



The Synthesis, Characterization and Biological Activity of Some Metal Ions Complexes with Schiff's Bases Derived from Reaction of 3-Hydrazone-1,3-Dihydro-Indole-2-One with 2- Pyridine Carboxaldehyde

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Abstract

Novel complexes were synthesized from Schiff base ligand (L) produced by reacting 3-hydrocyclo-1,3-dihydro-indole-2-one (A) with 2-pyridine carboxaldehyde in an ethanol medium. This study aims to synthesize the metal Schiff base ligands complexes of heterocyclic, which tested their biological activity as antimicrobial drugs. Metal complexes comprising manganese, cobalt, nickel, copper, and zinc with Schiff base have been produced at a molar ratio of 1:1 (M: L). These complexes were identified using M.P, FT-IR, UV-Vis, Mass, ¹H-NMR, and C.H.N. Chloride-containing, atomic absorption, molar conductance, and magnetic susceptibility have all been used to identify these compounds. Utilizing mass spectroscopy, the molecular ion peak was found at m/e 251.01, confirming the formula weight for L, which matches the estimated m+ value (250.26). The results show a hexadentate coordination geometry for each complex and the ligand with good yield. This study emphasizes the importance of using a metal complexation method to stabilize ligands and increase their bioactivity. The biological activities of the new compounds were valued against Gram-positive (*Escherichia coli*) and Gram-negative (*Staphylococcus aureus*). Hence, their results were good in inhibition.

Keywords: Biological activities, isatin, 2-pyridine carboxaldehyde, Schiff base complexes, metal complex.



1. Introduction

The Schiff base reaction was studied in 1984. Due to their high coordination number and capacity to form complexes with a wide range of metal ions, including those from transition metals, the Schiff bases are frequently utilized in coordination chemistry. In this research, the condensation of primary amines and active carbonyl groups can form Schiff's bases; there are two ways to produce an amine (1).

The Schiff base compounds are formed by reacting a primary amine with the carbonyl group of aldehydes (RHC=O) or ketone ($\text{R}_2\text{C=O}$). The functional group carbon-nitrogen double bond (-C=N-) in Schiff bases is known as azomethine (2). Many heterocyclic Schiff bases have potential physical, chemical, and biological features. The discovery of new hetero-aromatic azomethines has undoubtedly increased due to their demonstrated use as appealing lead structures for producing catalysts, organic synthesis intermediates, and dyes (3). Derivatives of hydrazone are well-recognized for a variety of biological functions. Numerous hydrazones have been used as antibacterial medications and are often employed to treat various biological activities. 3-Hydrazone-1,3-dihydro-indol-2-one and 2-pyridine carboxaldehyde compounds are significant classes of polydentate ligands in coordination chemistry and have many uses in multiple fields (4). Schiff bases may also be corrosion inhibitors in various metal electrolyte systems because their electron-rich centers, particularly the imine moiety, adsorb and create a corrosion mitigation surface coating. Because of its π - π -acceptor characteristics, this moiety may form strong bonds with metallic ions (5,6). Schiff bases have been shown to exhibit a wide range of biological properties in biological chemistry (7), including antimalarial, anti-proliferative (8), analgesic, anti-inflammatory, antiviral, antipyretic, antifungal, and antibacterial (9). Due to their chelating capabilities, ease of separation, and flexibility on the C=N group, Schiff bases are increasingly regarded as intriguing ligands for coordination chemistry (10). Compared to free Schiff bases, the complexation of Schiff bases with metals improves antibacterial and antifungal activities (11-13). This study aims to synthesize the metal Schiff base ligands complexes of heterocyclic, which tested their biological activity as antimicrobial drugs.

2. Materials and Methods

2.1. Materials

All of the chemicals and reagents used in this study were from (Sigma Aldrich) and were of analytical quality. Isatin (1H-indole-2,3-dione) 97%, Hydrazine monohydrate 99%, 2-pyridine carboxaldehyde 99%, $\text{MnCl}_2 \cdot 2\text{H}_2\text{O}$ 99%, $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ 99%, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ 99%, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ 99%, and ZnCl_2 98% were all supplied by BDH and used as soon as they were received.

2.2. Instrumentation

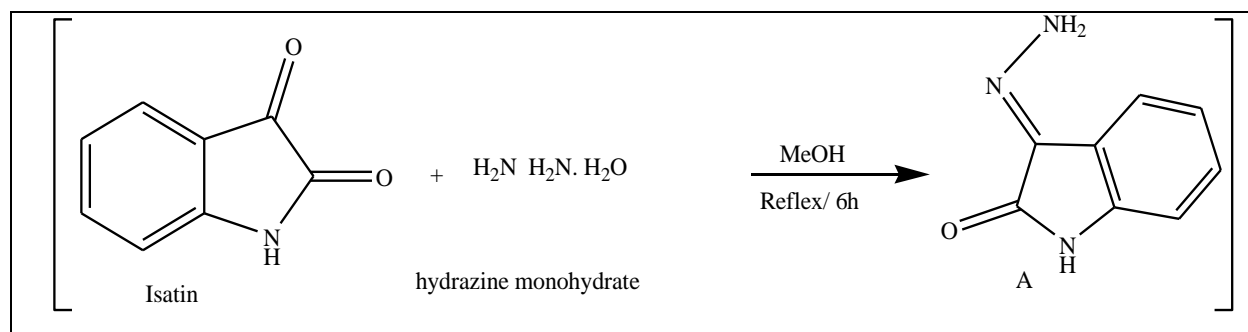
At the University of Baghdad/ College of Science/ Department of Chemistry, infrared spectra of bonds and their complexes were recorded using a device of type (Shimadzu FT-IR Spectrometer) and disc (KBr) for bonds and (CSI) for complexes, in the range (200- 4000) cm^{-1} . The John Mathey device imported from England was used in the Chemistry Department at Al-Nahrain University to measure magnetic sensitivity. The LC/Mass compensation is also based on the

mass100p-Shimadzu contribution. A Bruker 400-MHz-meter was used for the reported $^1\text{H-NMR}$, and a Perkin-Elmer-automatic instrument model-240B was used for the elemental microanalysis. A Shimadzu-(A-A)-680G AA-spectrometer was used to determine the composition of the minerals. At 300°C , a piece of machinery called a Stuart (SMP10), manufactured in England, was used to measure the melting point of the generated ligand and its complexes. The WTW meter was used to ascertain the molar conductivity, and the Shimadzu UV-Vis equipment was utilized to acquire the UV-visible spectra; ultraviolet spectrophotometer A 160, covering the wavelength range of 190.00-1100 nm, the solutions were produced at the Department of Chemistry in the College of Science at the University of Baghdad using dimethylformamide (DMF) solvent at a concentration of $(1 \times 10^{-3}$ molar).

2.3. Synthesis of ligand (L)

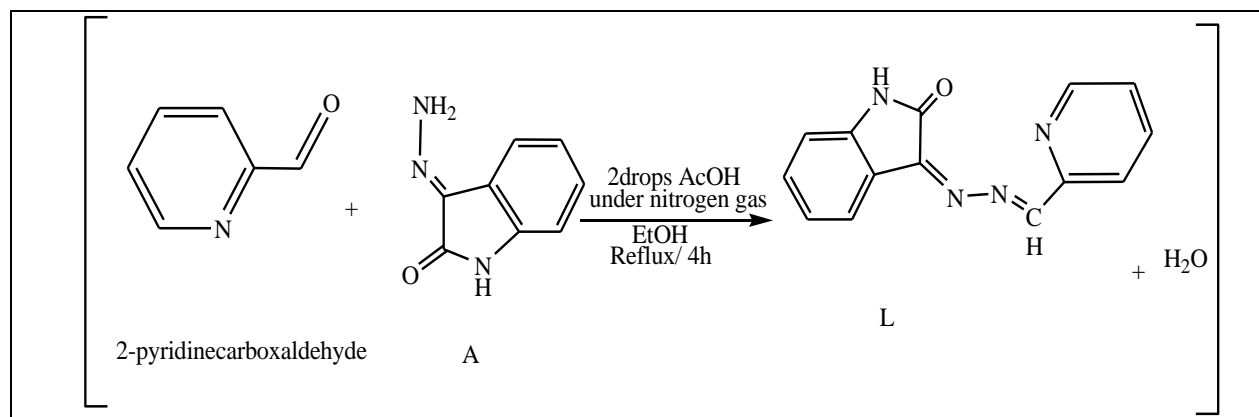
Step I: Including the preparation of 3-Hydrazone-1,3-dihydro-indol-2-one (A) the synthesis method is described below;

Condensing the isatin solution (1 g, 0.0067 mole) in 10 mL of methanol and adding it dropwise while stirring continuously was done to a mixture containing 0.34 g, 0.0067 mole, of hydrazine monohydrate in 10 mL of methanol. The reaction's mixture was stirred for a total of six hours throughout the refluxing process. Following the end of the procedure, the yellow precipitate was filtered, washed with methanol and dry ether, and then dried at a temperature of 50°C . TLC was the method that led to the discovery of the reaction's completion point (**Scheme 1**).



Scheme 1. Preparation of the (A) basic material.

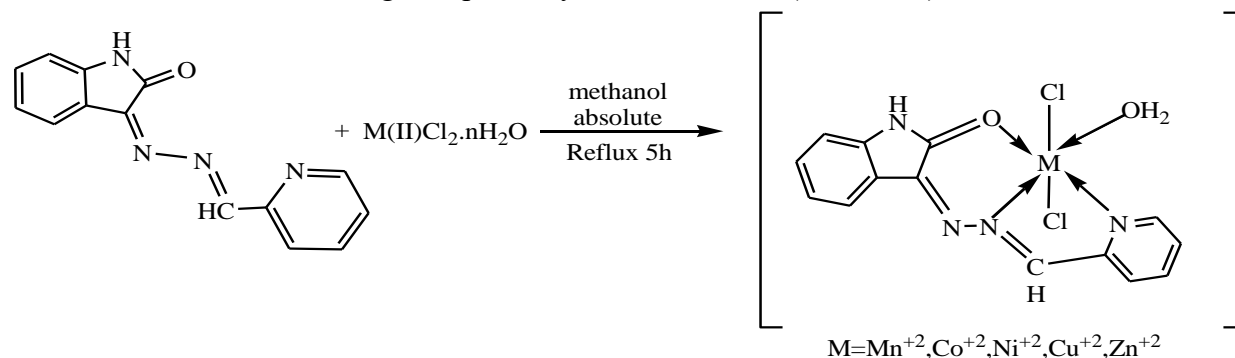
Step II: In a 100 mL round-bottom flask, 1.52 g, or 0.014 mol of 2-pyridinecarboxaldehyde was dissolved in 10 mL pure 99.9% ethanol to create a Schiff's bases ligand. After adding 0.006 mol, 1.0 g of (A) to 10 mL of ethanol under nitrogen gas and stirring until the components are homogeneous, boiling the mixture and refluxing it at 100°C for 4 to 6 hours yielded a pure form of (A). The pale orange crystals were precipitated, recovered by filtering, washed with absolute ethanol, dried for 24 hours, and then recrystallized from hot absolute ethanol. After being filtered and dried for hours, the crystallized powder had a melting point (M.P) of $226-228^\circ\text{C}$ and a yield of 85% (**Scheme 2**).



Scheme 2. The prepared of Schiff bases ligand.

2.4. The preparation of metal complexes using ligands based on Schiff bases

In a 25 mL circular glass vial with a flat bottom, the prepared ligand (L) (0.1 g, 0.3 mmol) was dissolved with agitation in 10 mL of methanol. Metal chloride hydrate (0.2 g, 0.3 mmol) was dissolved in 10 mL of methanol and added to the ligand solution, followed by one drop of DMF and vigorous agitation until complete dissolution. The mixture was subjected to the reflux procedure for 5 hours until a colorful precipitate indicated the formation of a complex. The reaction was then halted, and the product was allowed to settle at room temperature before being filtered, rinsed with clean cold water, and desiccated using ether. The product was filtered and desiccated at 50 °C. Providing exceptional yields of 75-85% (**Scheme 3**).



Scheme 3. Preparation of metal complexes.

3. Results and Discussion

The reaction between one mole of 3-hydrazono-1,3-dihydro-indol-2-one (A) and one mole of 2-pyridine carboxaldehyde resulted in the excellent yielding production of the tetradentate ligand [L]. The produced ligands and their complexes were identified by microscopic examination of the elements, the infrared spectrum, the proton NMR spectrum, the carbon NMR spectrum, and the molar conductivity. The physical properties of the prepared compounds are illustrated in **Table 1**.

Table 1. The physical properties of the prepared compounds.

Compounds	%Analysis (calculated)								
	Color	M.P °C	M.WT	%Yield	%C	%N	%H	%Cl	%M
L C ₁₄ H ₁₀ N ₄ O	Orange	226-228			68.09 (67.19)	22.27 (22.39)	3.64 (4.03)	---	---
[MnLCl ₂].3H ₂ O	Light yellow	245 Dec.	250.26 430.15	85% 76%	40.37 (39.09)	12.55 (13.03)	2.87 (3.75)	17.25 (16.48)	11.89 (12.77)
[CoLCl ₂].2H ₂ O	Peal Orange	250 Dec.	416.13	82%	41.14 (40.41)	12.67 (13.46)	2.65 (3.39)	18.65 (17.81)	13.35 (14.16)
[NiLCl ₂].2H ₂ O	Light Orange	265 Dec	415.89	78%	41.16 (40.43)	13.30 (14.11)	2.54 (3.39)	18.64 (17.82)	13.28 (14.11)
[CuLCl ₂].3H ₂ O	Light yellow	275 Dec.	438.75	75%	39.55 (38.32)	11.87 (12.77)	2.77 (3.68)	17.06 (16.16)	13.89 (14.48)
[ZnLCl ₂].H ₂ O	Light orange	235 Dec.	404.57	81%	42.39 (41.56)	12.99 (13.85)	2.65 (2.99)	18.33 (17.53)	15.26 (16.16)

3.1. The UV-visible ligands and complexes

At room temperature, electronic spectra of L and their complexes were measured in DMF solution in the range [200-1100] nm. The Schiff base ligand UV-Vis spectra exhibited one significant intensity absorption peak at (375) nm, which were attributed to intra-ligand interactions [$n \rightarrow \pi$] transitions of azomethine, respectively (14). Changes in the placement of absorption bands in the complex spectra were detected, indicating metal ion coordination via the azomethine and Pyridine nitrogen functional groups (15,16). The cobalt (Co²⁺) compound spectrum showed four bands (332,512,629 and 975) nm, representing the permitted transitions and having a magnetic moment of (4.96) MB. This is equivalent to the magnetic moment of hexagonal complexes within the octahedron [C.T, ${}^4T_{1g(F)} \rightarrow {}^4A_{2g(F)}$, ${}^4T_{1g(F)} \rightarrow {}^4T_{2g(F)}$ and ${}^4T_{1g(F)} \rightarrow {}^4T_{2g(F)}$]. Nickel complex demonstrated 4 bands (385,438,615 and 921) nm bands, which represent four transitions [C.T, ${}^3A_{2g(F)} \rightarrow {}^3T_{1g(P)}$, ${}^3A_{2g(F)} \rightarrow {}^3T_{2g(F)}$ and ${}^3A_{2g(F)} \rightarrow {}^3T_{2g(F)}$], while the value of the magnetic moment was equal (3.11) BM. The spectrum of the copper complex showed two bands in the (395 and 680) nm, resulting from the combined two transitions of [C.T and ${}^2E_g \rightarrow {}^2T_{2g}$]; it has a magnetic moment of (1.78) BM. The transitions in Zn and Mn complexes were not expected since their outer shells were stable during saturation or semi-saturation, respectively, and the observed bands were mentioned in **Table 2.** and **Figures 1-6.**

Table 2. Electronic spectra for Schiff base ligand and its complexes.

Compound	Molar Cond. Ohm ⁻¹ cm ² .mol ⁻¹	Electronic arrangement	μ_{eff} B.M	λ max (nm)	Assignments
L C ₁₄ H ₁₀ N ₄ O	-	-		375	n→ π^*
[MnLCl ₂]. 3H ₂ O	3.2	d ⁵	5.57	247	π → π^*
				288	π → π^*
				316	n→ π^*
				424	C.T
[CoLCl ₂]. 2H ₂ O	19	d ⁷	4.96	332	C.T
				512	⁴ T _{1g(f)} → ⁴ A _{2g(f)}
				629	⁴ T _{1g(f)} → ⁴ T _{2g(f)}
				975	⁴ T _{1g(f)} → ⁴ T _{2g(f)}
[NiLCl ₂].2H ₂ O	43.2	d ⁸	3.11	385	C.T
				438	³ A _{2g(f)} → ³ T _{1g(p)}
				615	³ A _{2g(f)} → ³ T _{2g(f)}
				921	³ A _{2g(f)} → ³ T _{2g(f)}
[CuLCl ₂]. 3H ₂ O	7.2	d ⁹	1.78	395	C.T
				680	² E _g → ² T _{2g}
[ZnLCl ₂]. H ₂ O	6.5	d ¹⁰	Dia	363	C.T

3.2. Infrared spectral analysis of ligands and complexes

There is a distinct band seen in the tetradentate Schiff base L, and the stretching of the azomethine group is responsible for developing a strong band at 1605 cm⁻¹, respectively (17), as seen in **Figure 7**. The coordination of metal ions to nitrogen azomethine causes a shift in the $\nu(\text{C}=\text{N})$ value frequency. This is because the metal ions donate nitrogen electrons to the partially filled d-orbitals of the metal ions (II), which causes the electron density on the nitrogen azomethine to drop (18,19). The complexes' IR spectra display distinctive lines at (1633-1617) cm⁻¹, indicating that the metal ions coordinate to the L through the azomethine nitrogen atom (20). The stretching vibrations of the pyridine group's nitrogen produce a prominent band at 634 cm⁻¹. At (424-449) cm⁻¹, (375-329) cm⁻¹, and (588-501) cm⁻¹, new stretching modes were observed in the far-infrared spectra of the complexes that were not present in the L spectrum. These modes are attributed to (M-N), (M-Cl), and (M-O) as evidence of the formation of bonds between the metal ions (II) and the nitrogen azomethine, chloride, and oxygen, respectively (21-23), as seen in **Table 3.** and **Figures 8-12.**

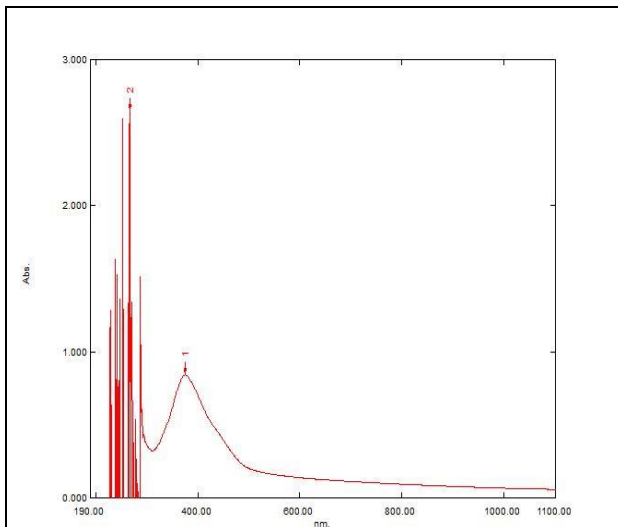


Figure 1. The UV-spectrum for L.

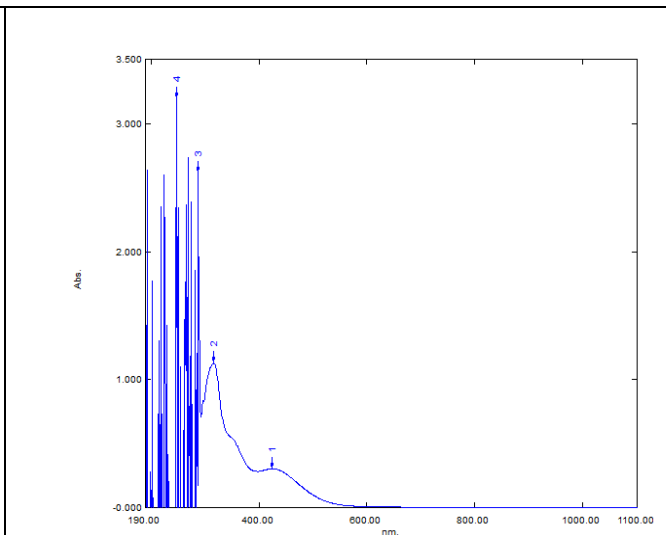


Figure 2. The UV-spectrum for Mn L complex.

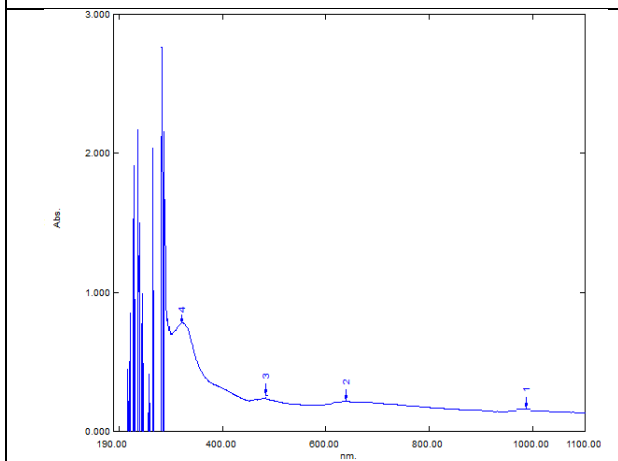


Figure 3. The UV-spectrum for Co L complex

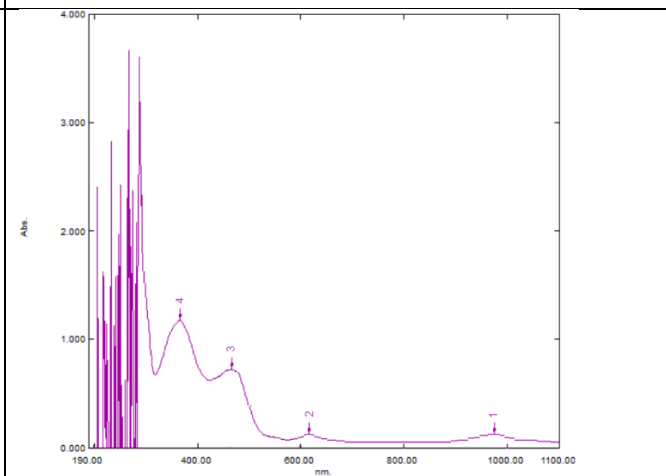


Figure 4. The UV-spectrum for Ni L complex

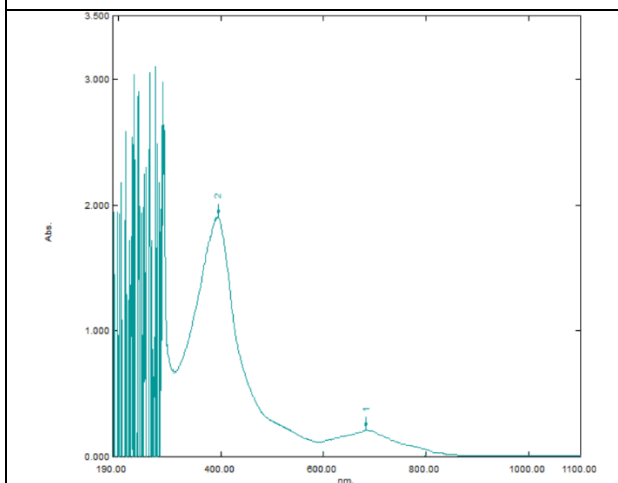


Figure 5. The UV-spectrum for Cu L complex.

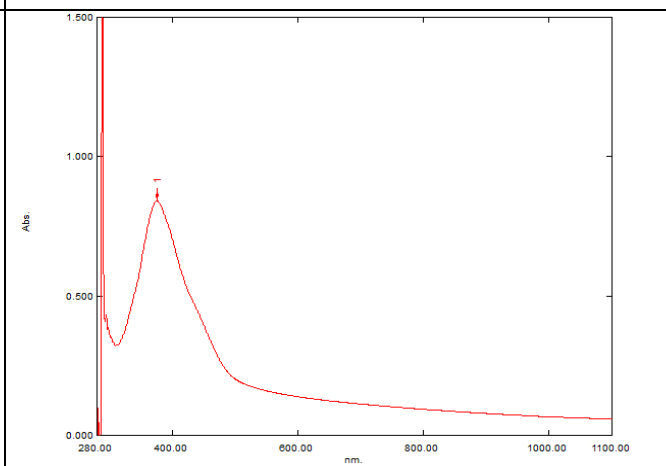


Figure 6. The UV-spectrum for Zn L complex.

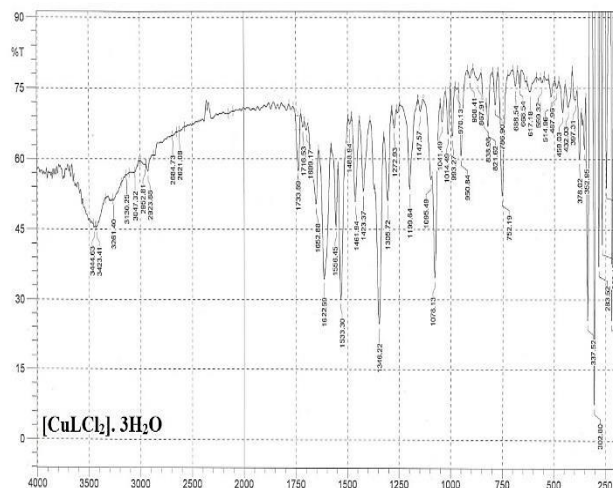


Figure 11. The FTIR-Spectrum of Cu L Complex.

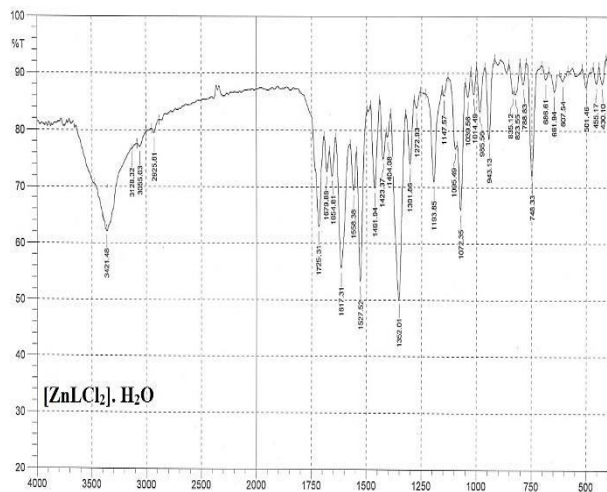


Figure 12. The FTIR-Spectrum of Zn L Complex.

3.3. Proton nuclear magnetic resonance spectroscopy ($^1\text{H-NMR}$)

Nuclear magnetic resonance spectroscopy is a method for determining the chemical surroundings of organic compounds. The $^1\text{H-NMR}$ spectra of the ligand (L) in dimethyl sulfoxide (DMSO- d_6) with tetramethyl silane (TMS) as the internal reference standard are shown in **Figure 13**. The $^1\text{H-NMR}$ spectrum revealed all the peaks required to confirm the chemical structure of the produced ligand (L). The proton of the azomethine group ($\text{HC}=\text{N}$) shows a singlet peak at a chemical shift of 8.775 ppm. The four protons of the pyridine ring unit show multiple peaks at regions between 7.763 ppm and 8.760 ppm. Meanwhile, the indole ring unit peaks in regions between 6.915-7.607 ppm and 8.760 ppm. This peak is highly shifted because the proton is connected to an unsaturated carbon atom next to a highly electronegative nitrogen atom within the aromatic system (24). Finally, the NH of the hydrazine group shows a singlet peak at a chemical shift of 10.949 ppm. Thus, the $^1\text{H-NMR}$ data are summarized in **Table 4**.

Table 4. The $^1\text{H-NMR}$ spectra for the L and the chemical shift in ppm.

Compound	$^1\text{H-NMR}$	δ ppm
L	Singlet (1H) NH	10.949
$\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}$	Singlet (1H) HC = N	8.775
	Singlet (4H) pyridine ring	7.763-8.7600
	Multiplet (4H) indole ring	6.915-7.607
	Solvent+ H_2O	2.499-3.345

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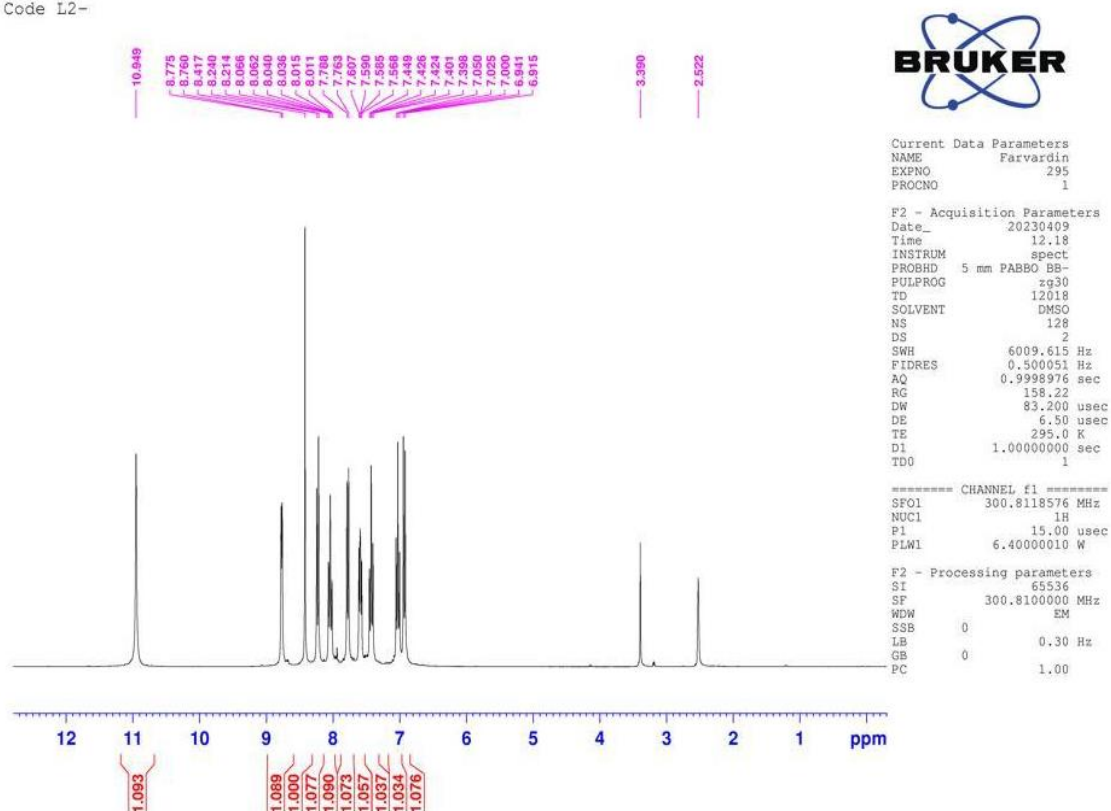


Figure 13. The $^1\text{H-NMR}$ of ligand L_2 .

3.4. Schiff bases ligand characterization by mass spectroscopy

The mass spectrum is used to ascertain the molecular weight of the produced molecule, and the fragmentation that belongs to the compound under investigation is identified. The mass spectra of the produced Schiff base ligand agreed with the suggested structural formula, $\text{C}_{14}\text{H}_{10}\text{N}_4\text{O}$. The predicted m value (250.26), as shown in **Figure 14.**, is matched by the molecular ion peak, which was discovered at m/e (251.01), validating their formula weight for the ligand. As it was successively fragmented, new unique peaks for the ligand were visible in the mass spectra.

3.5. Microbiological investigations

The experiment was carried out in aerobic circumstances at a temperature of 37°C . Drilling was used to expose each Agar active chemical Agar bacterium to two kinds of bacteria: negative (*Escherichia coli*) and positive (*Staphylococcus aureus*). Results from tests on the bacteria above at $1 \times 10^{-3}\text{M}$ concentrations of the DMF solvent and the produced Schiff-species and their complexes are documented in **Table 5**. These findings suggest that the Co^{2+} and zinc (Zn^{2+}) complexes inhibit *Staphylococcus aureus* bacteria negatively, whereas the remaining compounds were efficacious against both types of bacteria (25,26). **Figure 15.** displays all the specifics.

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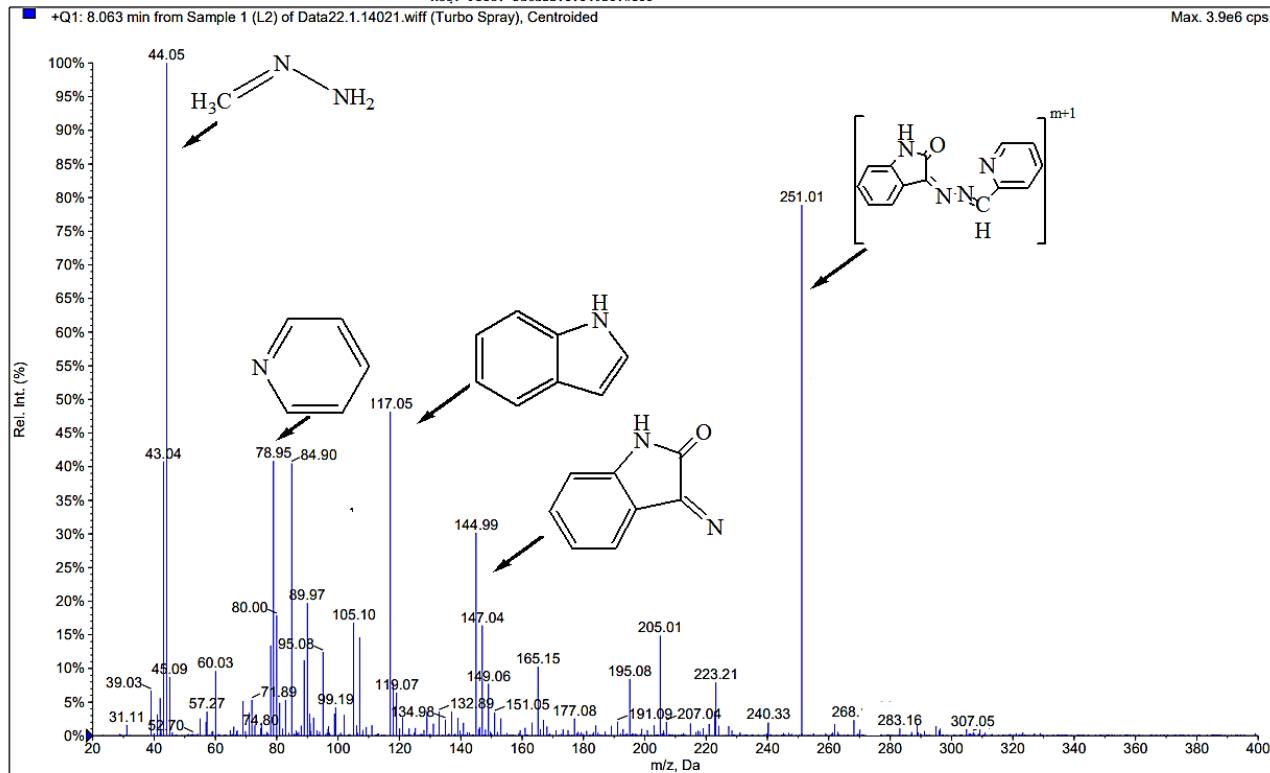


Figure 14. Mass spectrum of ligand.

Table 5. Antibacterial activity of preparation of Schiff bases ligand and complexes.

Compound	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
L	12	20
[MnLCl ₂].3H ₂ O	11	20
[CoLCl ₂].2H ₂ O	8	14
[NiLCl ₂].2H ₂ O	14	20
[CuLCl ₂].3H ₂ O	12	18
[ZnLCl ₂].H ₂ O	8	16

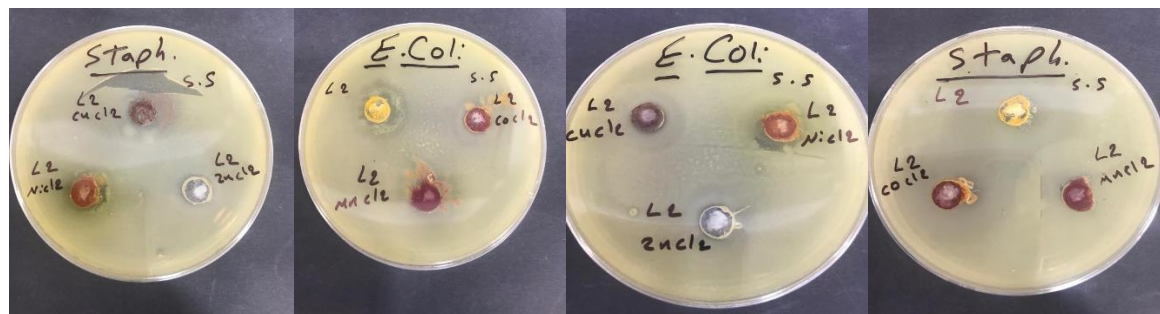


Figure 15. Biological activity of Schiff bases ligand and metal complexes.

4. Conclusion

All spectroscopic data from this investigation showed that the resulting Schiff base compound served as a tetrameric ligand with 3-hydrazone-1,3-dihydro-indole-2-one (A) and 2-pyridine carboxaldehyde. M:L is 1:1 in all complexes produced. Results from spectral and elemental analysis and the magnetic moment and molar conductivity of the complexes in the DMF solution indicate that all of the complexes were nonelectrolytes with octahedral geometries. All of the complexes and their ligands were tested for biological activity against two different bacterial strains, where the results showed that the Co^{2+} compound and the Zn^{2+} compound had a negative inhibitory effect on *Staphylococcus aureus*. In contrast, the remaining compounds were effective against both types of bacteria.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Ethical Clearance

This study was approved by Baghdad University, College of Science for Women/ University of Baghdad.

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