

Synthesis, Characterization and Antimicrobial Evaluation of Schiff Base Ligands Derived from Ampicillin and their Metal (II) Complexes

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ABSTRACT

Two Schiff base ligands were generated by the condensation of amoxicillin with furfuraldehyde (HL¹) and vanillin (HL²). The Cu(II) and Ni(II) complexes of the Ampicillin-Schiff base ligands were successfully produced under reflux in 1:2 metal-to-ligand molar ratio. Spectroscopic and physicochemical techniques such as elemental analysis, melting point, molar conductivity, UV-Visible, FTIR, ¹H NMR, ¹³C NMR, and mass spectrometry were utilized for the characterization of the synthesized compounds. The antimicrobial activity of the synthesized Schiff base ligands and their metal complexes against different strains of bacteria which include *Staphylococcus aureus*, *Staphylococcus pyogenes*, *Escherichia coli*, *Salmonella Typhi* and *Candida albicans*, were tested using disc diffusion method. According to the physical characteristic data, the compounds are stable at room temperature and exhibited various colour with melting/decomposition temperature ranging from 161-185 °C. The FTIR spectra reveal that the ligands coordinated to the metal ions through $\nu(\text{C}=\text{O})$, and $\nu(\text{C}=\text{N})$. The UV/Visible spectra suggested that the complexes have tetrahedral geometry. The results of microanalysis and mass spectrometry agreed with the proposed structure. The antimicrobial screening of the Schiff base ligands and the complexes revealed that the complexes of HL¹ and Ni(II) complex of HL² have better activity as compared to the free ligands.

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INTRODUCTION

Ampicillin is an important broad-spectrum antibiotic belonging to β -lactam family. However, bacterial resistance to ampicillin, mainly through the production of β -lactamases, poses challenges in its clinical use. Combining ampicillin with β -lactamase inhibitors has been an effective strategy to overcome resistance (Safak *et al.*, 2012; Sarangi *et al.*, 2020; Mohamadzadeh *et al.*, 2020). Therefore, derivatization and functionalization of antibiotic drugs can improve their therapeutic applications. One of such derivation is through condensation of the amino group of the ampicillin molecule with carbonyl compound to produce the class of compound called Schiff base (Khonsary, 2017). Schiff bases, named after Hugo Schiff, are produced through the condensation of primary amines with carbonyl compounds, creating an imine (C=N) group. These molecules are capable of forming stable metal ion complexes with broad biological and catalytic properties (Ceramella *et al.*, 2022).

In continuation of our earlier work Mshelia *et al.* (2025) on ampicillin-derived Schiff bases, we report herein the synthesis of complexes of Ni(II) and Cu(II) from Schiff base ligands derived from ampicillin and furfuraldehyde or vanillin, coded as HL¹ and HL², respectively. Ampicillin condensed with furfuraldehyde or vanillin influences the electron properties of the Schiff base ligands and improves their coordination with Ni(II) and Cu(II) ions. In addition, ampicillin has antimicrobial properties that could enhance the biological activity of the complex compounds (Usman *et al.* 2013). The furfuraldehyde and vanillin on the other hand contribute to the aromaticity and position of hydroxyl group capable of coordinating with the metal ion, which also stabilize the complexes.

MATERIALS AND METHODS

The reagents and solvents used in this study were obtained from BDH. All were of analytical grade and were used without further purification. These include ampicillin, furfuraldehyde and vanillin, nickel (II) chloride hexahydrate, copper(II) chloride dehydrate, concentrated sulphuric acid and methanol. Melting points were determined using Griffin melting apparatus and were used without correction. Infrared spectra were recorded using a Bruker Tensor 27 and Perkin – Elmer FTIR spectrometer, Elemental analysis (CHN) was performed using Vario Elemental (III) CHNS analyzer. Electronic spectra were obtained with Shimadzu UV-1900, UV-Visible spectrophotometer at room temperature (500 MHz for ¹H and 125 MHz for ¹³CNMR spectra with DMSO-d₆ for both proton and carbon analysis. Chemical shift was reported in parts per million (ppm) relative in deuterated dimethyl sulfoxide (DMSO-d₆), with $\delta_{\text{H}} = 2.50$ and $\delta_{\text{C}} = 39.50$ for both ¹H and ¹³CNMR spectra, respectively. Mass spectra were obtained using high resolution mass spectrometry on a waters Aquity UPLC synapt G2HD machine. Thermogravimetric (TGA) was conducted on a STDQ600 thermoanalyzer with a heating rate of 10 °C /min under nitrogen flow.

Synthesis of the Schiff base ligands HL¹

The synthesis was done using a modified literature method by Wasaf *et al.* (2023). Ampicillin (1.0 g, 10 mmol, 1eq) was dissolved in 30 mL of methanol. The methanolic solution of the ampicillin was reacted with solutions of each of the following aldehydes: furfuraldehyde (1.5 g, 10 mmol, 1eq) or vanillin (1.7 g, 10 mmol, 1eq), followed by 2-3 drops of H₂SO₄, which acted as a catalyst to give HL¹. The mixture

was refluxed at 65 °C for 3 hours, after which the precipitate formed after three days, was filtered, washed with methanol, and dried in a desiccator over fused calcium chloride (CaCl₂). The equations for the reactions are shown in Figure 1 and 2.

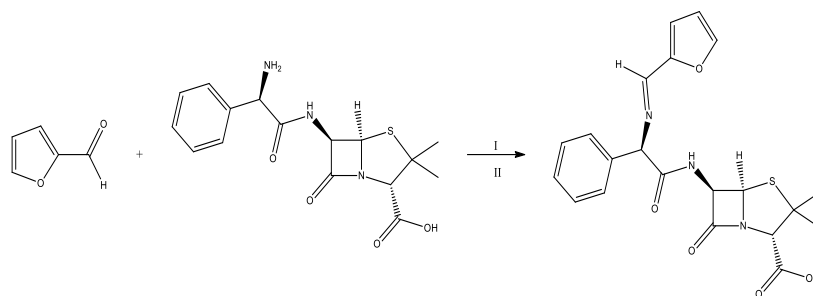


Figure 1: Route for the synthesis of the Schiff base ligands HL¹; i = CH₃OH/H₂SO₄, ii = 65 °C/3 hours

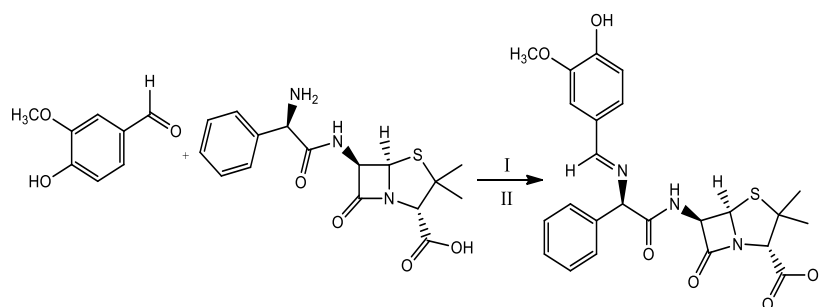


Figure 2: Route for the synthesis of the Schiff base ligands HL²; i = CH₃OH/H₂SO₄, ii = 65 °C/3 hours

Synthesis of the Metal Complexes

Metal complexes of Ni (II) and Cu (II), with synthesized Schiff base ligands (HL¹ and HL²) were utilized at room temperature in the synthesis of the complexes, using 1:2 mole ratio of metal to ligand as reported by Subitha *et al.* (2021). Each of the synthesized ligands (4 mmol, 2eq) was weighed and dissolved in 20 mL of methanol. The methanolic solution

of the free ligands were mixed with 20 mL of each of the methanolic solution of the metal (II) chlorides (2.0 mmol, 1eq). The mixture was refluxed at 65 °C for 4 hours, after which the product formed were filtered, washed with methanol and dried in a desiccator over calcium chloride. The proposed reaction pathways are presented in Figure 3 and 4.

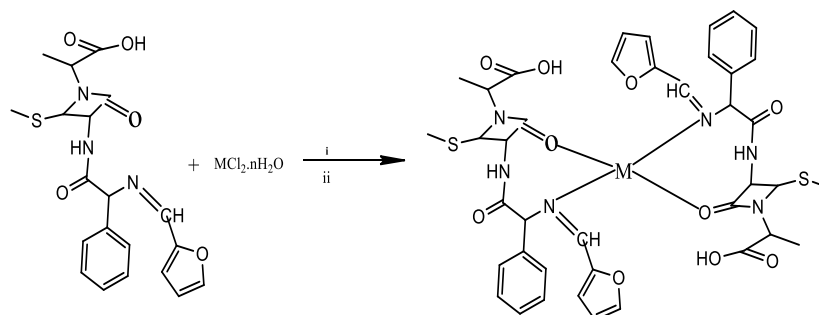


Figure 3: Route for the synthesis of the complexes: i = CH₃OH, ii = 65 °C/3 hours, M = Ni or Cu, n = 2 or 6

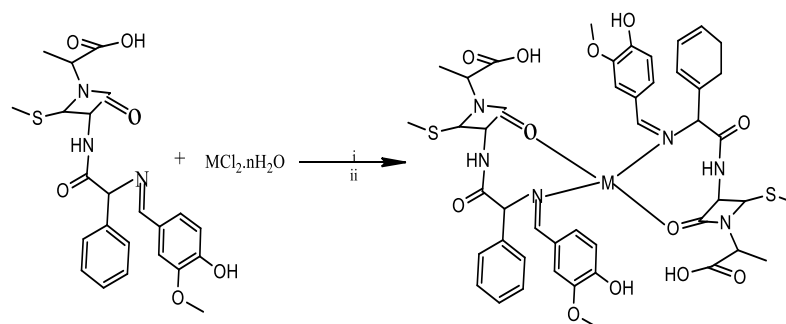


Figure 4: Route for the synthesis of the complexes: i = CH₃OH, ii = 65 °C/3 hours, M = Ni(II) or Cu(II), n = 2 or 6

Antibacterial study

The antibacterial and antifungal potentials of the free ligands (HL¹ and HL²) and their Ni(II) and Cu(II) complexes comparative to ampicillin were screened using disc-diffusion method against some selected bacteria which comprises of two Gram-positive bacteria (*Staphylococcus aureus*, and *Streptococcus pyogenes*), two Gram-negative bacteria, (*Salmonella Typhi* and *Escherichia coli*) and fungus (*Candida albicans*). The suspension containing species of micro-organisms were freshly prepared using nutrient agar medium and poured into petri dishes and were allowed to set. The solution of the test compounds, i.e., the Schiff base ligands and their metal(II) complexes were introduced in various concentrations (30, 20 and 10 µg/mL) in methanol which ampicillin serves as control were then placed on culture media and incubated for 24 hours at 37 °C. The activities were determined by measuring the diameter of the zone of inhibition (mm) (Alshater *et al.*, 2023). Statistical analysis is expressed as mean (mean ± SEM). This was done to determine significant differences in the concentrations of the new compounds.

RESULTS AND DISCUSSION

Physical properties of the ligands and their metal complexes

The reaction between Ampicillin and furfuraldehyde or vanillin in 1:1 molar ratio gave synthesized Schiff base

ligands HL¹ and HL² with white and milky colour, respectively. The Schiff base ligands were formed with a percentage yield of 57%, for HL¹ and 86%, for HL² with sharp melting points of 184 °C and 183 °C, respectively. This indicates that the compounds are likely to be pure. The Ni(II) and Cu(II) complexes were synthesized using their chlorides, which interacted with the Schiff base ligands in methanol in a molar ratio of 1:2 (M: L). The complexes are air stable with melting points ranging from 182-183 °C and formed a percentage yield of 40–67%. The physical and elemental data are presented in Table 1. The experimental elemental compositions of the Schiff bases and metal(II) complexes agreed with the proposed structures and are coded as M(L)₂, M = Cu(II) or Ni(II) and L = ligand. The different colours of the synthesized compounds, green for Ni(II) complexes, and blue for Cu(II) complexes, are due to d-d transition between energy levels (Mshelia *et al.*, 2025). Conductivity values of the complexes were found in the range of 1.8–7.0 Scm²mol⁻¹ indicating that they are non-electrolytes (Naz *et al.*, 2013; Umar *et al.*, 2025).

The elemental compositions of the ligands were determined using microanalysis. The results were found to be in agreement with the theoretical data and validated the proposed molecular formula [ML₂], where M denotes Cu(II) or Ni(II) and L the ligands.

Table 1: Physical characteristics of the Synthesized Schiff bases ligands and their Metal (II) complexes

Compounds	M. F.(Molar mass)	Colour	M. P (°C)	Yield (%)	Elemental analysis % found				Molar (Scm ² mol ⁻¹)	Conductivity
					C	H	N	M		
HL ¹	C ₂₃ H ₂₅ N ₄ O ₆ S (430.14)	Ash	182	50	58.49 (58.62)	4.89 (5.90)	9.47 (9.76)	-	-	
HL ²	C ₂₃ H ₂₅ N ₄ O ₆ S (471.15)	Yellow	182	86	59.33 (68.60)	8.45 (9.22)	8.45 (9.22)	-	-	
CuL ¹	[Cu(C ₂₁ H ₂₃ N ₃ O ₅ S ₂) (932.826)]	Blue	184	58	54.78 (50.48)	4.16 (5.53)	7.54 (6.14)	6.68 (6.88)	2.0	
CuL ²	[CuC ₂₃ H ₂₄ N ₃ O ₆ S ₂] (897.846)]	Blue	182	67	56.01 (54.13)	4.68 (5.00)	8.14 (6.14)	6.11 (6.33)	7.0	
NiL ¹	[NiC ₂₁ H ₂₄ N ₃ O ₅ S ₂] (918.973)]	Green	183	40	55.18 (40.45)	4.33 (5.00)	9.20 (6.14)	6.25 (6.38)	2.3	
NiL ²	[NiC ₂₃ H ₂₄ N ₃ O ₆ S ₂] (892.29)]	Green	184	60	56.25 (53.03)	4.67 (6.86)	8.19 (7.49)	5.64 (5.85)	1.8	

Characterization

¹H NMR of the Schiff Base Ligands (HL¹ and HL²)

Nuclear magnetic resonance (NMR) is an essential analytical technique that provides information about molecular structure. The ¹H NMR data of the free Schiff base ligands are presented in Table 2 and the spectra are in Figures 1 and 2. The spectra of the ligands HL¹ and HL² showed a sharp singlet peaks at δ = 8.26 ppm due to the imine protons (Banbela *et al.*, 2025). The signal due to the amide protons were observed at a downfield region with δ values of 8.40 and

8.39 ppm, respectively. The ¹H NMR spectra of HL¹ and HL² exhibited singlet signal at δ = 12.78 and 12.71 ppm that are assigned to the protons of carboxylic acid –COOH group (Wasaf *et al.*, 2023). Additionally, they exhibit multiplet signals for aromatic –CH protons around 7.42–7.50 ppm. At the upfield region, the protons due to the –CH₃ displayed at 1.37 – 3.90 ppm corresponding to the beta-lactam of both ligands and methoxy protons of the vanillin-ligand (Albotani *et al.*, 2025).

Table 2: ¹H NMR data for the Schiff Base Ligands HL¹ and HL² in ppm

Compounds	δ (OH-COOH)	δ (H-Amide)	δ (H-Imine)	δ (H-Aromatic)	δ (CH ₃)	δ (Solvent) DMSO
HL ¹	12.78	8.40	8.26	7.50-7.42	1.37, 3.90	2.50
HL ²	12.74	8.39	8.26	7.50-7.48	2.38-3.67	2.50

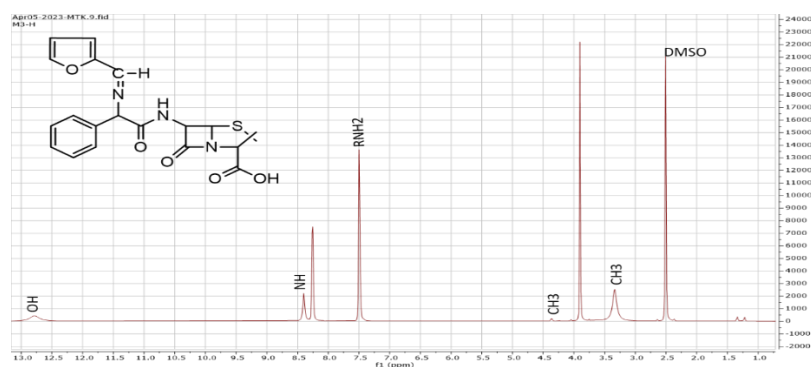
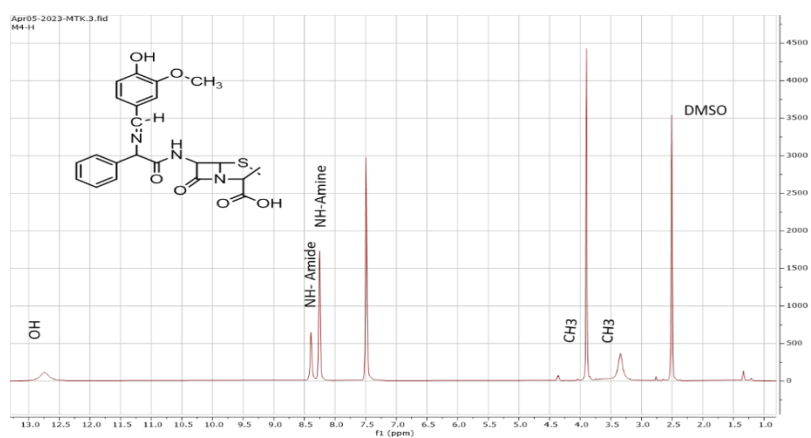
¹³C NMR of the Schiff Base Ligands (HL¹ and HL²)

The Carbon nuclear magnetic resonance (¹³C NMR) is analogous to proton nuclear magnetic resonance (¹H NMR) and is used for the identification of carbon atoms in a molecule just as proton NMR identifies hydrogen atoms. It also ascertains how atoms within a particular molecule are related. The spectra showed a signal at 163.9 ppm for the COOH of the ampicillin moiety. The signals at 156.3 and

135.70 ppm are attributed to C-amide and imine carbon, respectively. Additionally, the signals that show up in the range of 128.54 – 129.51 ppm are associated with the aromatic carbons of the phenyl rings. The characteristics C=O appeared at 128.54 – 130.78 ppm while the –CH₃ exhibited shift between 53.17 – 62.22 ppm. The data are presented in Table 3.

Table 3: ^{13}C NMR data for the Schiff Base Ligands HL^1 and HL^2 in ppm

Compound	$\delta(\text{C-COOH})$	$\delta(\text{C-NH})$	$\delta(\text{C=N})$	$\delta(\text{C=O})$	$\delta(\text{C-Aromatic})$	$\delta(\text{C-CH}_3)$	ΔDMSO
HL^1	162.93	156.43	135.70	130.75 – 128.55	129.51-128.55	62.22, 53.18	40.12
HL^2	162.92	156.43	135.70	130.75 – 128.54	129.51-128.54	62.21, 53.17	40.19

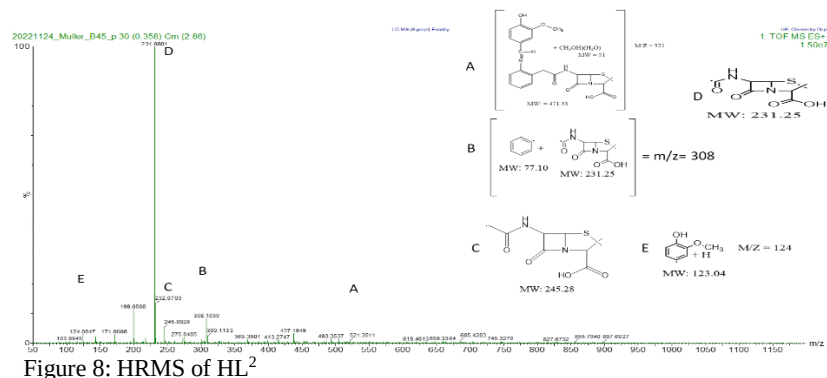
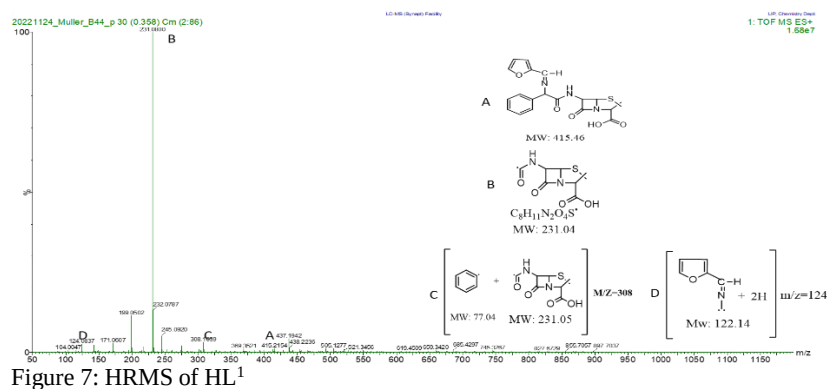
Figure 5: Proton NMR spectrum of HL^1 using (500 MHz, DMSO-d_6)Figure 6: Proton NMR spectrum of HL^2 using (500 MHz, DMSO-d_6)**Mass spectroscopy**

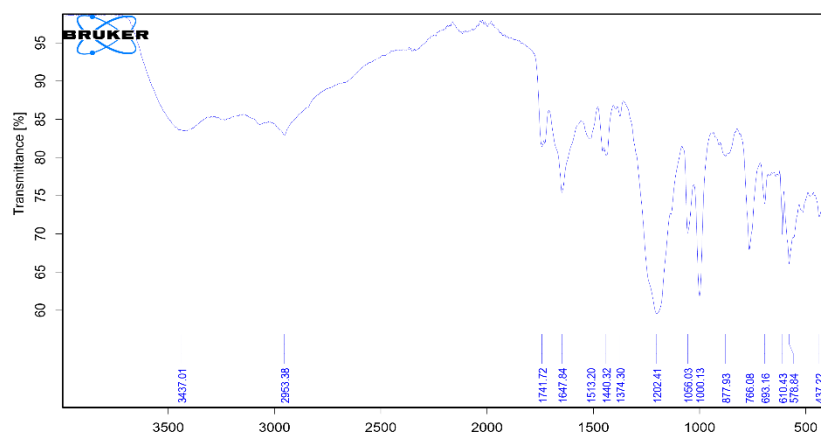
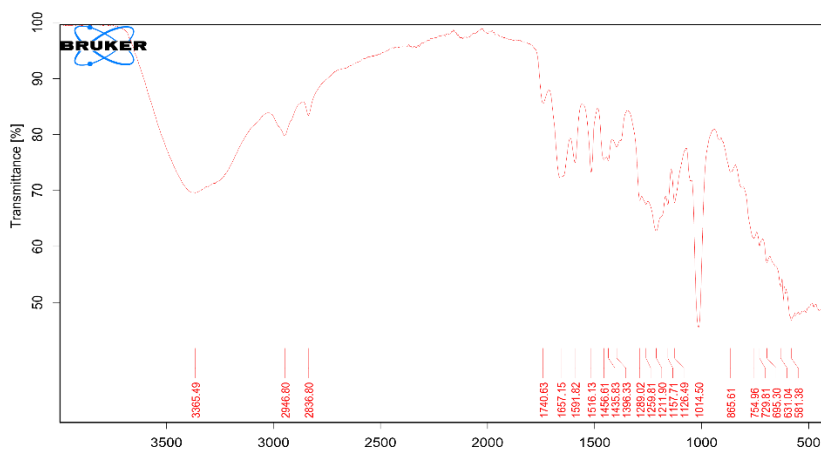
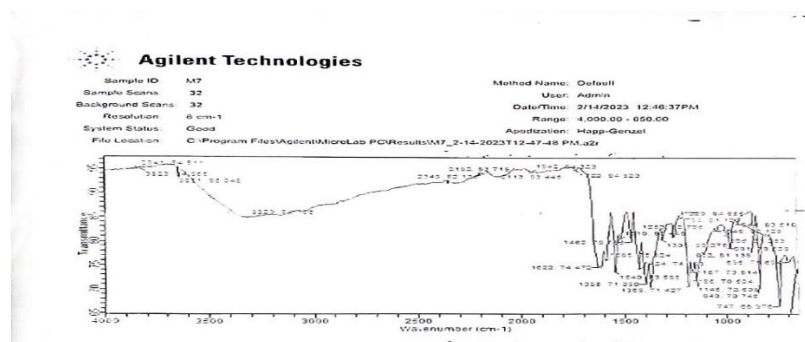
Mass spectroscopy is an analytical technique that is used to measure the mass-to-charge ratio of ions. The molecular ion peak of HL^1 and HL^2 have been successfully confirmed by mass spectrometry, and the fragment species have been investigated. The mass-spectrum fragment pattern, which consists of a sequence of peaks corresponding to different fragments, provides an impression of the target compound's progressive degradation. The intensity of peaks provides insight into the stability of fragments, particularly in relation to the base peak. The mass spectral data are presented in Table 4. The molecular ion peaks in the HL^1 have background contamination of methanol and water cluster and is located at

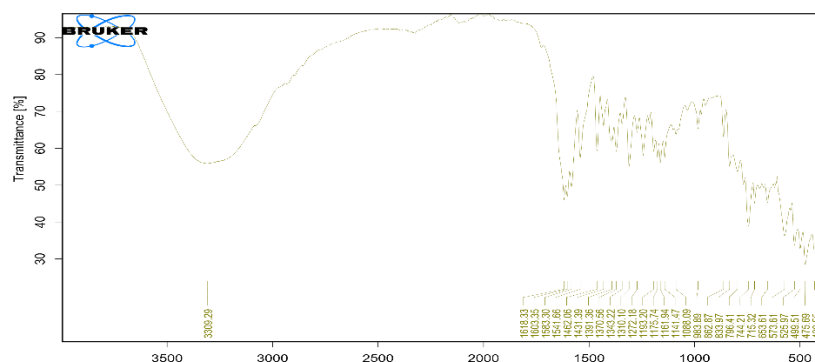
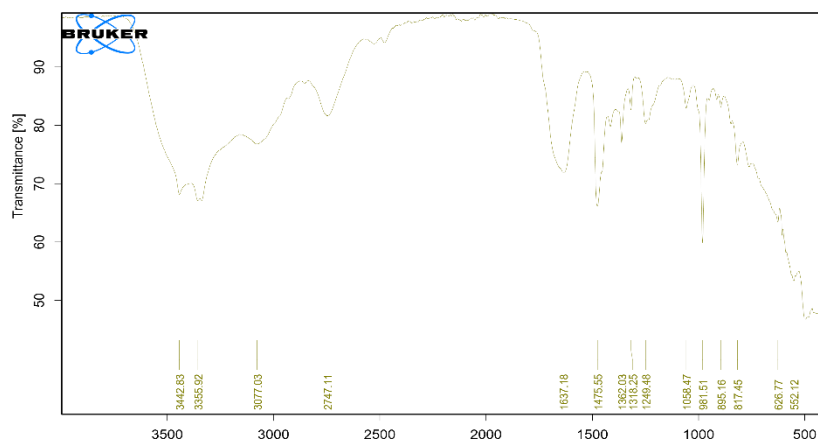
m/z : 415 corresponds to (M^+). The peak at m/z : 231 attributed to ($\text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{S}^+$). The base peak is located at m/z : 308 ($\text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{S}^+$) and peak at m/z : 199, is attributed to ($\text{C}_8\text{H}_{11}\text{NO}_2\text{S}^{3-}$). Other fragments include peak at m/z : 124 ($\text{C}_{10}\text{H}_6^{2+}$). For the ligand HL^2 , peak at m/z : 521 [$9\text{M}^+ - \text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{S}^+ - \text{C}_6\text{H}_5 - \text{CH}_3\text{OH}$] (H_2O). The peak at m/z 308 ($\text{C}_6\text{H}_5^{2+} + \text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{S}^+$ corresponds to phenyl ring and the beta lactam position molecular peak m/z appeared at 245. The base peak m/z : 231 attributed to $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{S}^+$ of the HL^2 spectra (Ramachandran *et al.*, 2019). Other fragments include peak at m/z : 199 which corresponds to $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{S}^+$ and peak at m/z : 171 for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_4\text{S}^{5+}$ and peak at m/z : 124, ($\text{C}_2\text{H}_4^{4+}$).

Table 4: Mass Spectroscopy of the Schiff Base Ligands

Compounds	Relative Abundance %	Fragmentation	Chemical formula	Base Peak / m/z
HL^1	0.5	124.0837	$\text{C}_2\text{H}_4^{4+}$	231.0800
	0.7	171.0607	$\text{C}_7\text{H}_9\text{NO}_2\text{S}^+$	
	2.1	199.0502	$\text{C}_8\text{H}_{11}\text{NO}_2\text{S}^{3-}$	
	100	231.0800	$\text{C}_8\text{H}_{11}\text{NO}_2\text{S}^{3-}$	
	0.1	415.2154	$\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2\text{S}^+$	
HL^2	1.0	124.0847	$\text{C}_2\text{H}_4^{4+}$	231.0801
	0.5	171.0608	$\text{C}_8\text{H}_{10}\text{O}_2\text{S}^{5+}$	
	3.0	199.0508	$\text{C}_8\text{H}_{11}\text{NO}_2\text{S}^{3+}$	
	3.4	231.0800	$\text{C}_8\text{H}_{11}\text{NO}_2\text{S}^{3-}$	
	2.1	245.0928	$\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2^{4+}$	
	2.5	308.1106	$\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_3\text{S}^{3+}$	



Figure 9: FTIR spectrum of HL¹Figure 10: FTIR spectrum of HL²Figure 11: FTIR spectrum of CuL¹Figure 12: FTIR spectrum of CuL²

Figure 13: FTIR spectrum of NiL¹Figure 14: FTIR spectrum of NiL²

Electronic Spectral Study

The UV-Visible spectra of the free ligands (HL¹ and HL²) were recorded in methanol at a concentration of 10⁻³ M and assignment are reported in Table 6. An absorption band at 245 nm (40816 cm⁻¹), observed in both ligands are attributed to π - π^* of the phenyl ring (Naz *et al.*, 2013). Band displayed at 275 nm (37037 cm⁻¹), and 300 nm (3.3333 cm⁻¹) attributed to

the n- π^* transition originating in -CH=N chromophore. The additional band at 300 nm (33333 cm⁻¹) to 390 nm (25641 cm⁻¹) are attributed to metal-to-ligand charge transfer (Mshelia *et al.*, 2025). Four-coordinated tetrahedral geometry planar geometry is expected for Cu (II) and Zn (II) complexes.

Table 6: UV/Vis spectra data of the Schiff bases and their metal(II) complexes

Compounds	Wave length (nm)	Wave number (cm ⁻¹)	Assignment
CuL ¹	245	39570	π - π^*
	300	33333	π - π^*
	310	30395	MLCT
CuL ²	245	39570	π - π^*
	300	33333	π - π^*
	310	32258	MLCT
NiL ¹	245	41666	π - π^*
	295	33898	π - π^*
	390	25641	MLCT
NiL ²	245	37570	π - π^*
	275	36363	π - π^*
	300	33333	MLCT

Biological Screening

The antibacterial behaviour of all the synthesized Schiff base transition metal complexes were evaluated against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Salmonella Typhi*, and *Candida albicans*. The extent of effectiveness was determined by measuring diameter of clear inhibitory zone caused by samples and reported in Table 7. The HL¹ Schiff base ligand shows no any activity against all test microorganisms. However, its complexes demonstrated amplified antimicrobial consequences when contrast with the

free Schiff base but less potent than the unadulterated ampicillin. The HL² showed zone of inhibition of 16 $\pm$ 0.00, 15 $\pm$ 0.00, and 13 $\pm$ 0.00 mm against *Streptococcus aureus*, *Streptococcus pyogenes* and *Escherichia coli* respectively. The inhibitory zone of the complex NiL² increased to 28 $\pm$ 0.00 mm against *Streptococcus aureus* at the highest test concentration of 30 μ g/mL while its activity against the other microorganisms diminished. All the synthesized compound did not show zone of inhibition against *Candida albicans*.

Table 7: In Vitro Antimicrobial Activity of the Schiff Bases and Their Metal (II) complexes (Zone of inhibition in mm)

Compounds	Conc. (µg/mL)	<i>Streptococcus Aureus</i>	<i>Streptococcus Pyogenes</i>	<i>Escherichia coli</i>	<i>Salmonella Typhi</i>	<i>Candida albicans</i>
HL ¹	30	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
	20	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
	10	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
HL ²	30	16±0.00	15±0.00	13±0.00	0±0.00	0±0.00
	20	11±0.00	10±0.00	8±0.00	0±0.00	0±0.00
	10	7±0.00	7±0.00	0±0.00	0±0.00	0±0.00
CuL ¹	30	10±0.00	10±0.00	10±0.00	18±0.00	0±0.00
	20	0±0.00	7±0.00	0±0.00	12±0.00	0±0.00
	10	0±0.00	0±0.00	0±0.00	7±0.00	0±0.00
CuL ²	30	10±0.00	0±0.00	0±0.00	10±0.00	0±0.00
	20	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
	10	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
NiL ¹	30	12±0.00	11±0.00	14±0.00	10±0.00	0±0.00
	20	7±0.00	7±0.00	8±0.00	0±0.00	0±0.00
	10	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
NiL ²	30	28±0.00	13±0.00	10±0.00	13±0.00	0±0.00
	20	21±0.00	8±0.00	7±0.00	7±0.00	0±0.00
	10	13±0.00	0±0.00	6±0.00	0±0.00	0±0.00
Ampicillin	1000	12.0±2.00	0±0.00	17.0±2.00	24.±4.67	13±.00
	500	13.0±1.53	0±0.00	16.6±5.69	18.0±2.65	13±.00
	125	15.33±2.52	0±0.00	16.0±1.00	21.3±2.08	13±.00
	100	15.67±1.51	0±0.00	14.6±2.52	15.6±0.58	13±.00

CONCLUSION

This study presents the results of synthesis of Ni(II) and Cu(II) complexes derived from two synthesized Schiff base ligands HL¹ and HL². The ligands and complexes were characterized using UV-Vis, FTIR, elemental analysis (C, H, and N), mass spectrometry, as well as ¹H and ¹³C NMR spectroscopy. Results indicated that the ligands coordinated to the metal ions through the nitrogen atom of azomethine and oxygen of the ν(C=O) of the ligands. The complexes are all air stable and generally soluble in polar solvents which indicated that the synthesized Schiff base ligands and metal complexes are probably polar. The ¹H NMR and ¹³C NMR spectra of the synthesized Schiff bases ligands confirmed the structure of the ligands while the UV/Vis spectra and the microanalysis as well as mass spectrometry results are in good agreement with the structures or geometry of the synthesized complexes. The antimicrobial screening of the Schiff bases ligands and the complexes revealed the Ni(II) complex of HL² showed the greatest efficacy against *Streptococcus aureus*. Importantly, the antibacterial activity of the compounds was found to be dependent on concentration. The findings of this study provide a robust basis for further optimization of the compounds through introduction of other functional groups so as to investigate its therapeutic potential in addressing the growing challenge of bacterial resistance to antibiotics.

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