioxidant activities have shown to be higher than their free, uncoordinated ligands (Khatun et al., 2025; Ramgeetha et al., 2025). This enhanced bioactivity inspired us to synthesize two new copper (II) complexes derived from salicylaldehyde – based Schiff bases, characterize them, and assess their antimicrobial and antioxidant properties.

2.0 Experimental section

2.1 Materials and methods

The Schiff base ligands and their Cu (II) complexes were synthesized using the reflux method in the Chemistry GoK Laboratory of JKUAT. The chemicals and solvents used were of analytical grade (Aldrich), available commercially without further purification. The FT-IR spectra of synthesized compounds were recorded in the 4000–400 cm^{-1} region on a SHIMADZU FTIR-8400 spectrophotometer.

The electronic spectra of the synthesized compounds were measured using AOE Instruments UV-1800 PC spectrophotometer, covering a range of 200-800 nm. A quartz cuvette with a 1 cm path length was used for the measurements. The NMR spectra of the Schiff base compounds were obtained in deuterated dimethyl sulfoxide (DMSO-d_6) using TMS as an internal standard. The analysis was conducted at 25 °C using a Bruker Avance III HD Nanobay 400-MHz NMR spectrometer equipped with a 5-mm BBO probe. The elemental analysis was performed on a LECO CNHS-932 micro-analyser. The conductivity measurements of the Schiff base ligands and their Cu(II) complexes were carried out on a SIBATA Conductivity meter Model SC–17A, at room temperature while the melting points were measured using a Gallenkamp apparatus. The disc diffusion method was used to investigate their antimicrobial activity, while the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method was used for the antioxidant studies due to its simplicity, rapidness, reliability and stability of DPPH radicals (Kedare & Singh, 2011).

2.2 Synthesis of Schiff Base ligands

2.2.1 2-{[(4-fluorophenyl) imino] methyl} phenol, L1

Ethanolic solutions (10mL) of 4-fluoroaniline (0.5556 g; 5 mmol) and salicylaldehyde (0.6106 g; 5 mmol) were prepared separately. To the ethanolic solution of 5-bromosalicylaldehyde, the 4-fluoroaniline solution was added dropwise while stirring continuously in a 50 mL round-bottom flask. The solution turned yellow almost immediately. Two drops (0.2 mL) of glacial acetic acid were added to the mixture, which was refluxed for 4 hours with magnetic stirring at room temperature. The yellow precipitate formed was separated by filtration and subsequently purified through recrystallization from ethanol. The crystals were washed with cold ethanol and diethyl ether to eliminate any unreacted amine and aldehyde and dried in a desiccator over $CaCl_2$. The crystals were then analyzed using FT-IR, UV-Vis, ^1H NMR, elemental analysis, molar conductance and melting points.

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Yield, 99.9%. Color: yellow. Molecular formula: $C_{13}H_{10}FNO$. M.p: 88 °C. Molar conductance (Λ): 4.29 Ω^{-1} cm^2 mol^{-1}. Elemental analysis: calculated: C; 72.56%, H; 4.65 %, N; 7.44%, found: C; 72.47%, H; 4.62%, N; 7.41%. ^{1}H NMR (ppm d_6-DMSO, 400 MHz): δ 13.11 (s, 1H, OH), 8.51 (s, 1H, CH=N), 6.9–7.4 (m, 7ArH). FT-IR: 3327 υ(O-H), 1611 υ(HC=N), 1298 υ(C-O). UV-Vis (acetonitrile) λ_{max} (nm): 215.5, 250, 309.5 & 349.

2.2.2 4-Bromo-2-{[(4-Fluorophenyl) imino] methyl} phenol, L2

Ethanolic solutions (10 mL) of 4-fluoroaniline (0.5556 g; 5 mmol) and 5-bromosalicylaldehyde (1.005 g; 5 mmol) were separately prepared and mixed in a 50 mL round-bottom flask. The rest of the procedure was as described in section 2.2.1

Yield, 96.0%. Color: yellow – orange. Molecular formula: $C_{13}H_9BrFNO$. M.p: 143 °C. Molar conductance (Λ): 4.37 Ω^{-1} cm^2 mol^{-1}. Elemental analysis: calculated: C; 53.06%, H; 3.06%, N; 4.76%, found: C; 53.47%, H; 3.51%, N; 4.52%. ^{1}H NMR (ppm d_6-DMSO, 400 MHz): δ 13.12 (s, 1H, OH), 8.53 (s, 1H, CH=N), 6.9–7.5 (m, 7ArH). FT-IR: 3456 υ(O-H), 1616 υ(HC=N), 1226 υ(C-O). UV-Vis (acetonitrile) λ_{max} (nm): 225, 246, 308 & 359.5.

2.3 Synthesis of Schiff Base Copper (II) Complexes

2.3.1 Copper (II) complex, C1 $[Cu(L1)_2]2H_2O$

The Schiff base ligand **L1** (2 mmol, 0.4300 g) and copper (II) chloride dihydrate ($CuCl_2.2H_2O$) (1 mmol, 0.1705 g) salt were dissolved separately in 10 mL hot ethanol. The $CuCl_2.2H_2O$ solution was then added dropwise to the ligand solution in a 50 mL round-bottom flask while stirring. The mixture was refluxed for 3 hours on an oil bath at 65 °C, and then concentrated by removing excess solvent. The dark brown solid was filtered, washed with methanol, hot ethanol, and diethyl ether, and dried over anhydrous $CaCl_2$. The crystals were then analyzed using FT-IR, UV-VIS, ^{1}H NMR, elemental analysis, molar conductance and melting points.

Yield: 84.7%. Color: dark brown. Molecular formula: $C_{26}H_{22}F_2CuN_2O_4$. M.p: 250 °C. Molar conductance (Λ): 1.589 Ω^{-1} cm^2 mol^{-1}. Elemental analysis: calculated: C; 59.15%, H; 3.79% N; 5.31%, found: C; 59.01%, H; 3.73%, N; 5.26 %. FT-IR: 3446 υ(OH-O), 1605 υ(HC=N), 1215 υ(C-O), 555 υ(M-O), 420 υ(M-N). UV-Vis (acetonitrile): λ_{max} (nm): 224.5, 252.03, 297, 346, 464 & 561.5.

2.3.2 Copper (II) complex, C2 $[Cu(L2)_2]2H_2O$

The Schiff base ligand **L2** (2 mmol, 0.5880 g) and copper (II) chloride dihydrate ($CuCl_2.2H_2O$) (1 mmol, 0.1705g) salt were dissolved separately in 10 mL ethanol. The $CuCl_2{\cdot}2H_2O$ solution was added to the ligand **L2** solution dropwise in a 50 mL round-bottom flask, and the rest of the procedure was as described in 2.3.1.

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Yield: 80.7%. Color: dark brown. Molecular formula: $C_{26}H_{20}F_2Br_2CuN_2O_4$. M.p: 285 °C. Molar conductance (Λ): 1.655 Ω^{-1} cm^2 mol^{-1}. Elemental analysis: calculated: C; 45.09%, H; 2.95% N; 4.14%, found: C; 45.05%, H; 2.94%, N; 4.09%. FT-IR: 3462 υ(OH-O), 1604 υ(HC=N), 1220 υ(C-O), 536 υ(M-O), 424 υ(M-N). UV-Vis (acetonitrile): λ_{max} (nm): 230, 263.5, 297, 335, 464.5, 594.5.

2.4 Antibacterial assay

The antibacterial activities of Schiff base ligands and their Cu (II) complexes were investigated against four bacterial strains, gram-positive: *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 25923), and gram-negative: *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), using the disc diffusion method as described by Sitati and coworkers (2021). Bacteria were cultured in nutrient agar and incubated at 30 °C for 24 hours. Sterilized Petri dishes were inoculated with 0.01 mL of the prepared bacterial culture media (10^5 - 10^6 bacteria per mL). Mueller–Hinton agar kept at 45–50 °C was then pipetted (15 mL) into each inoculated Petri dish. sterilized filter paper discs (⌀ = 6mm) saturated with the synthesized compounds were gently pressed onto the solid agar medium. Negative controls consisted of discs immersed in 5% dimethyl sulfoxide (DMSO), while positive controls consisted of standard antibiotic discs (ampicillin). The samples, negative and positive controls, were applied to the inoculated media in triplicate. The treated Petri dishes were incubated at 4 °C for 2 hours, and then at 35 °C for 24 hours. The inhibition zones surrounding the discs were measured in millimetres.

2.5 Antifungal assay

The Schiff base compounds were screened against *C. albicans* fungi as outlined by (Sitati et al., 2021). Potato dextrose agar (PDA) was utilized to prepare the culture medium following the manufacturer's instructions. *Candida albicans* (ATCC 90028) maintained in the Department of Botany at JKUAT was aseptically inoculated onto petri dishes containing autoclaved, cooled, and settled medium. Incubation of the petri dishes at 31 °C for 48 hours formed white round colonies against a yellowish background. Subsequent aseptic subculturing was performed on PDA slants.

Colonies of Candida albicans from PDA slants were suspended in sterilized 0.9% sodium chloride solution (normal saline), and the concentration was adjusted to 2×10^7 cells/mL using McFarland solution for standardization. Sterilized petri dishes (9 cm diameter) were inoculated with 1 mL of the microbial suspension. PDA, sterilized in a flask and cooled to 45 °C, was then distributed into each inoculated petri dish (15 mL) and swirled to ensure even distribution of the medium. Sample-injected disks were gently pressed onto the solid Potato dextrose agar medium. The positive control consisted of Nystatin, while the negative control consisted of 5% DMSO. Each application was conducted in triplicate. The treated petri dishes were placed at 4 °C for 2 hours and then incubated for 48 hours at 37 °C. Following this incubation period, the inhibition zones formed on the media were measured with a transparent ruler in millimeters.

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2.6 Antioxidant assay

The antioxidant assay was conducted using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method as described by (Nibila et al., 2021) with ascorbic acid serving as the reference. A stock solution of 1 mg/1000 µL was prepared by dissolving each compound in distilled water. Before UV measurements were made, a fresh DPPH solution (60 µM) in methanol was prepared. This solution (3.9 mL) was mixed with various concentrations (10 - 100 µL) of the test compounds. The samples were left in the dark at room temperature for 15 minutes, and the decrease in absorbance was measured at 517 nm. A control sample, without any compound, was prepared using the same volume. Methanol (95%) was used as a blank. The following equation determined the percentage of inhibition (%) of the free radical: % Inhibition = $(C_0 - T)/C \times 100$, where C_0 = absorbance of the control sample (t = 0 min), C = absorbance of the control (t = 15 min) and T = absorbance of the test compound. The concentration at which the compounds exert half their maximal inhibitory effect, IC_{50} (µg/mL) was determined and recorded.

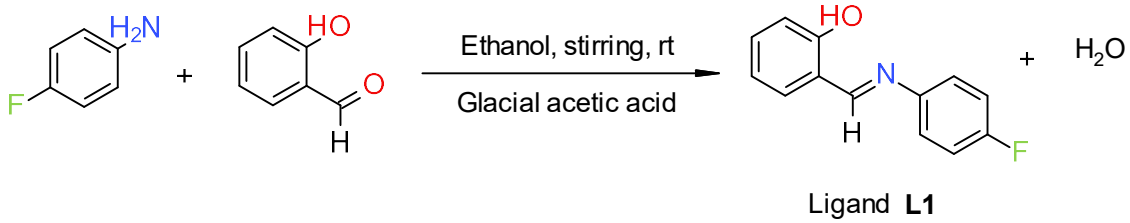
2.7 Statistical data analysis

Raw data were tabulated in a Microsoft Excel spreadsheet and subsequently exported to SigmaPlot V16.0 software for analysis. Descriptive statistics of the tests were presented as mean ± standard deviation (SD). Statistical differences among the treatment groups were determined using one-way analysis of variance, followed by Tukey's post hoc test for pairwise comparisons. A significance level of $p \leq 0.05$ was applied.

3.0 Results and discussion

3.1 Synthesis and characterization of Schiff base ligands

The Schiff base ligand **L1** was formed by the condensation reaction of 4-fluoroaniline and salicylaldehyde (Scheme 1), while **L2** was obtained by the reaction of 4-fluoroaniline and 5-bromosalicylaldehyde (Scheme 2). These reactions were performed in ethanol at room temperature. The Schiff base ligands were obtained as pale yellow (L1) to yellow-orange (L2) crystals, which were soluble in hot ethanol, methanol, dimethyl sulfoxide (DMSO), and acetonitrile. The crystals were then characterized by FT-IR, NMR, UV-Vis and elemental analysis.



Scheme 1: Synthesis of Schiff base ligand L1

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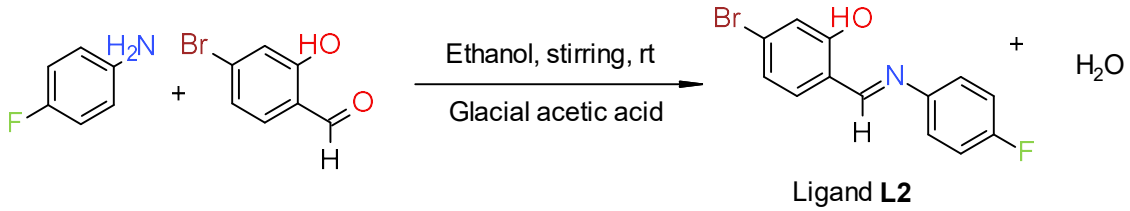


Scheme 2: Synthesis of Schiff base ligand L2

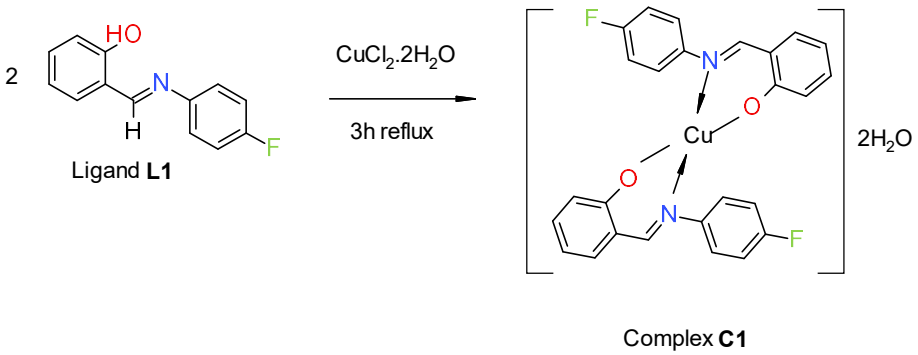
The FT-IR spectra of the Schiff base ligands showed the characteristic azomethine *v*(HC=N) stretching band at 1611 cm^{-1} for **L1** and 1616 cm^{-1} for **L2**. The disappearance of the carbonyl *v*(C=O) bands in the 1690 – 1650 cm^{-1} region and the appearance of the azomethine *v*(HC=N) stretching frequency indicate that the azomethine group replaced the carbonyl group in the formation of the Schiff base (Nyawade et al., 2020).

The formation of the Schiff base ligands was further confirmed by the presence of the azomethine proton peak in the ^{1}H NMR spectra at 8.55 ppm for **L1** and at 8.53 ppm for **L2,** and the absence of the carbonyl proton at 9.80 ppm (Mohammed & Hasan, 2022; Naureen et al., 2021; Pushpanathan et al., 2023). The phenolic proton peaks were observed at 13.10 ppm and 13.12 ppm for **L1** and **L2** respectively (Ahmad et al., 2019; Bilgin et al., 2016).

The UV-Vis absorption bands were observed at 215 – 225 nm, assignable to the π – π* (benzene rings) transition, 246 – 250 nm, assignable to the n – π* (-HC=N) transition and 349 – 359.5 nm, assignable to the n – π* (phenolic group) transition (Ahmad et al., 2019; Bilgin et al., 2016).

3.2 Synthesis and characterization of Copper (II) complexes

The Cu (II) complexes were synthesized by the reaction of the Schiff base ligands with copper (II) chloride dihydrate ($CuCl_2.2H_2O$) in the ratio of 2:1 (Scheme 3 and 4). The complexes obtained were dark brown in colour, soluble in dimethyl sulfoxide (DMSO) but insoluble in ethanol, methanol and water. The complexes were characterized by FT-IR, ^{1}H NMR, UV-Vis and elemental analysis.



Scheme 3: Synthesis of Complex C1

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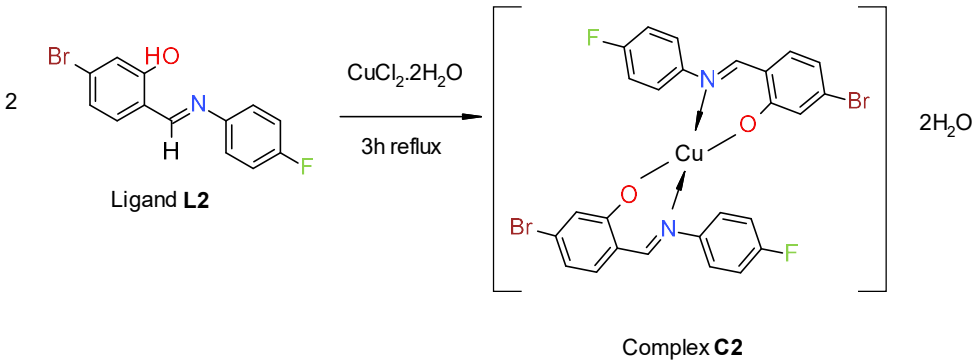

Scheme 4: Synthesis of Complex C2

The melting points of the Cu (II) complexes were higher than those of their respective ligands, measuring 250 °C for **C1** and 285 °C for **C2**. This indicates that the coordination of the Schiff base ligands with the Cu (II) ion can stabilize the Schiff bases (Devi & Arora, 2025; Singh et al., 2025). The molar conductance measurements of the solutions of the copper (II) complexes in DMSO showed very low values below 2 Ω^{-1} cm ^{2} $mol^{-1,}$ showing their non-electrolytic nature (Kalarani et al., 2020). These values are lower than those of their respective ligands.

Table 1: The molar conductance and melting point values for the Schiff base ligands and their Cu(II) complexes.

Compound	Molar conductance (Ω^{-1} cm ^{2} mol^{-1})	Melting point (°C)
L1	4.290	88
C1	1.589	250
L2	4.370	143
C2	1.655	285

The FT-IR spectra of the free Schiff base ligands and their Cu (II) complexes showed the coordination mode of the Schiff base ligands to the Cu (II) ions (Table 2). The *v*(HC=N) band shifted from 1611 cm^{-1} to 1605 cm^{-1} in **C1**, while in **C2** it shifted from 1616 cm^{-1} to 1604 cm^{-1} confirming coordination through the azomethine nitrogen (Dragojević et al., 2025a; Khatun et al., 2025). The υ (C–O, phenolic) band also shifted to lower stretching frequencies in the complexes, 1215 cm^{-1} for **C1** and 1220 cm^{-1} for **C2,** indicating coordination via the phenolic oxygen (Manvatkar et al., 2025). New weak bands in the far IR region infer *v*(M–O) and *v*(M–N) bonding (Dhanya, et al., 2025; El-Sayed et al., 2025). These observations are consistent with previously reported research.

Table 2: FT-IR and NMR Spectral data of the Schiff base ligands and their Cu (II) complexes.

Compound	FT-IR cm^{-1}					^{1}H NMR	
	υ(O-H)	υ(HC=N)	υ(C-O)	υ(M-N)	υ(M-O)	δ (O-H)	δ (H–C = N)
L1	3327	1611	1269	-	-	13.10	8.55
C1	-	1605	1215	555	420	-	-
L2	3456	1616	1226	-	-	13.12	8.53
C2	-	1604	1220	536	424	-	-

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The electronic spectra of the Cu (II) complexes in the ultraviolet – visible (UV-Vis) region were obtained in acetonitrile solvent, and the resulting data are shown in Table 3. A bathochromic shift of 5-11 nm was observed for the π – π* (benzene ring) transition. A bathochromic shift of 2 nm and 17.5 nm was observed in **C1** and **C2,** respectively in the azomethine (-HC=N) band, indicating coordination to the metal ions via the azomethine nitrogen (Abu-Yamin et al., 2022; Shyni et al., 2023). A hypochromic shift of 3 and 24.5 nm was observed in **C1** and **C2,** respectively, for the n–π* (phenolic group) transition, indicating that the phenolic oxygen was involved in the complex formation (Abu-Dief et al., 2025). The new bands in the region 464 nm – 594.5 nm, representing the d-d transitions, further confirm the coordination of the Schiff base ligands to the metal centers (Bag et al., 2023; Ramírez et al., 2025). The bands at 464 nm in **C1** and 464.5 nm in **C2** are assignable to the $^{2}B_{1g} \longrightarrow {}^{2}B_{2g}$ transition, and the bands at 561.5 nm **(C1)** and 594.5 nm **(C2)** correspond to the 2B1g ⟶ 2A1g transition, supporting a square planar geometry in copper (II) complexes.

The theoretical and the experimental values of the elemental analysis showed good agreement, indicating the purity of the Schiff base ligands and their Cu (II) complexes (Kargar et al., 2022).

Table 3: Elemental analysis and UV-Vis Spectral data of the Schiff base ligands and their Cu (II) complexes.

Compounds	Elemental Analysis: Found (Calculated) (%)			UV-Vis (λ_{max}, nm)
	C [%]	H [%]	N [%]	
L1	72.47 (72.56)	4.62 (4.65)	7.41 (7.44)	215.5, 250, 309.5, 349
C1	59.01 (59.15)	3.73 (3.79)	5.26 (5.31)	224.5, 252.03, 297, 346, 464, 561.5
L2	53.04 (53.06)	3.04 (3.06)	4.52 (4.76)	225, 246, 308, 359.5
C2	45.05(45.09)	2.94 (2.95)	4.09 (4.14)	230, 263.5, 297, 335, 464.5, 594.5

3.3 Antibacterial susceptibility tests

The synthesized Schiff base ligands (**L1** and **L2**) and their copper (II) complexes (**C1** and **C2**) were screened against gram-negative (*E. coli* and *P. aeruginosa*) and gram-positive bacteria (*B. subtilis* and *S. aureus*) using the disc diffusion method. Their activity was compared to that of ampicillin, and the average zones of inhibition were tabulated in Table 4.

The Schiff base ligands and their copper (II) complexes showed antibacterial activity against all the bacterial strains tested. The inhibition of the Schiff base compounds showed a concentration-dependent increase in their antibacterial activity. The negative control (5% DMSO) showed no antibacterial activity against the tested bacterial strains, indicating that the observed antibacterial activity was due to the tested compounds. The compounds showed comparable activity against *B. Subtilis,* but there were significant differences ($p < 0.05$) in their activity against *E. coli, P. aeruginosa*, and *S. aureus*. Gram-positive bacteria exhibited significantly higher susceptibility to the tested compounds compared to the gram-negative bacteria, following the order: *B. subtilis* ≈ *S. aureus* > *E. coli* > *P. aeruginosa*. This difference can be explained by the structural differences in their cell envelope. Gram-positive bacteria lack an outer membrane present in gram-negative bacteria, which acts as an additional permeability

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barrier. Schiff base ligand **L2** showed a significantly higher activity against *E. coli* compared to **L1** ($p < 0.05$). At lower concentrations (100 – 200 µg/mL), significant differences were observed between L1 and L2 for *P. aeruginosa, B. subtilis,* and *S. aureus*; however, at higher concentrations, their activities converged and no significant differences were observed.

The copper(II) complexes, **C1** and **C2**, showed a significantly higher inhibition than their respective Schiff base ligands, **L1** and **L2**, across all bacterial strains ($p < 0.05$). Therefore, coordinating the Schiff base ligand to the Cu (II) ions increased their antibacterial potency. This observation is consistent with previously reported studies (Dragojević et al., 2025b; Ngece et al., 2025; Yusuf et al., 2025a). The brominated compounds, **L2** and **C2**, showed enhanced antibacterial activity against the selected bacterial strains compared to their non-brominated compounds, **L1** and **C1**. **C2** exhibited significantly greater activity than **C1** at all tested concentrations, indicating that the ligand structure of **L2** conferred greater antibacterial potency upon coordination to Cu (II) ions compared to **L1**. Among the synthesized compounds, C2 showed the highest antibacterial potency, often comparable to ampicillin at higher concentrations; however, it was not significantly different from ampicillin against *E. coli* and *P. aeruginosa* ($p > 0.05$).

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Table 4: Antibacterial screening data for the Schiff base ligands and their Cu(II) complexes

Sample	Conc. (µg/mL)	The average inhibition zone (mm ± SD, n=3)			
		E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*
L1	100	8.0 ± 0.0^{d}	6.0 ± 0.0^{d}	6.0 ± 0.0^{d}	6.0 ± 0.0^{d}
	200	10.0 ± 0.0^{c}	6.3 ± 0.6^{e}	8.3 ± 0.6^{d}	7.3 ± 0.6^{d}
	300	11.3 ± 0.6^{d}	9.0 ± 0.0^{d}	13.3 ± 0.6^{c}	10.0 ± 0.0^{d}
	400	13.3 ± 0.6^{d}	10.3 ± 0.6^{d}	14.3 ± 0.6^{c}	13.3 ± 0.6^{e}
$[Cu(L1)_2]2H_2O$, **(C1)**	100	11.0 ± 0.0^{b}	9.0 ± 1.0^{c}	8.3 ± 0.6^{c}	7.3 ± 0.6^{d}
	200	12.7 ± 0.6^{b}	11.0 ± 0.0^{d}	10.0 ± 0.0^{cd}	9.0 ± 0.0^{d}
	300	15.0 ± 0.0^{b}	14.3 ± 0.6^{bc}	15.0 ± 0.0^{b}	12.0 ± 0.0^{c}
	400	17.0 ± 0.0^{b}	16.3 ± 0.6^{b}	16.0 ± 0.0^{b}	14.3 ± 0.6^{d}
L2	100	9.0 ± 0.0^{c}	9.0 ± 0.0^{c}	8.0 ± 0.0^{c}	8.7 ± 0.6^{c}
	200	11.3 ± 0.6^{b}	10.3 ± 0.6^{c}	10.3 ± 0.6^{cd}	11.0 ± 0.0^{c}
	300	13.0 ± 0.0^{c}	12.0 ± 0.0^{c}	13.3 ± 0.6^{c}	13.3 ± 0.0^{c}
	400	15.0 ± 0.0^{c}	13.7 ± 0.6^{c}	15.0 ± 0.0^{c}	15.3 ± 0.6 ^{c}
$[Cu(L2)_2]2H_2O$, **(C2)**	100	12.3 ± 0.6^{a}	11.3 ± 0.6^{b}	11.3 ± 0.6^{b}	11.7 ± 0.6^{b}
	200	15.7 ± 0.6^{a}	13.0 ± 0.0^{b}	13.0 ± 0.0^{b}	13.0 ± 0.0^{b}
	300	18.3 ± 0.6^{a}	15.0 ± 0.0^{a}	16.0 ± 0.0^{b}	14.0 ± 0.0^{b}
	400	20.0 ± 0.0^{a}	17.7 ± 0.6^{b}	17.3 ± 0.6^{b}	16.0 ± 0.0^{b}
Ampicillin *(positive control)*	100	13.3 ± 0.6 ^{a}	12.0 ± 0.0^{a}	13.3 ± 0.6^{a}	13.7 ± 0.6^{a}
	200	17.0 ± 0.0^{a}	14.3 ± 0.6^{a}	16.0 ± 0.0^{a}	17.0 ± 0.0^{a}
	300	19.0 ± 0.0^{a}	15.3 ± 0.6^{a}	19.3 ± 0.6^{a}	18.3 ± 0.6^{a}
	400	21.3 ± 0.6^{a}	19.3 ± 0.6^{a}	21.7 ± 0.6^{a}	20.0 ± 0.0^{a}
5% DMSO *(negative control)*	-	0.0 ± 0.0 ^{e}	0.0 ± 0.0 ^{f}	0.0 ± 0.0 ^{e}	0.0 ± 0.0 ^{e}

L1: 2-{[(4-fluorophenyl) imino] methyl} phenol, L2: 4-Bromo-2-{[(4-Fluorophenyl) imino] methyl}phenol. Values with the same letter across each concentration and bacterial strain are not significantly different (one-way ANOVA, Tukey's HSD, $p < 0.05$).

The enhanced antibacterial activity in the copper (II) complexes can be explained using Tweedy's chelation theory. Upon chelation, the metal ion's polarity is significantly lowered due to the overlap of ligand orbitals and the partial sharing of the metal's positive charge with the oxygen and nitrogen donor atoms (Al-Shamry et al., 2022). Additionally, the π-electrons of the ligands are further delocalized within the chelate ring, reducing the overall polarity of the complex, and hence it dissolves more readily in the hydrophobic portion of the phospholipid bilayer, a requirement for passive diffusion through cell membranes (Poornima et al., 2025b).

Studies have shown that the lipophilicity value (log Po/w) of ligands is moderately increased by about 1 unit upon complexation to a favorable value, typically around 2.5, that allows better cell membrane penetration while maintaining enough solubility to navigate the aqueous cell environment (Kumar et al., 2024; Yusuf et al., 2021, 2025b). Once the complex penetrates the cell membrane, it binds to metal-active sites on the bacterial enzymes, disrupting essential cell

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processes such as protein synthesis and respiration, and hence inhibiting further bacterial growth (Sharma et al., 2022).

The higher inhibition observed in the brominated compounds can be attributed to the halogen substitution effect on the compounds (Jitareanu et al., 2018). Bromine is a relatively large and hydrophobic atom compared to hydrogen, and therefore, it increases the overall hydrophobicity of the compound. As a result, the compounds can easily dissolve in lipid bacterial cell membranes (Kolarič et al., 2021; Slivka et al., 2025). The electron-withdrawing bromide substituent creates a region of positive electrostatic potential, known as a σ-hole, along the halogen bond (Thakur et al., 2020). As a result, it acts as an electrophilic site, forming strong halogen bonds with electron-rich donor atoms in biomolecules, and thereby enhancing the binding affinity of the compounds (Kordestani et al., 2021). Additionally, the electron-withdrawing nature of bromine can also affect the conformation and electronic distribution of the compound, rendering its dimensions, morphology, and electrostatics more compatible with particular proteins (Yu et al., 2025). Therefore, rather than binding to an off-target site, the compound preferentially binds to the desired target biomolecules (Potapskyi et al., 2024).

3.4 Antifungal studies

The synthesized compounds were screened against *C. albicans* and their inhibitory activity was recorded (Table 5). The synthesized compounds exhibited significant differences ($p < 0.05$) in their antifungal activities across all concentrations, with activity increasing in a concentration-dependent manner. The negative control showed no antifungal activity, confirming that the inhibition observed was due to the tested compounds. The Cu (II) complexes, **C1** and **C2**, exhibited significantly higher activity compared to their respective free Schiff base ligands, **L1** and **L2** ($p < 0.05$), indicating that upon complexation, the antifungal activity of the Schiff base ligands was increased (Liu et al., 2024; Moreno-Narváez et al., 2025). The brominated compounds (**L2** and **C2**) showed significantly higher antifungal activities compared to their non-brominated analogs (**L1** and **C1**). This could be due to the increased chemical stability, binding affinity, hydrophobicity and molecular interactions with fungal agents caused by the bromine substituent (Karatas et al., 2025). Among the complexes, **C2** was the most potent against *C. albicans*, which was statistically comparable to Nystatin at higher doses.

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Table 5: Antifungal activity of the synthesized Schiff base ligands and their Cu(II) complexes

Sample	Conc. (µg/mL)	Average inhibition zone (mm ± SD, n=3)
L1	100	7.0 ± 0.6 [e]
	200	8.3 ± 0.0 [e]
	300	10.0 ± 0.6 [e]
	400	12.7 ± 0.0 [e]
$[Cu(L1)_2]2H_2O$, **(C1)**	100	9.7 ± 0.6 [c]
	200	11.0 ± 0.0 [c]
	300	13.0 ± 0.0 [c]
	400	15.0 ± 0.0 [c]
L2	100	10.7 ± 0.0 [d]
	200	12.3 ± 0.6 [d]
	300	14.0 ± 0.0 [d]
	400	16.0 ± 0.6 [d]
$[Cu(L2)_2]2H_2O$, **(C2)**	100	12.0 ± 0.0 [b]
	200	14.0 ± 0.6 [b]
	300	16.0 ± 0.0 [b]
	400	19.3 ± 0.6 [b]
Nystatin *(positive control)*	100	14.7 ± 0.6 [a]
	200	17.3 ± 0.0 [a]
	300	20.3 ± 0.6 [a]
	400	22.7 ± 0.6 [a]
5% DMSO *(negative control)*	-	0.0 ± 0.0[f]

L1: 2-{[(4-fluorophenyl) imino] methyl} phenol, L2: 4-Bromo-2-{[(4-Fluorophenyl) imino] methyl} phenol. Values with the same letter across each concentration are not significantly different (one-way ANOVA, Tukey's HSD, $p < 0.05$).

3.5 Antioxidant studies

The antioxidant potential of the Schiff base ligands and their copper (II) complexes was evaluated using the DPPH method, and their IC50 values were recorded (Table 6). The Schiff base ligands and their Cu (II) complexes exhibited IC_{50} values ranging from 2.02 – 5.75 µg/mL, all below 10 µg/mL, indicating good antioxidant activity (Sankar & Sharmila, 2023). However, these IC_{50} values were higher than that of ascorbic acid (the positive control), indicating lower antioxidant activities. The Cu (II) complexes (**C1** and **C2**) exhibited a significantly higher ($p < 0.05$) antioxidant activity than their respective Schiff base ligands (**L1** and **L2**), indicating that coordination enhanced the reducing power of the ligands. The complexes exhibited no significant differences in their antioxidant properties, and a similar observation was noted between the ligands, resulting in the following order of antioxidant potency: **C2**≈ **C1** > **L2** ≈ **L1**. Therefore, the bromine substitution resulted in an insignificant increase in antioxidant potency.

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The antioxidant ability of the ligands can be attributed to the presence of their nitrogen and oxygen donor atoms (Rana et al., 2024b). Studies have shown that coordinating ligands to metal ions stabilizes the oxidation states of the metal centers, promoting efficient redox cycling, which facilitates electron transfer essential for radical neutralization (Chukwu, 2025). The redox potential of ligands is positively shifted upon coordination, and the redox potential of the metal ion is lowered, thereby increasing its reducing power (Rao et al., 2025a). Additionally, the electron delocalization across the metal-ligand framework increases the electron availability for scavenging free radicals (Rao et al., 2025b). The concentration-dependent increase in DPPH scavenging is due to the increased availability of antioxidant molecules at higher concentrations.

Table 6: $1C_{50}$ (µg/mL) values of Schiff Base compounds.

Compound	$1C_{50}$ (µg/mL)
L1	5.75^{c}
$[Cu(L1)_2]2H_2O$, (C1)	2.34^{b}
L2	5.25^{c}
$[Cu(L2)_2]2H_2O$, (C2)	2.02^{b}
Ascorbic Acid	1.23^{a}

L1: 2-{[(4-fluorophenyl) imino] methyl} phenol, L2: 4-Bromo-2-{[(4-Fluorophenyl) imino] methyl} phenol. Values with the same letter along the column are not significantly different (one-way ANOVA, Tukey's HSD, $p < 0.05$).

4.0 Conclusion

The new copper (II) complexes were successfully synthesized from salicylaldehyde based Schiff base ligands: 2-{[(4-fluorophenyl) imino] methyl} phenol, (**L1**) and 4-Bromo-2-{[(4-Fluorophenyl) imino] methyl} phenol, (**L2**) and characterized. The Schiff base ligands coordinated to the Cu(II) centers via the azomethine nitrogen and phenolic oxygen atoms. A square planar geometry has been proposed for the copper (II) complexes based on their electronic spectra. The Cu (II) complexes are neutral non-electrolytes, as indicated by their molar conductance values. The Cu (II) complexes showed enhanced antimicrobial and antioxidant activity compared to the free Schiff base ligands, with a concentration-dependent increase in biological activity. This demonstrated that coordination enhanced the effectiveness of the Schiff base ligands. Notably, the halogenated compounds (**L2** and **C2**) showed higher antimicrobial activity compared to their non-halogenated analogs (**L1** and **C1**). Among the synthesized compounds, **C2** showed the highest antimicrobial and antioxidant potency, and hence the most promising compound for pharmaceutical applications. Future studies can explore the mechanistic studies, in vivo evaluations, ligand modifications for bioactivity optimization, and potential clinical applications of the copper (II) complexes.

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5.0 Acknowledgment

5.1 Data availability

All supporting data for this study are provided in the text.

5.2 Conflicts of Interest

The authors declare that there are no conflicts of interest with respect to this publication.

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