

Research Article

Design, Synthesis, and Antimicrobial Profiling of Novel Schiff Base Metal (II) Complexes: Structural Characterization and Structure

Shem Ongechi Nyang'ate^{1,*} , Joel Mwangi Gichumbi¹ , Esther Wanja Nthiga² 

¹Department of Physical Sciences, Chuka University, Chuka, Kenya

²Department of Physical Chemistry, Dedan Kimathi University of Technology, Nyeri, Kenya

Abstract

This study aimed to design, synthesize, and characterize novel ruthenium (II) Schiff base complexes as potential antimicrobial agents to address the growing crisis of multidrug-resistant bacterial infections. Despite advances in antibiotic development, resistance to existing drugs, particularly in *Staphylococcus aureus* and *Escherichia coli*-demands new compounds with alternative mechanisms of action. A key research gap lies in the limited exploration of pyridine-imine Schiff base ruthenium complexes with systematic substitution (-Br, -OH) and a comparison between simple Ru (II) and Ru(II)-p-cymene architectures. Ligands and their Ru (II) complexes were synthesized and characterized by FT-IR, UV-Vis, ¹H NMR, and melting point. Antimicrobial activity was evaluated using agar disc diffusion against both bacterial strains at concentrations ranging from 125 to 1000 µg/mL, with data analyzed using two-way ANOVA and Fisher's LSD test ($\alpha = 0.05$). Results showed Ru (II) complexes exhibited significantly higher inhibition than free ligands ($p \leq 0.05$), with bromo- and hydroxy-substituted cymene complexes (e.g., L-C2, L1-C2) displaying the strongest activity (up to 14 -15 mm zones). Although all compounds were less potent than gentamycin, the enhanced bioactivity upon metal coordination supports Tweedy's chelation theory. These findings validate Ru (II)-Schiff base complexes as promising scaffolds for future antimicrobial development, warranting further studies on MIC, toxicity, and antifungal activity.

Keywords

Schiff Base, Ruthenium (II) Complexes, Antibacterial Activity, Pyridine-imine Ligands, Spectral Characterization, p-Cymene Ruthenium

1. Introduction

The alarming rise of antimicrobial resistance (AMR) represents one of the most pressing global public health crises of the 21st century. Pathogenic bacteria are evolving mechanisms to evade the effects of conventional antibiotics at an unprecedented rate, rendering many first-line therapeutics ineffective

[1, 2]. This phenomenon has been exacerbated by the overuse and misuse of antimicrobial agents in clinical, agricultural, and veterinary settings, leading to the emergence of multi-drug-resistant (MDR) strains that cause life-threatening infections with limited or no treatment options [3, 4]. Infections

*Corresponding author: shemongechy@gmail.com (Shem Ongechi Nyang'ate)

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caused by MDR *Staphylococcus aureus* and extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli*, for example, are now commonly reported in both hospital and community environments, contributing significantly to global morbidity and mortality [5]. Consequently, there is an urgent and unmet need for the development of novel antimicrobial agents that function through distinct mechanisms of action to circumvent existing resistance pathways and effectively combat resistant pathogens [6, 7].

In this context, medicinal inorganic chemistry has emerged as a fertile frontier for the rational design of next-generation therapeutics. The field leverages the unique physicochemical properties of metal ions and their coordination complexes to generate bioactive molecules with enhanced efficacy, selectivity, and novel modes of action [8]. The paradigm-shifting discovery of cisplatin, a square-planar platinum (II) complex, in the 1960s marked the dawn of metal-based chemotherapy and catalyzed extensive research into transition metal complexes as potential drugs [9]. While platinum drugs like carboplatin and oxaliplatin have since become mainstays in oncology, their clinical utility is often limited by severe systemic toxicities and the development of resistance [10]. As a result, this has prompted a strategic shift toward non-platinum metals, particularly ruthenium (Ru), which exhibits a more

favorable toxicity profile, rich redox chemistry, and versatile coordination behavior [11, 12].

Ruthenium-based organometallic compounds are especially promising due to their iron-mimetic properties, which allow them to exploit endogenous iron-transport pathways for targeted delivery to diseased tissues [13]. Ru(II/III) complexes typically adopt an octahedral geometry, providing a three-dimensional scaffold that enhances their potential for site-specific interactions with biological macromolecules, such as DNA, RNA, and proteins [12]. Furthermore, ruthenium complexes exhibit tunable ligand exchange kinetics and accessible redox states, allowing for fine control over their reactivity and cellular localization [7]. These attributes have propelled ruthenium into the spotlight not only as an anti-cancer agent (e.g., NAMI-A and KP1019 in clinical trials) but also as a potent antimicrobial scaffold [14, 5].

A key strategy in optimizing the biological activity of such metallodrugs is the rational design of organic ligands that modulate the complex's electronic structure, lipophilicity, and target affinity. Among the most versatile and synthetically accessible ligand classes are Schiff bases-organic compounds characterized by an azomethine ($-\text{HC}=\text{N}-$) functional group formed via the condensation of a primary amine with a carbonyl compound [15].

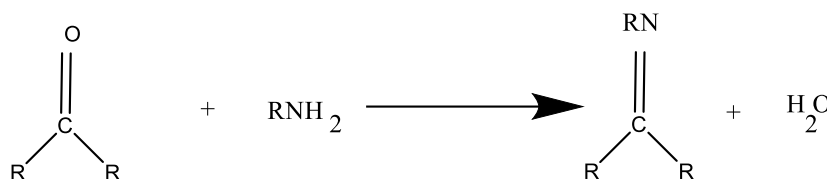


Figure 1. General preparation method of Schiff base.

Schiff bases are often referred to as “privileged ligands” in coordination chemistry due to their structural flexibility, ease of synthesis, and strong chelating ability through nitrogen, oxygen, or sulfur donor atoms [16, 17]. The imine nitrogen possesses a lone pair of electrons that readily coordinates to metal centers,

while substituents on the aromatic rings can be systematically varied to fine-tune steric and electronic properties [18].

The biological potency of Schiff base metal complexes is frequently enhanced upon coordination, a phenomenon widely rationalized by Tweedy's chelation theory [19].

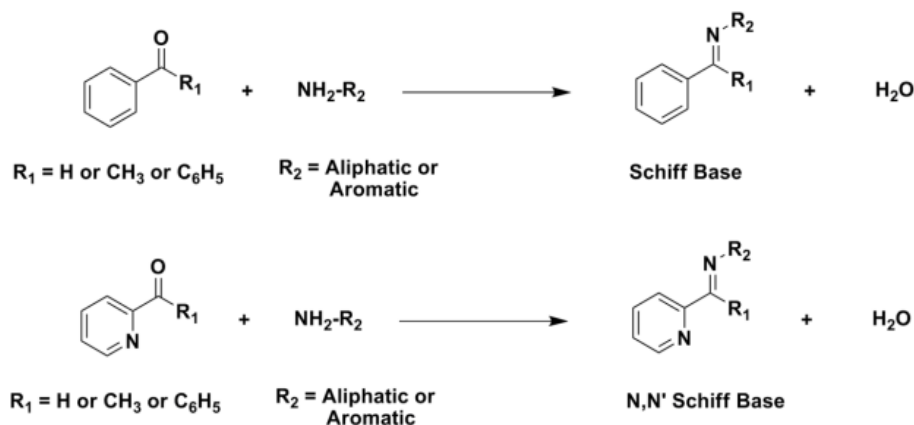


Figure 2. Formation of bidentate Schiff base (Shafi et al., 2012).

According to this principle, the formation of a metal-ligand chelate reduces the overall polarity of the metal ion through charge delocalization over the chelate ring. Thus, this increases the complex's lipophilicity, thereby facilitating its passive diffusion across the hydrophobic lipid bilayer of microbial cell membranes [20, 21]. Once inside the cell, the complex can disrupt essential physiological processes by binding to vital cellular components—such as enzymes involved in respiration or DNA replication—through coordination to key metal-binding sites [22, 23]. This multi-target mechanism of action makes it more difficult for microbes to develop resistance compared to conventional, single-target antibiotics.

Of particular interest are pyridine-imine Schiff bases, which act as N, N'-bidentate ligands, forming stable five-membered chelate rings with transition metals. The

pyridyl nitrogen and the imine nitrogen both serve as strong σ -donor and π -acceptor sites, stabilizing lower oxidation states of the metal and enhancing complex stability [24]. Pyridine itself is a privileged pharmacophore in medicinal chemistry: numerous clinically approved drugs, including the anti-inflammatory piroxicam, the antibacterial sulfapyridine, and the antihistamine tripeleminamine, contain a 2-aminopyridine core [25]. Pyridine derivatives have demonstrated a broad spectrum of biological activities, including antiviral, anticonvulsant, antitubercular, and antidiabetic effects [26, 27]. When incorporated into a Schiff base framework and coordinated to ruthenium, these ligands create hybrid molecules that synergistically combine the inherent bioactivity of the organic scaffold with the unique redox and coordination chemistry of the metal center.

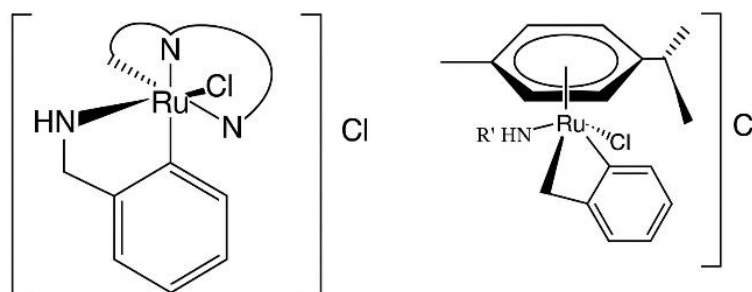


Figure 3. Pyridine-based Ru (II) complexes bearing (N, N, N') and (N, N') ligands.

Recent studies have highlighted the antimicrobial potential of ruthenium-Schiff base complexes. For instance, [7] reported that ruthenium (II) arene complexes bearing N, N'-bidentate Schiff base ligands exhibited significant activity against both Gram-positive and Gram-negative bacteria. Similarly, [18] demonstrated that Ru (II) complexes with Schiff base co-ligands derived from phenanthroline displayed enhanced antibacterial effects compared to their free ligands. The structure-activity relationship (SAR) in these systems is highly sensitive to ligand substitution: electron-donating groups (e.g., -OH) or electron-withdrawing groups (e.g., -Br) on the aryl ring can profoundly influence the complex's electronic density, lipophilicity, and DNA-binding affinity [28]. Such subtle modifications offer a powerful tool for optimizing antimicrobial potency.

Half-sandwich ruthenium (II) complexes, featuring an arene ligand (e.g., p-cymene) in a characteristic "piano-stool" geometry, represent a particularly active and tunable class of organometallic compounds [29, 30]. The arene moiety occupies three coordination sites, leaving three labile sites for binding to bidentate ligands and anionic co-ligands (e.g., Cl^-). This architecture not only imparts kinetic stability but also allows for modular functionalization to modulate solubility, charge, and biological targeting [31]. The precursor $[(\eta^6\text{-p-cymene})\text{RuCl}_2]_2$, a chloro-bridged dimer, is synthetically versatile and

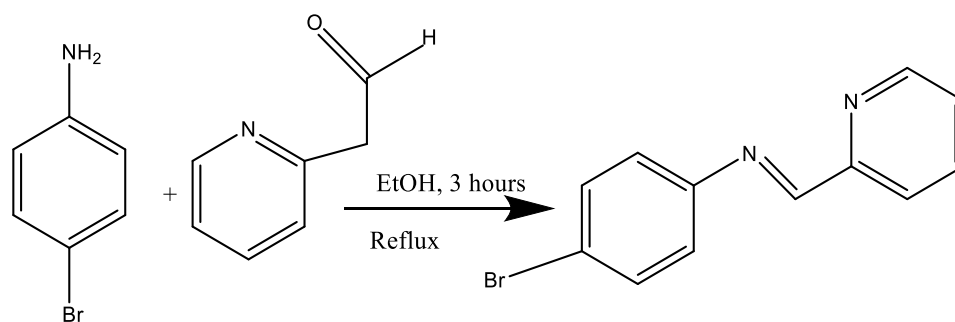
readily undergoes bridge-splitting reactions with N, N'-donor ligands to yield cationic or neutral mononuclear complexes [32]. These complexes have found applications not only in catalysis but also in biological settings, where their cationic nature promotes electrostatic interactions with the negatively charged phosphate backbone of DNA [14].

The interaction of ruthenium complexes with nucleic acids is a well-established antimicrobial mechanism. Cationic Ru(II) polypyridyl complexes can bind DNA via intercalation, groove binding, or covalent coordination [12]. Inert complexes (e.g., $[\text{Ru}(\text{phen})_3]^{2+}$) typically bind reversibly through intercalation, while labile complexes (e.g., Ru-arene species) can form covalent adducts at guanine N7 sites, disrupting replication and transcription [5]. Additionally, some Ru complexes can generate reactive oxygen species (ROS) under physiological conditions, inducing oxidative stress and triggering bacterial cell death [33]. These multi-modal mechanisms—combined with the inherent difficulty microbes face in evolving resistance to metal-based agents—make ruthenium complexes highly attractive candidates for antimicrobial development.

Despite these advances, there remains a significant gap in the systematic exploration of structurally diverse pyridine-imine Schiff base ligands coordinated to ruthenium in the context of antibacterial SAR. In particular, the influence of

electron-donating (-OH) versus electron-withdrawing (-Br) substituents on the aryl ring of the Schiff base on the antimicrobial efficacy of the resulting Ru(II) complexes has not been fully elucidated. Moreover, comparative studies between simple Ru(II) Schiff base complexes and their half-sandwich p-cymene analogues are scarce, yet crucial for understanding how the arene moiety modulates biological activity.

Therefore, this study was designed to address these knowledge gaps through the rational design, synthesis, and comprehensive characterization of a new series of ruthenium (II) complexes derived from three structurally related pyridine-imine Schiff base ligands: (i) unsubstituted (from aniline), (ii) hydroxyl-substituted (from 4-aminophenol), and (iii) bromo-substituted (from 4-bromoaniline). The synthesized ligands and their corresponding Ru(II) and Ru(II)-p-cymene complexes were fully characterized using FT-IR, UV-Vis, ^1H NMR spectroscopy, and melting point analysis, with spectral data providing unambiguous evidence for coordination through the imine and pyridyl nitrogen atoms. This structural elucidation forms the essential foundation for interpreting the subsequent in vitro antibacterial screening against representative Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) pathogens. By correlating structural features-such as ligand substitution pattern and the presence of the p-cymene moiety with observed biological activity, this work aims to establish critical structure-activity relationships that will inform the future development of ruthenium-based antimicrobial agents capable of overcoming the growing threat of AMR.



(*E*)-*N*-(4-bromophenyl)-1-(pyridin-2-yl)methanimine

Figure 4. Synthesis of (*E*)-*N*-(4-bromophenyl)-1-(pyridin-2-yl)methanimine.

The mixtures were stirred at room temperature for 12 h, yielding precipitates that were filtered, washed with cold diethyl ether, and dried under vacuum.

- 1) (*E*)-*N*-(4-Bromophenyl)-1-(pyridin-2-yl)methanimine (L): yellowish-grey microcrystalline solid, 90% yield.
- 2) (*E*)-*N*-Phenyl-1-(pyridin-2-yl)methanimine (L¹): red-dish oil, 85% yield.
- 3) (*E*)-4-((Pyridin-2-ylmethylene)amino)phenol (L²): pale yellow microcrystalline solid, 90% yield.

2. Materials and Methods

2.1. Chemicals and Instrumentation

All reagents were of analytical grade and used as received without further purification. 2-Pyridinecarboxaldehyde, aniline, 4-bromoaniline, 4-aminophenol, ruthenium (III) chloride hydrate, and $[(\eta^6\text{-p-cymene})\text{RuCl}_2]_2$ were purchased from Sigma-Aldrich. Solvents (diethyl ether, acetonitrile, DMSO, methanol) were used as supplied.

Melting points were determined using an open capillary method. FT-IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer ($4000\text{--}400\text{ cm}^{-1}$) using KBr pellets. UV-Vis spectra were acquired on a Shimadzu UV-1800 spectrophotometer (200–600 nm) in acetonitrile (1 cm path length). ^1H NMR spectra were recorded at 25 °C on a Bruker Avance III HD 400 MHz spectrometer in DMSO- d_6 , with tetramethylsilane (TMS) as internal standard. Antibacterial assays were conducted at the Kenya Medical Research Institute (KEMRI).

2.2. Synthesis of Schiff Base Ligands

The Schiff base ligands were prepared by equimolar condensation of 2-pyridinecarboxaldehyde (1.0 mmol) with the respective aniline derivative (1.0 mmol) in 30 mL diethyl ether under nitrogen, with a catalytic amount of p-toluene-sulfonic acid.

2.3. Synthesis of Ruthenium (II) Complexes

Non-cymene Ru(II) complexes: To a suspension of $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (0.5 mmol) in acetonitrile (20 mL) was added the Schiff base ligand (1.0 mmol). The mixture was refluxed under N_2 for 3 h, cooled, and the precipitate filtered, washed with diether, and dried (yield: 89–91%).

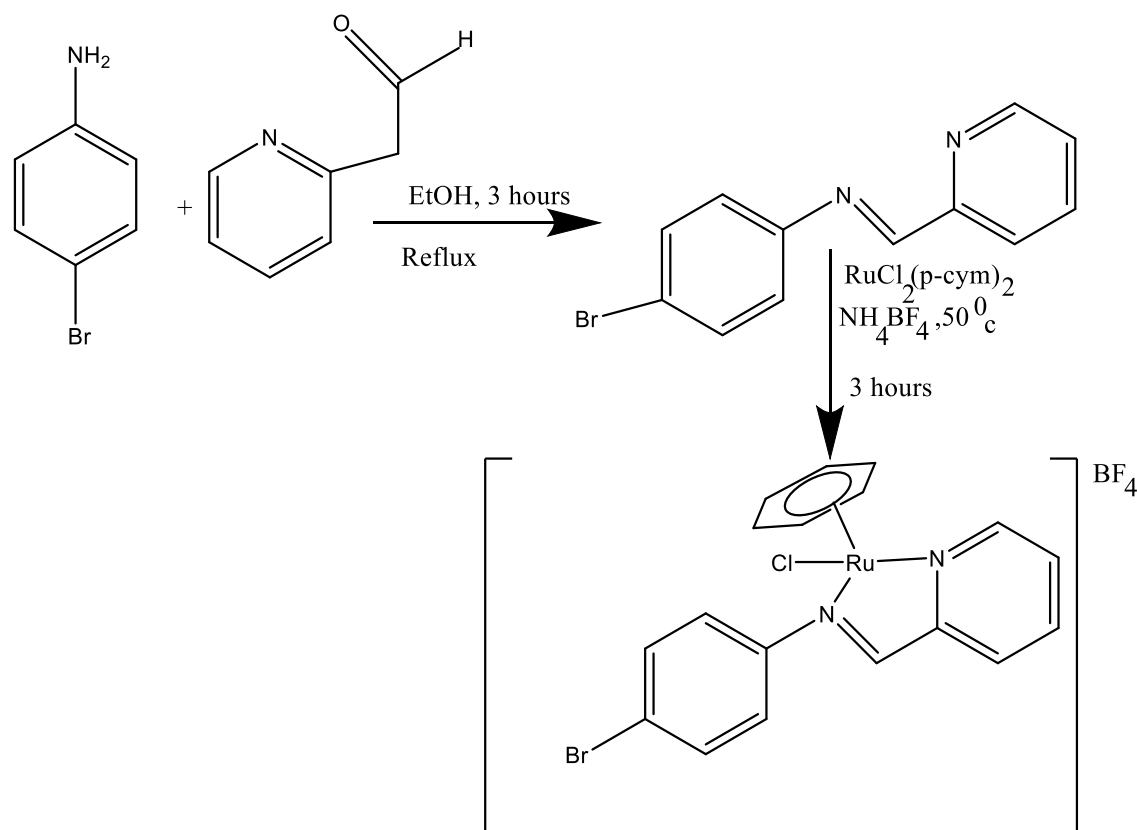


Figure 5. Synthesis of $[RuCl(C_{10}H_{14})(L)]BF_4$ {where $L = (E)\text{-}N\text{-(4-bromophenyl)-1-(pyridin-2-yl)methanimine}$.

Half-sandwich Ru(II)-cymene complexes: $(\eta^6\text{-p-cymene})RuCl_2]_2$ (0.27 mmol) in acetonitrile (30 mL) was treated with the Schiff base ligand (0.55 mmol) and refluxed for 3 h. The solvent was reduced in vacuo, and NH_4BF_4 (0.55 mmol) was added to the residue. The mixture was cooled in ice, and the resulting precipitate was collected by vacuum filtration, washed with diethyl ether, and dried under vacuum (yield: 87-92%).

2.4. Characterization

FT-IR, UV-Vis, 1H NMR, and melting point characterized all compounds. Spectral assignments confirmed coordination through the imine nitrogen and pyridyl nitrogen atoms, as detailed in the Results and Discussion.

2.5. Antimicrobial Assay

Antibacterial activity was evaluated against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) using the agar disc diffusion method (CLSI guidelines). Mueller-Hinton agar plates were inoculated with standardized bacterial suspensions (0.5 McFarland). Sterile filter paper discs (6 mm) impregnated with 20 μ L of test solutions (125, 250, 500, and 1000 μ g/mL in DMSO) were placed on the agar surface. Gentamycin (10 μ g/disc) served as the positive control; DMSO alone served as the negative

control. Plates were incubated at 37°C for 24 hours, and the zones of inhibition (mm) were measured. Experiments were performed in triplicate.

2.6. Statistical Analysis

Data were analyzed by two-way ANOVA followed by Fisher's Least Significant Difference (LSD) test ($\alpha = 0.05$) using R v4.3.0. Values are expressed as means $\pm$ standard deviation.

3. Results

3.1. Synthesis and Physical Properties

Three bidentate Schiff base ligands—(E)-N-(4-bromophenyl)-1-(pyridin-2-yl)methanimine (L), (E)-N-phenyl-1-(pyridin-2-yl)methanimine (L^1), and (E)-4-((pyridin-2-ylmethylene)amino)phenol (L^2)—were synthesized in high yields (85-90%) via a one-pot condensation of 2-pyridinecarboxaldehyde with 4-bromoaniline, aniline, or 4-aminophenol, respectively (Scheme 1). The corresponding simple Ru(II) complexes (L-Ru, L^1 -Ru, L^2 -Ru) and half-sandwich Ru(II)-cymene complexes (L-C1, L^1 -C2, L^2 -C3) were obtained in 87-92% yield by reacting the ligands with $RuCl_3 \cdot xH_2O$ or $[(\eta^6\text{-p-cymene})RuCl_2]_2$, followed by anion exchange with NH_4BF_4 (Scheme 2).

All complexes were air-stable, crystalline solids. The Ru-cymene complexes were orange/green crystals, while the simple Ru(II) complexes appeared as purple solids (Table 1). All compounds were soluble in polar aprotic solvents (DMSO, ace-

tonitrile) but insoluble in non-polar solvents (diethyl ether, hexane). Melting points of the complexes (175-235 °C) were consistently higher than those of the free ligands (70-180 °C), indicating enhanced thermal stability upon coordination (Table 1).

Table 1. Melting points of ruthenium (II) complexes and ligands.

Ligand/Complex	Calculated Molecular Weight	Mpt (°C)	Colour	Yield (%)
L ₁	182	-	Reddish oil	85
L	261	70	Yellow powder	89
L ₂	198	180	Yellow powder	90
L-C ₁	616	175	Orange crystals	90
L ₁ -C ₂	537	205	Green crystals	92
L ₂ -C ₃	553	220	Orange crystals	87
L-Ru	693	210	Purple crystals	89
L ₁ -Ru	567	224	Purple crystals	91
L ₂ -Ru	535	235	Purple crystals	89

3.2. Spectroscopic Characterization

FT-IR Spectroscopy

FT-IR confirmed coordination through imine (-CH=N-)

and pyridyl nitrogen atoms. The free ligands exhibited strong C=N(imine) stretches at 1625-1632 cm⁻¹. Upon complexation, this band shifted to lower frequencies (1600-1620 cm⁻¹), consistent with electron donation from the imine nitrogen to the Ru(II) center (Table 2).

Table 2. FT-IR Spectral Data for Ligands and Complexes.

Ligand/ Complex	C=C (cm ⁻¹)	C=N _{imine} (cm ⁻¹)	C=N _{pyridine} (cm ⁻¹)
L	1470	1630	1628
L ₁	1584	1628	1634
L ₂	1573	1629	1632
L-C ₁	1479	1631	1631
L ₁ -C ₂	1498	1600	1570
L ₂ -C ₃	1500	1604	1500
L-Ru	1448	1604	1585
L ₁ -Ru	1479	1600	1570
L ₂ -Ru	1496	1629	1479

The C=N(pyridine) stretch also shifted from 1573-1584 cm⁻¹ (free ligands) to 1479-1570 cm⁻¹ (complexes), further supporting bidentate N, N'-coordination. Additionally, the -OH stretch of L² (3200 cm⁻¹) disappeared in L²-Ru and L²-C₃, confirming participation of the phenolic oxygen or

H-bonding disruption upon metal binding. New bands at 400-405 cm⁻¹ were assigned to ν(Ru-N), and bands at 763-778 cm⁻¹ confirmed the presence of [BF₄]⁻ in cymene complexes. Consider Figures 6, 7, and 8.

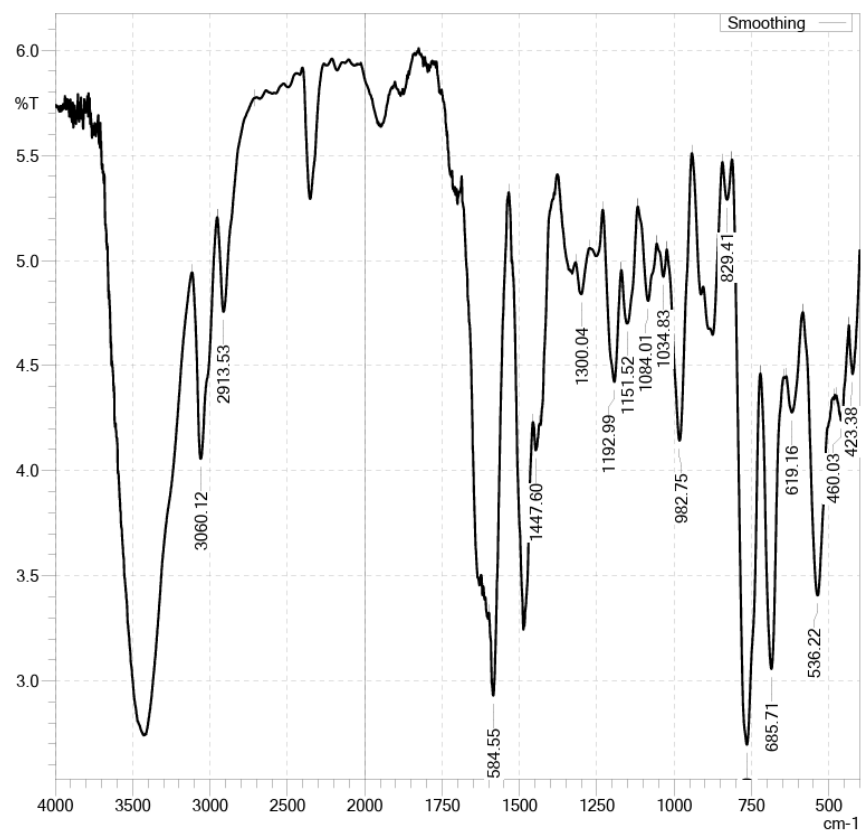


Figure 6. IR Spectra of (L1).

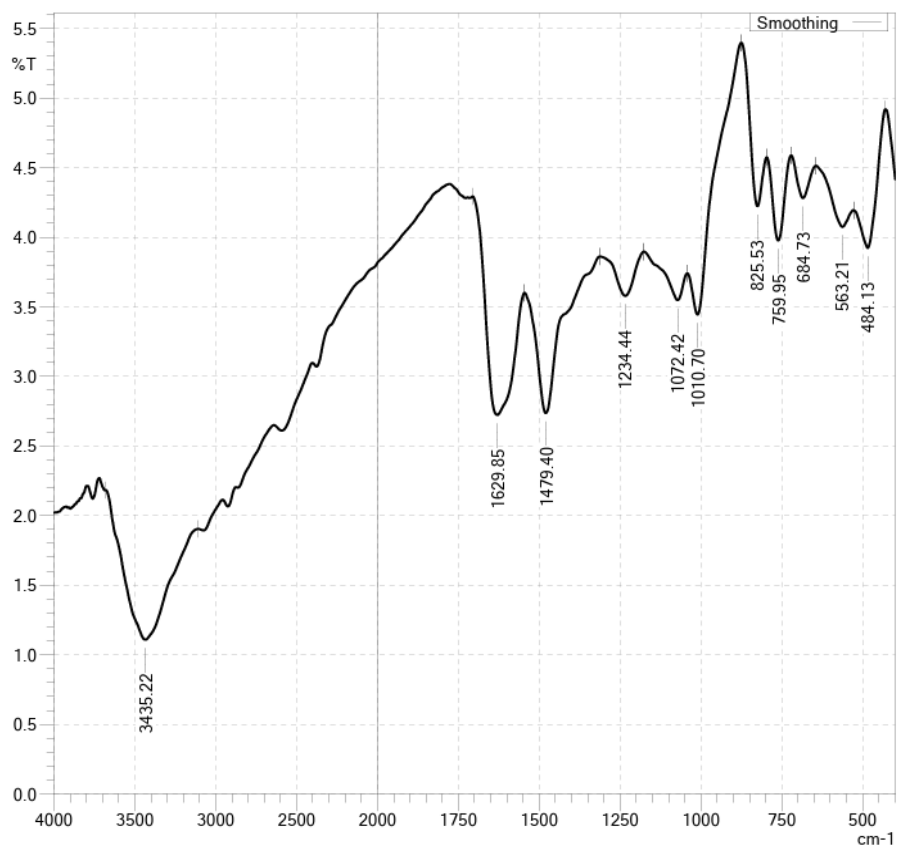


Figure 7. IR Spectra of L2-Ru complex.

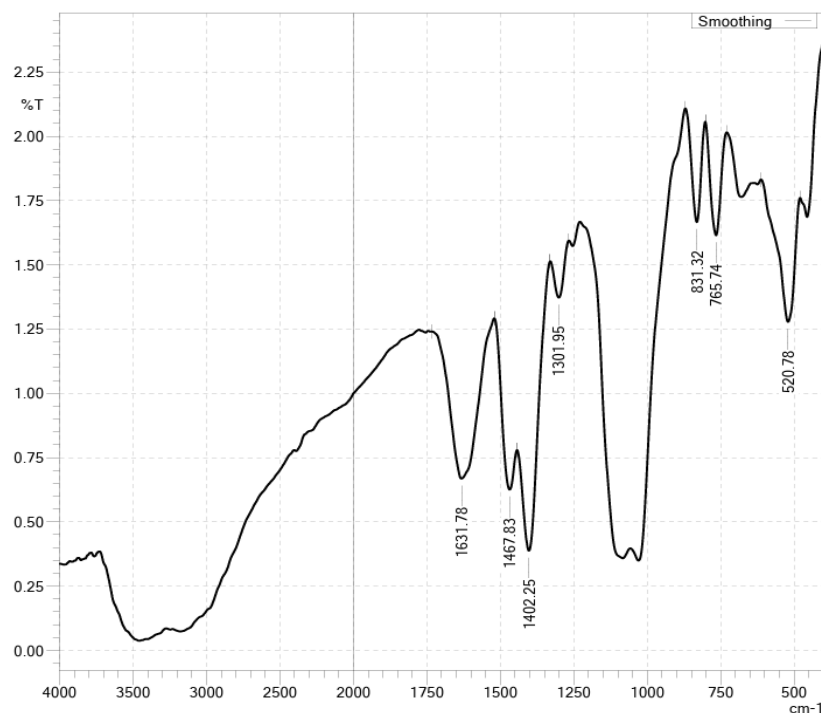


Figure 8. IR Spectra of L1-C1 complex.

3.3. ^1H NMR Spectroscopy

In DMSO- d_6 , the imine proton ($-\text{CH}=\text{N}-$) of free ligands appeared as a sharp singlet at δ 7.63-7.66 ppm. Upon coordination, this signal shifted downfield to δ 7.43-7.55 ppm,

confirming involvement of the imine nitrogen in Ru binding (Figures 9-11). For the Ru-cymene complexes, the p-cymene protons appeared as four distinct doublets in the range δ 5.38-6.28 ppm, indicating loss of symmetry due to chelation—consistent with a pseudo-octahedral “piano-stool” geometry. Consider Figures 2, 10, and 11.

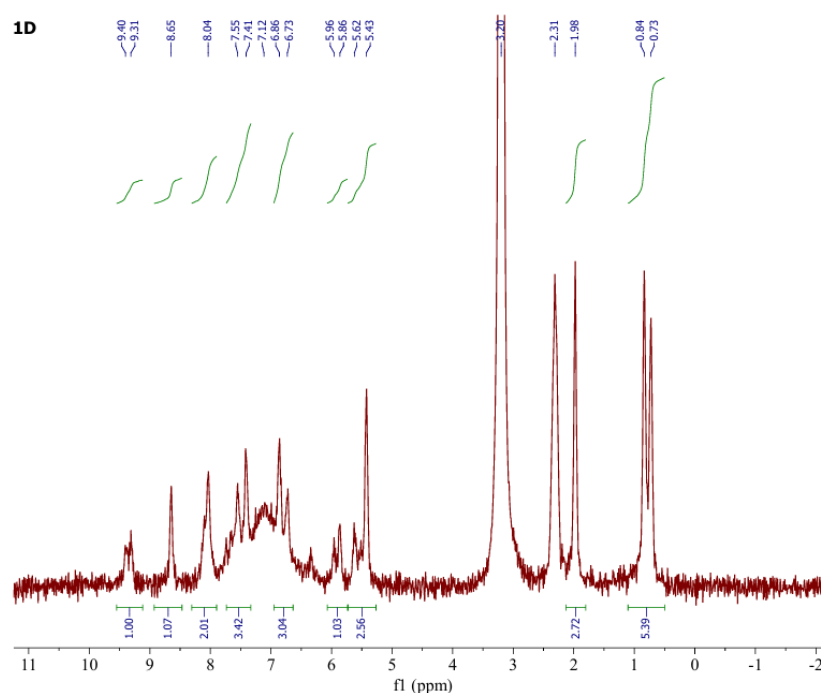


Figure 9. ^1H NMR of L2C3.

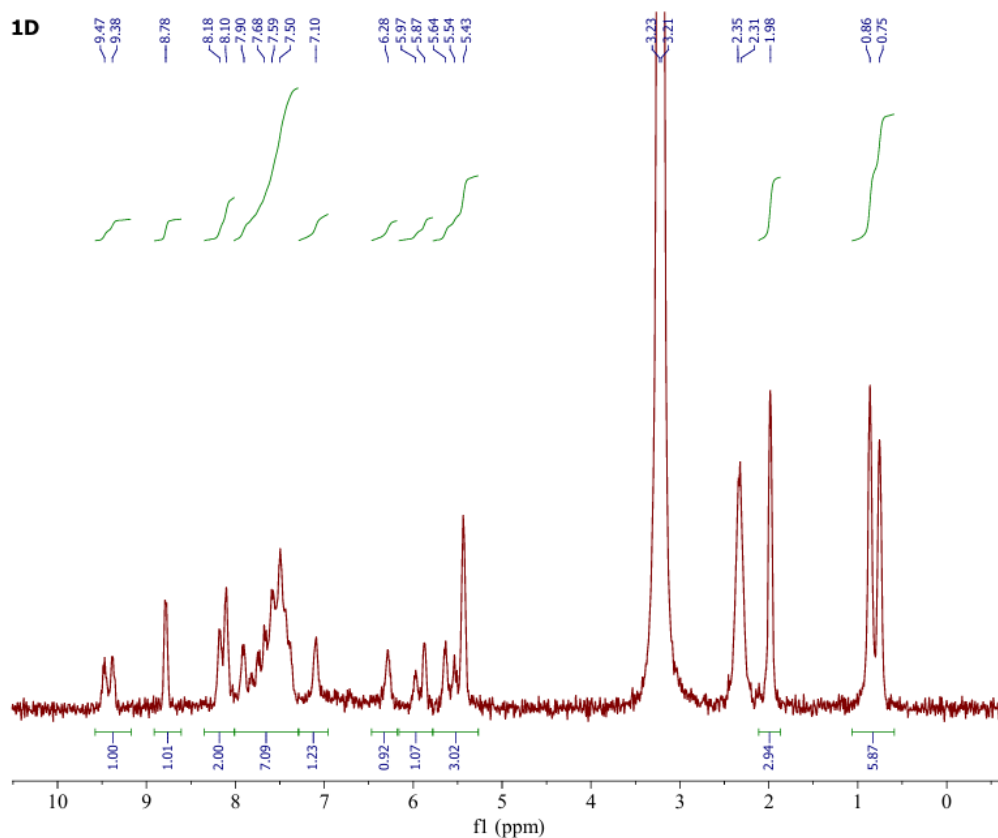


Figure 10. ^1H NMR of L1C2.

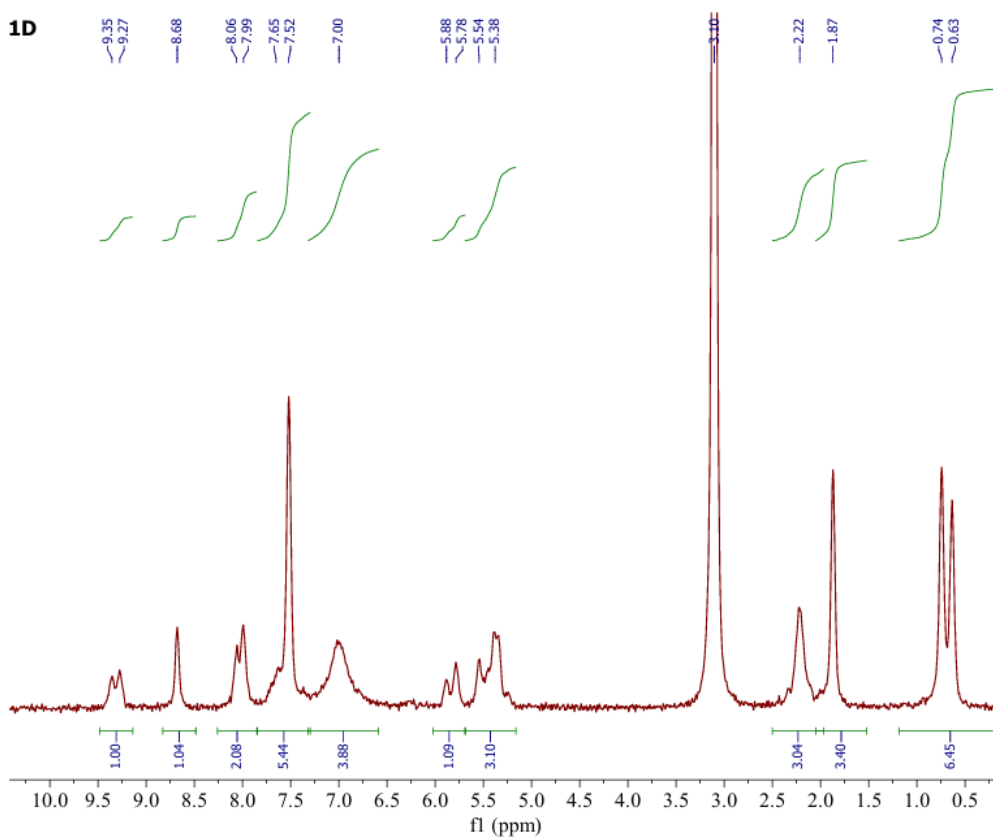


Figure 11. ^1H NMR of L1C1.

4. Discussion

The observed enhancement in antimicrobial activity upon coordination of Schiff base ligands to Ru(II) aligns with Tweedy's chelation theory, wherein metal complexation reduces the polarity of the metal ion, increases lipophilicity, and facilitates membrane penetration [20, 19]. This trend is consistent with prior studies [7], which reported that Ru(II)-arene complexes with N, N'-bidentate ligands exhibit superior activity against both Gram-positive and Gram-negative bacteria compared to the free ligands. Similarly, [14] noted that cationic Ru(II) polypyridyl complexes disrupted bacterial membranes via electrostatic interactions and ROS generation. The moderate activity against *E. coli* relative to *S. aureus* reflects the protective role of the Gram-negative outer membrane—a pattern also observed by [30] for Ru(II) triazole complexes. Notably, complexes with electron-donating (-OH) and electron-withdrawing (-Br) substituents (e.g., L2-C3, L-C2) displayed higher inhibition than unsubstituted analogues, echoing findings by [28] that substituent electronics modulate bioactivity. While none surpassed gentamycin, the dose-dependent response and significant ($p \leq 0.05$) differences confirm that structural features—ligand substitution and Ru-cymene coordination—critically influence antibacterial efficacy, supporting further development of Ru-Schiff base scaffolds as alternatives to conventional antibiotics.

5. Conclusions

In this study, three bidentate pyridine-imine Schiff base ligands and their corresponding Ru(II) and Ru(II)-p-cymene complexes were successfully synthesized and characterized by FT-IR, UV-Vis, ^1H NMR spectroscopy, and melting point analysis. Spectroscopic data confirmed coordination through the imine and pyridyl nitrogen atoms, consistent with an N, N'-bidentate binding mode. The complexes exhibited enhanced thermal stability and distinct electronic transitions—including metal-to-ligand charge transfer (MLCT) bands—absent in the free ligands, which verified the successful complexation. While antimicrobial activity was modest compared to gentamycin, Ru(II) complexes consistently outperformed their parent ligands, with substituted derivatives (-Br, -OH) showing superior inhibition against both *Staphylococcus aureus* and *Escherichia coli*. These findings support Tweedy's chelation theory and underscore the role of ligand electronics and Ru coordination in modulating bioactivity. The results validate Schiff base Ru(II) complexes as promising scaffolds for developing novel antimicrobial agents to combat resistant pathogens.

Abbreviations

SB	Schiff Base
FT-IR	Fourier Transform Infrared Spectroscopy

UV-Vis	Ultraviolet-Visible Spectroscopy
NMR	Nuclear Magnetic Resonance
^1H NMR	Proton Nuclear Magnetic Resonance
TMS	Tetramethylsilane
MLCT	Metal-to-Ligand Charge Transfer
DMSO	Dimethyl Sulfoxide
MHA	Mueller Hinton Agar
MIC	Minimum Inhibitory Concentration
DNA	Deoxyribonucleic Acid
Cym	p-Cymene (or $\text{C}_{10}\text{H}_{14}$)

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Author Contributions

Shem Ongechi Nyang'ate: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing

Joel Mwangi Gichumbi: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing

Esther Wanja Nthiga: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing

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Data Availability Statement

The data is available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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