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Synthesis, characterization and comparative antibacterial study of Copper II and Zinc II Vanillin-2-aminophenol Schiff base and their mixed ligand Complexes

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ABSTRACT

Schiff bases are organic compounds that form by the reaction of aldehyde and amino or ketone groups to produce a new chemical bonding known as azomethine (-HC=N), which shows an impact on microbial activities. Schiff base was synthesized by reacting vanillin with 2-aminophenol in a 1:1 mole ratio. Transition metal complexes of Cu (II) and Zn (II) were complexes using a Schiff base in a 1:2 mole ratio metal-ligand (M-L). Additionally, mixed ligand complexes were prepared using the synthesized Schiff base and 2-aminophenol in a 1:1:1 mole ratio of ligand-metal-ligand (L-M-L). These were characterized by solubility, conductivity, melting point, UV, and IR spectroscopy. The solubility analysis indicates that all the complexes were soluble in acetone, ethanol, dimethyl sulfoxide (DMSO), methanol, and dimethyl formamyde (DMF). The melting point suggests that the complexes are pure; the conductivity measurement shows the lower values indicate the complexes exhibit non-electrolytic behavior. The infrared date for the metal complexes demonstrated that the ligand binds to the metal ion via nitrogen from immine backbone, oxygen from the methoxy group, and oxygen from the phenolic group, suggesting a six-coordinate geometry. The infrared data of the mixed ligand complex indicates the ligand attached to the metal ion through azomethine nitrogen, oxygen from the methoxy group, oxygen from the phenolic group, and nitrogen from the amino group, indicating a six-coordinate geometry. The compounds were assessed for their effectiveness against gram-negative bacteria, including Escherichia coli, Streptococcus pyrogens, Klebsiella pueumonia, and gram-positive bacteria, such as Bacillus subtilis, utilizing the disc diffusion technique. In comparative analysis of the complexes, Cu $(HL^1)_2$ and Cu (HL^1) (HL^2) were observed to be more potent than Zn $(HL^1)_2$ and Zn (HL^1) (HL^2).

Keywords: Antibacterial activity, infrared spectroscopy, Copper (II) complex, Schiff base, Zinc (II) complex

INTRODUCTION

Schiff bases are compounds derived by the reaction of a primary amine with a carbonyl compound, often an aldehyde or ketone, resulting in the formation of an imine group (C=N) through the elimination of water molecules. Schiff bases, initially reported by German Scientist Hugo Joseph Schiff (1864), are obtained by condensing carbonyl compounds such as aldehydes or ketones with primary amines, resulting in the elimination of water molecules (Rafique *et al.,* 2010). Schiff bases are stable imines with the typical formula R3R2C=N-R3, where R3 is an aryl or alkyl group (Ndahi *et al*., 2012). Schiff bases of aromatic aldehydes with an efficient conjugation are more stable than those of aliphatic aldehydes, which are more easily polymerized and comparatively unstable (Nasira *et al.*, 2016).

Schiff bases are typically formed by heat, acid or base catalysis, or both. The lone pair of electrons in the nitrogen atom's sp2 hybridized orbital of the azomethine has significant chemical and biological significance (Sunil, 2014). Schiff bases act as intermediates in a variety of enzymatic processes, including the interaction of an enzyme with an amino or carbonyl group of the substrate (Verma *et al.*, 2004; Anand *et al.*, 2012). The mechanism of contact and inhibitory efficiency of Schiff bases with bacteria and fungus is predicted to be determined by the compounds' molecular structures. Thus, improvements in this sector will require an analysis of the structure-activity connections of Schiff bases as well as an investigation of the mechanism of action of these compounds (Ejiah *et al.*, 2013).

The basis of coordinate complexes is produced by the complex formation between the Schiff base ligand and the transition metal ion (Shazia *et al.*, 2010). Metal-ligand complexation refers to the formation of a complex compound where a central metal ion is bonded to surrounding molecules or ions, known as ligands. This process significantly alters the chemical and physical properties of both the metal and the ligands. The resulting metal complexes can exhibit unique characteristics, such as enhanced stability, solubility, and biological activity (Chandraleka *et al.,* 2022). Metal compounds open up new possibilities for designing structures with specific features (Rehab *et al.*, 2024). The metabolism of inorganic substances is important for the treatment of certain disorders (Judge and Dodd, 2020).

Utilizing metal complexes as medicinal agents is now more feasible because of developments in inorganic chemistry (Karges *et al.,* 2021). Studying the complexation behaviors and biological activities of metal-antibiotic complexes is important for a number of reasons. Firstly, it offers understanding into the structural and electronic modifications that occur upon complexation, which can influence the drug's mechanism of action. Secondly, metal complexes can exhibit enhanced antibacterial, antifungal, and anticancer activities compared to the parent drugs (Patel *et al.,* 2020).

Our previous research provided significant insights into the synthesis, characterization, and antibacterial activity of Schiff base and its mixed ligand complexes of Cr (II) and Co (II) containing vanillin and 2-aminophenol (Isiyaku *et al.*, 2021). The current research is continuing to investigate the synthesis, characterization, and comparative antibacterial study of Copper II and Zinc II Vanillin-2-aminophenol Schiff bases and their mixed ligand complexes.

MATERIAL AND METHODS

Materials and Microorganisms

All chemicals employed were of analytical grade quality, and the metal salts were provided and utilized in their chloride form. The melting points were measured using an electric thermal device. The infrared spectra were recorded using Fourier transform infrared spectroscopy (FTIR) over a range of 450–4000 cm^{-1}. The absorption spectra were measured with UV-Visible spectrophotometer covering a wavelength range of 200–800 nm and employing dimethyl sulfoxide (DMSO) as the solvent. The conductivity measurements were conducted with a 10^{-2} molar solution of dimethyl sulfoxide (DMSO) using a digital conductivity meter. The antibacterial activity were evaluated against *Escherichia coli, Streptococcus pyrogens, Klebsiella pueumonia* and *Bacillus subtillis* utilizing the disc diffusion technique.

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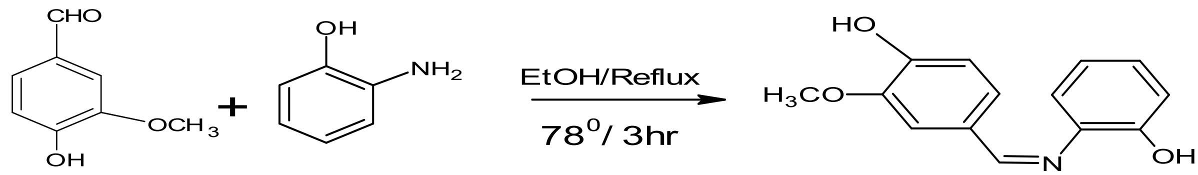
Synthesis of Schiff Base

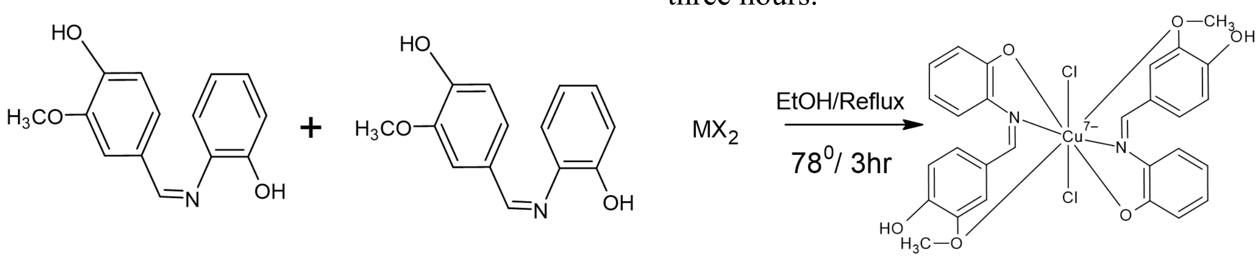
The preparation of Schiff base was carried out by a slightly altered version of the method reported by Raman et al. (2004) and Ndahi *et al.,* (2012). 1.5 g of vanillin and 1.1 g of 2-aminopheenol were mixed in 30 mL of ethanol and heated under reflux for four to three hours. The resulting product was filtered and dried within 24 hours (Isiyaku *et al.*, 2021).



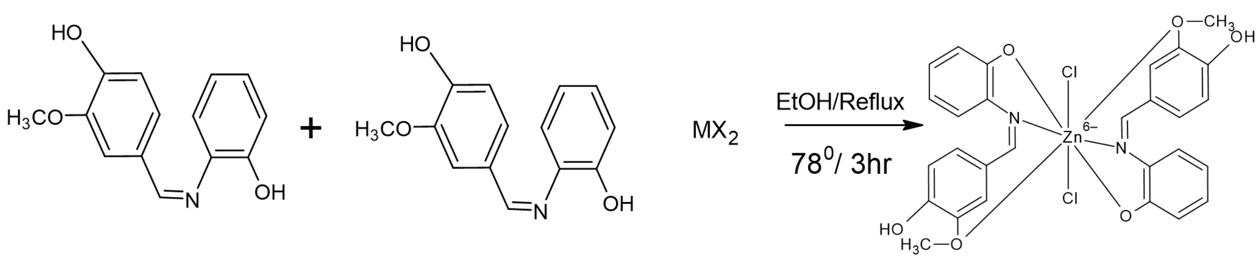
Scheme 1: Synthesis of Schiff base.

Synthesis of Schiff Base Metal Complexes

Schiff base metal complex was synthesized in a mole ratio of metal to ligand of 1:2. 1.1 g of Schiff base and 0.48 g of either Cu (II) chloride or Zn (II) chloride were each dissolved in 20 mL of ethanol. The solutions were then mixed and stirred continuously while being heated under reflux at 78 ^{O}C for three hours.



Scheme 2: Synthesis of Cu (II) Schiff base complexes.



Scheme 3: Synthesis of Zn (II) Schiff base complexes.

Synthesis of Mixed Ligand Complexes of Schiff and 2-Aminophenol

A mixed ligand complex of Schiff base and 2-aminophenol was prepared in a 1:1:1 mole ratio ligand to metal to ligand. 0.55 g 2-aminophenol, 0.55 g Schiff base, and 0.48 g of either Cu (II) chloride or Zn (II) chloride were each dissolved in 10 mL ethanol; these were slowly mixed together while heating under reflux for three hours.

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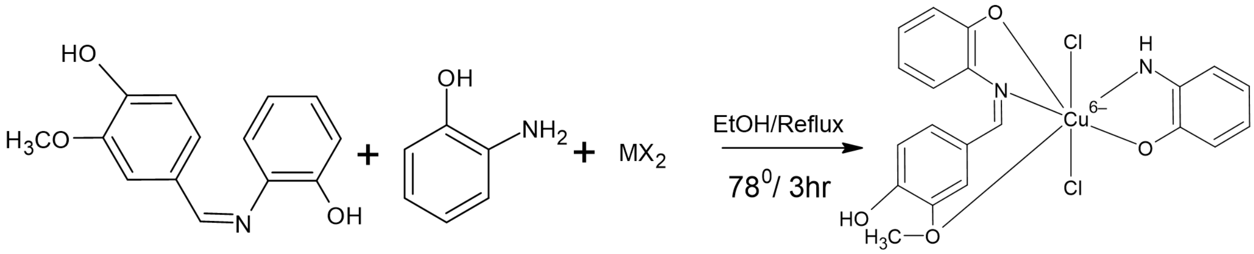
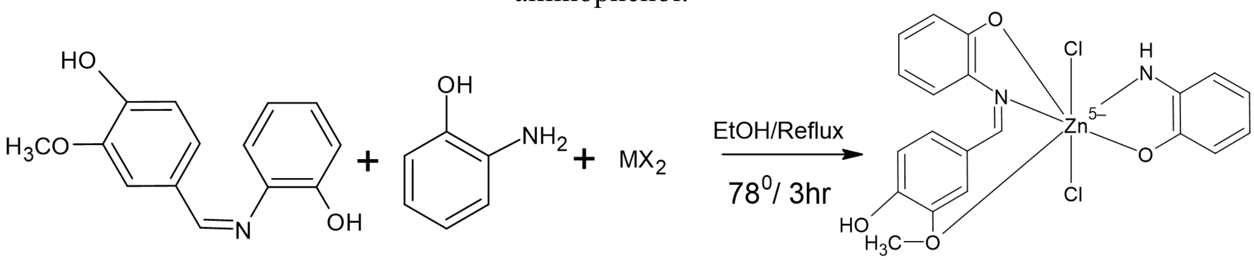


Scheme 4: Synthesis of Cu (II) mixed ligand complexes of Schiff and 2-aminophenol.



Scheme 5: Synthesis of Zn (II) mixed ligand complexes of Schiff and 2-aminophenol.

Antibacterial Activity

The Schiff base and the associated metal complexes were examined against gram negative bacteria, including *Escherichia coli, Streptococcus pyrogens, Klebsiella pueumonia*, and gram-positive bacteria, such as *Bacillus subtilis*. The disc diffusion technique was chosen for the analysis due to its simplicity and inexpensiveness, as a single test can evaluate the effectiveness of multiple anti-bacterial agents simultaneously. The bacterial strains were collected with a sterilized loop, spread on to nutrient agar plates, and a 6 mm disc infused with the complexes was placed on the agar. The plates were incubated at 37 ^{O}C for twenty-four hours. The complexes' activity inhibited the growth and development of bacterial species, as measured by measuring the diameter of the zone of inhibition Ochei, J. *et al* (2000).

RESULTS AND DISCUSSION

Tables 1–4 present the results of Schiff Base and its mixed ligand complexes of Cu (II) and Zn (II).

Table 1: Physical characteristic of ligands and the metal complexes

Compounds	M F ($gmol^{-1}$)	Color	Yield (%)	Conductivity($\Omega^{-1}cm^{-1}mol^{-1}$)	M.P (°C)
HL^1	$C_{14}H_{13}NO_3$	Black	58	2×10^{-3}	365
$Cu(HL^1)_2$	$Cu(C_{14}H_{13}NO_3)$	Blue	63	7×10^{-3}	190
$Cu(HL^1)(HL^2)$	$Cu(C_{20}H_{20}N_2ON_4)$	Blue	74	4.7×10^{-2}	180
$Zn(HL^1)_2$	$Zn(C_{14}H_{13}NO_3)$	Brown	60	6×10^{-3}	196
$Zn(HL^1)(HL^2)$	$Zn(C_{20}H_{20}N_2ON_4)$	Brown	69	4×10^{-2}	175

Where M P= melting points, M F= molecular formular.

Table 2: Solubility of Schiff Base and its mixed ligand metal complexes

Sample	Distilled H_2O	Chloroform	Acetone	Methanol	Ethanol	DMSO	DMF
HL^1	NS	SS	S	S	S	S	S
$Cu(HL^1)_2$	NS	SS	S	S	S	S	S
$Cu(HL^1)(HL^2)$	NS	SS	S	S	S	S	S
$Zn(HL^1)_2$	NS	SS	S	S	S	S	S
$Zn(HL^1)(HL^2)$	NS	SS	S	S	S	S	S

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Where DMSO= dimethylsulphuroxide, NS= not soluble, S= soluble, DMF= dimethylformamide, SS= slightly soluble.

Table 3: Infrared data of Schiff Base and its mixed ligand metal complexes

Compounds	*v*OH	*v*OCH_3	*v*C=N	*v*C-O	*v*C-N	*v*M-N	*v*M-O
HL^1	3376	2827	1581	1353	1498	-	-
$Cu(HL^1)_2$	3285	3216	1552	1361	1513	599	526
$Cu(HL^1)(HL^2)$	3285	3256	1593	1267	1514	620	529
$Zn(HL^1)_2$	3376	3232	1558	1369	1512	639	541
$Zn(HL^1)(HL^2)$	3363	3247	1575	1374	1515	725	560

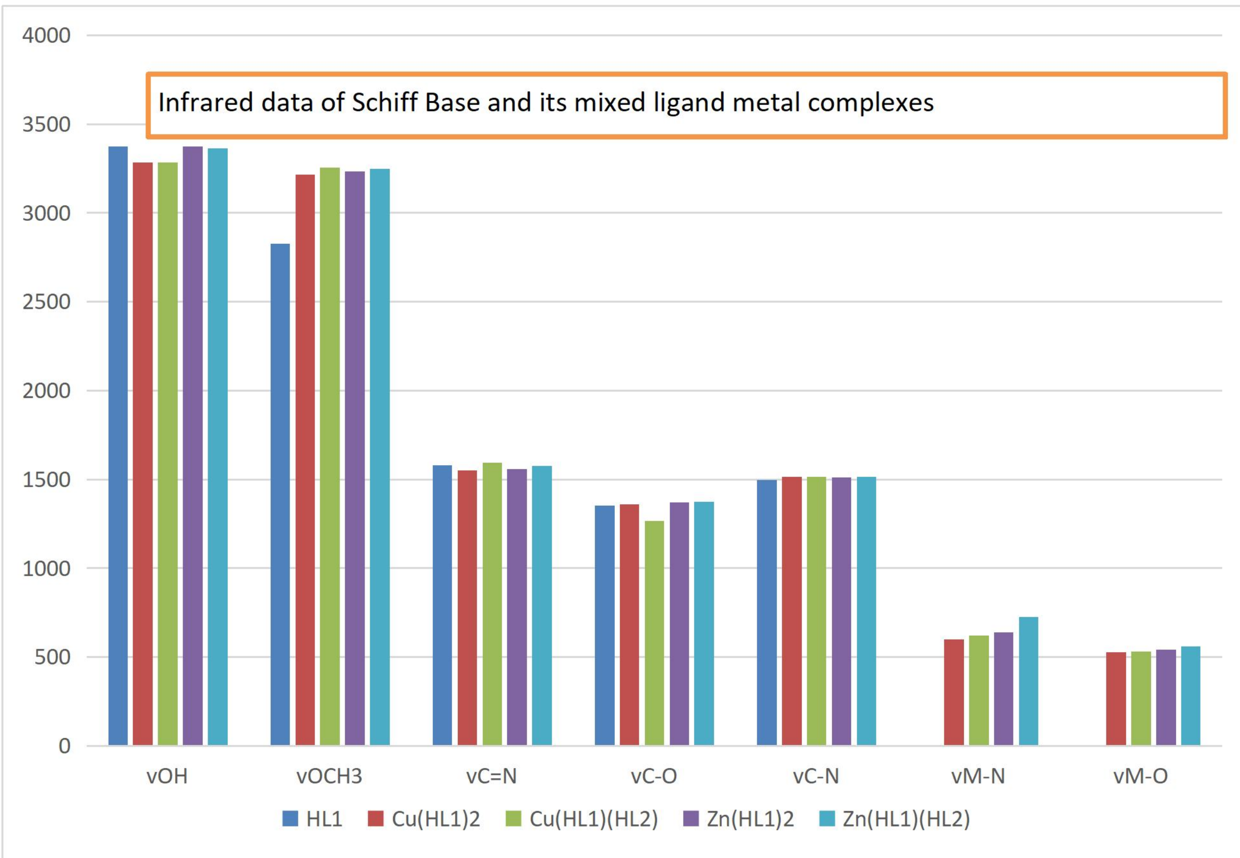

Figure 1: Infrared data of Schiff Base and its mixed ligand metal complexes

Table 4: Antibacterial activity of Schiff Base and its mixed ligand metal complexes

Compounds	zone of inhibition (mm)				
	E. coli	*S. pyrogene*	*K. pneumonia*	*B. subtilis*	*S. aureus*
HL^1	14	07	12	07	05
$Cu(HL^1)_2$	19	00	14	19	21
$Cu(HL^1)(HL^2)$	15	07	17	00	11
$Zn(HL^1)_2$	16	09	11	08	16
$Zn(HL^1)(HL^2)$	13	00	08	00	12

Where 00: absence of inhibition, < 9: weak, 9-16: moderate, > 16: significant, size of disc: 6m

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DISCUSSION

The Schiff base (HL^1) Synthesis

The Schiff base (HL^1) was synthesized using vanillin and 2-aminophenol, yielding a 58% yield. It was black in color and had a melting point of 365 ^{O}C. Its electrical conductivity was measured at 2×10-3 Ω-1$cm^{-1}mol^{-1}$, indicating a moderate level of stability and non-electrolytic nature. The lower values are a result of the compounds' non-electrolytic nature (Shelke, 2011). The Schiff base interacted with Cu (II) and Zn (II) to produce complexes with colors ranging from blue to brown; they exhibited a percentage yield between 63 – 74%, the melting point of the complexes varied from 175 – 196 ^{O}C and their conductivity measurement fell within the range of 4×10-3 - 7×10-3 Ω-1$cm^{-1}mol^{-1}$, indicating variation in thermal stability, and the color range suggests the presence of diverse metal-ligand interaction. According to Lee (1996), the d-d electron transition causes the hue variation, which is typical of transition metals. The complexes' solubility analysis in distilled water, chloroform, acetone, methanol, ethanol, dimethyl sulfoxide (DMSO), and dimethyl formamyde (DMF) is shown in Table 2. The compounds dissolved in all the solvents stated above with the exception of chloroform and water, which were slightly soluble and insoluble, respectively.

The infrared spectroscopy (IR) analysis was performed to reveal the critical information regarding the functional groups present and their interaction within the complexes, which is presented in Table 3. The IR spectrum of Schiff base revealed the significant absorption peak at 3376 cm^{-1} for vOH and 2827 cm^{-1} for vOCH3 stretching; these results indicated the presence of methoxy and phenolic groups, respectively. The peak at 1581cm^{-1} was assigned to v C=N stretching, indicating the formation of an azomethine group in the Schiff base. The band shifted to a lower frequency, appearing at 1552 cm^{-1} in the $Cu(HL^1)_2$ complex, 1558 cm^{-1} in the $Zn(HL^1)_2$ complex, and 1575 cm^{-1} in the $Zn(HL^1)$ (HL^2) complex. This downward shift suggests a change in bonding environment within these complexes, likely due to participation of the metal ion through the azomethine link (Gupta, 2012). In contrast, it shifted to a higher frequency at 1593 in the Cu (HL^1) (HL^2) complex, implying a stronger interaction between the metal and the ligand. This result was in close alignment with the findings reported by Fugu *et al.* (2013).

The new absorption bands at 526cm^{-1} , 529cm^{-1} 541cm^{-1} 560cm^{-1} and were attributed to the M-O stretching vibration in both the complexes of Schiff base and the mixed ligand complexes; these frequencies at which these bands appear are due to coordination between the metal ions (Cu and Zn) and the oxygen atoms present in the ligands. Specifically, the bands at 526cm-1 and 529cm-1 were assigned to the Cu-O stretching modes in the Cu $(HL^1)_2$ and Cu (HL^1) (HL^2) complexes, while the bands at 541cm^{-1} and 560cm^{-1} were assigned to Zn-O stretching modes in the Zn $(HL^1)_2$ and Zn (HL^1) (HL^2) complexes, respectively. The appearance of these bands confirms the successful coordination of the metal ions with the ligands, forming stable metal-oxygen bonds within the complex structures. Similarly, in the mixed ligand complexes, new bands were identified at 599cm^{-1}, 620cm^{-1} 639cm^{-1} 725cm^{-1} corresponding to M-N stretching. These bands were linked to Cu-N in the Cu (HL^1) (HL^2) complex and Zn-N in the Zn (HL^1) (HL^2) complex, confirming the coordination of metal ions with nitrogen atoms and supporting the formation of mixed ligand complexes. It is consistent with the result obtained by Jasmin *et al.* (2017). The complexes exhibited six-coordinate octahedral geometry.

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Antibacterial Activity

Table 4 provides an overview of the antibacterial assessment of the metal complexes and the ligands against *Klebsiella pueumonia, Escherichia coli, Streptococcus pyrogens* (gram negative bacteria), and *Bacillus subtilis* (gram positive bacteria) utilizing the disc diffusion technique. The evaluation was conducted using the disc diffusion method in a dimethyl sulfoxide (DMSO) solvent, illustrating the potential effectiveness of the tested compounds on bacterial growth. The Schiff base ligand demonstrated moderate inhibition against *Escherichia coli* and *Klebsiella pueumonia,* while showing weaker activity against *Streptococcus pyrogens, Bacillus subtilis,* and *Staphylococcus aureus.* In contrast, the metal complexes of Schiff base Cu $(HL^1)_2$ and Zn $(HL^1)_2$ exhited notably stronger antibacterial effects, with both compounds significantly inhibiting the growth of *Escherichia coli, Bacillus subtilis,* and *Staphylococcus aureus*. Zn $(HL^1)_2$ in particular displayed pronounced inhibition against *Escherichia coli* and *Staphylococcus aureus*. The mixed ligand complexes Cu (HL^1) (HL^2) and Zn (HL^1) (HL^2) were moderately effective against *Escherichia coli*, while their inhibitory effects on *Streptococcus pyrogens* and *Staphylococcus aureus* were comparatively weaker. The metal complexes derived from Schiff base exhibited superior antibacterial activity compared to both the mixed ligand complexes and the free ligand. This suggests the coordination of metal ions with Schiff bases enhances the overall effectiveness of the complexes, making them more potent than the mixed ligand complexes and the uncoordinated ligand. This finding is in accordance with the observation made by Ndahi and Pindiga, (2012).

CONCLUSION

In conclusion, the Schiff base derived from vanillin and 2-aminophenol, along with its metal complexes and the mixed ligand complexes were successfully synthesized and characterized. The complexes demonstrated notable stability and were soluble in solvents such as acetone, methanol, ethanol, dimethyl sulfoxide (DMSO), and dimethyl formamyde (DMF). The low conductance values indicate their non-electrolytic behavior. The infrared spectroscopic analysis provides strong evidence for the successful coordination between the metal ions and the ligands, confirming the M-O and M-N bonds. These findings collectively support the presence of octahedral geometry in the complexes. The antibacterial study revealed that these metal complexes exhibited significantly higher activity against *Escherichia coli, Bacillus subtilis,* and *Staphylococcus aurous* compared to the free ligand alone.

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