

Synthesis, Spectroscopy and Biological Activity Study of Some New Complexes with Schiff Base Derived from Malonic Acid Dihydrazide with 2-pyridine Carboxaldehyde

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Abstract

From synthesized novel ligand (L) made of Malonic acid dihydrazide and 2-pyridine carboxaldehyde, new complexes have been created. Ni(II), Cu(II), and Zn(II) complexes were created as a result. FT-IR, UV-Vis, Mass, ¹H-NMR, ¹³C-NMR, C.H.N., Chloride-containing, Molar Conductance, Magnetic Susceptibility, and Atomic Absorption have all been used to identify these compounds. For each Nickel, Copper, and Zinc complexes the characterization findings revealed complexes with hexadentate octahedral coordination geometry and tetradentate ligand. Two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria, as well as *candida fungus*, were evaluated for the biological activities of the novel compounds. With the exception of the Nickel complex, which failed to produce any effective inhibitory effects against *pseudomonas*, their results in inhibition were good.

Keywords: Biological activities, Malonic acid dihydrazide, Metal complexes, Pyridine carboxaldehyde, Schiff Base.

Introduction

Hydrazone derivatives are widely used for a number of biological processes. Many hydrazones have been utilized as antimicrobial drugs that are frequently used to treat a range of biological functions¹. In coordination chemistry, malonyldihydrazide compounds are important classes of polydentate ligands and have many uses in various fields². Additionally, the presence of an imine group is important for understanding how transformation and racemization reactions occur in biological systems³. Due to the vast range of uses for hydrazone and its derivatives, including antibacterial, anti-tubercular,

carbonic anhydrase inhibitors, and anti-inflammatory⁴. Properties, the transition metal complexes of these compounds have been substantial study. Malonyldihydrazides and 2-pyridine carboxaldehyde are important moieties of polydentate ligands in coordination chemistry and have several applications in numerous industries⁵. Understanding transformation and racemization processes in biological systems also require the existence of an imine group⁶. Owing to hydrazone's and its derivatives' wide variety of applications, which include its antibacterial⁷, antitubercular, carbonic

anhydrous inhibitors, and anti-inflammatory⁸ qualities. Since it has been recognized that several of these complexes may have some uses in health, the transition-metal complexes of these molecules have undergone much research. Interest in macrocyclic complexes comprising oxygen and nitrogen atoms has increased as a result of discoveries in the field of

bioinorganic chemistry^{9,10}. The new Schiff base is synthesized in this work, and it is used as a ligand to offer sites that may act as donors and form complexes with Ni(II), Cu(II), and Zn (II). Full characterization of the ligand and its complexes has been completed.

Materials and Methods

Materials:

The chemicals were used in this study Diethyl Malonate (sigma Aldrich 99%), Hydrazine monohydrate 99%, 2- pyridine carboxaldehyde (sigma Aldrich 98%), absolute ethanol (B.DH, 99%) and NiCl₂.6H₂O 99%, CuCl₂.2H₂O 99%, ZnCl₂ 98% were provided from BDH.

Instrumentation:

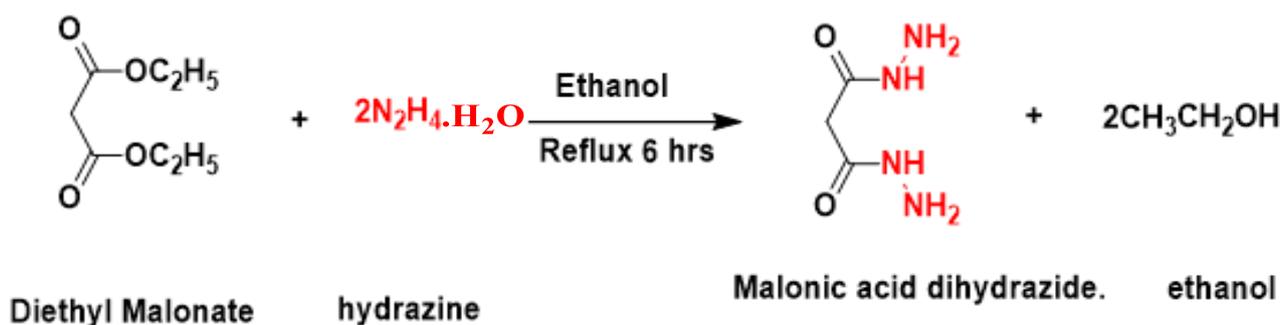
The carbon hydrogen and nitrogen contents were determined by Euro Vector EA 3000 A and FT-IR spectra were recorded on Shimadzu FT-IR-8100 spectrometer. ¹H-¹³C-NMR spectra of the ligand (L) were measured in d₆-DMSO solvent using TMS as internal standard on Bruker 300 MHz. Using UV-1650 PC Shimadzu spectrophotometer were measured the electronic spectra at 25°C. Electrical conductivity measurements of the complexes were recorded at 25 °C ± 2 °C for (1×10⁻³M) M solution of the samples in DMF using a Philips PW-digital conductivity meter. Magnetic susceptibility results were also obtained at 25°C at the solid state by applying Gouy balance. The molecular weight of the prepared ligand was determined by GCMS-QP2010

PLUS ; DI analysis Shimadzu, Japan ,spectrometer in the laboratory of the University of Samarra. Moreover, all melting points results were recorded on (Gallen Kamp melting apparatus) at College of Science for Women, University of Baghdad.

Synthesis of Ligand in Two Steps:

Step 1: The following description of the synthesis technique includes procedure on making Malonic acid dihydrazide.^{10a}

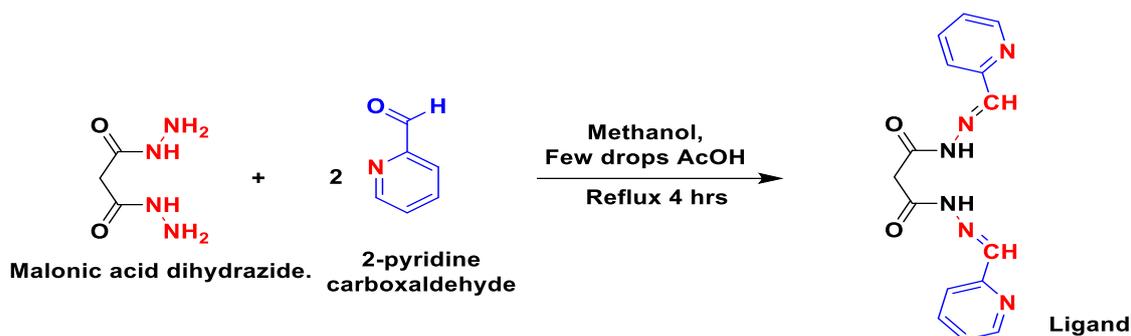
Diethyl Malonate (10 g, 0.062 mol) was dissolved in 10 ml of ethanol and agitated at room temperature in a round bottom flask. Aqueous hydrazine monohydrate (6.2 g, 0.124 mol) was then added dropwise in 1:2 molar ratio while being continuously stirred, and the mixture was then refluxed for 6 hours. The white precipitate was filtered when the reaction was stopped and cooled at room temperature, and it was then washed with methanol and dry ether. Re-crystallization of a white precipitate from 100% ethanol produced a very good yield of 80% (7.1g), m.p. 159 °C. Malonic acid dihydrazide. preparation is shown in Scheme 1.



Scheme 1. Synthesis of Malonic acid dihydrazide.

Step 2: As illustrated in Scheme 2, pyridine carboxaldehyde (1.62 g, 0.015 mol) was added to a combination of Malonic acid dihydrazide (1.0 g, 0.007 mol) and methanolic solution (15 ml), 1:2 molar ratio followed by 0.1 ml of anhydrous acetic acid. The mixture was then refluxed for 4 hours

under N_2 , while being stirred. White crystal was created, filtered, washed, and then re-crystallized from ethanol after the fluid had been cooled to room temperature. A pure product of 86% (2.0 g), m.p. 214-216 °C, was produced by vacuum-assisted drying of the product on anhydrous $CaCl_2$.

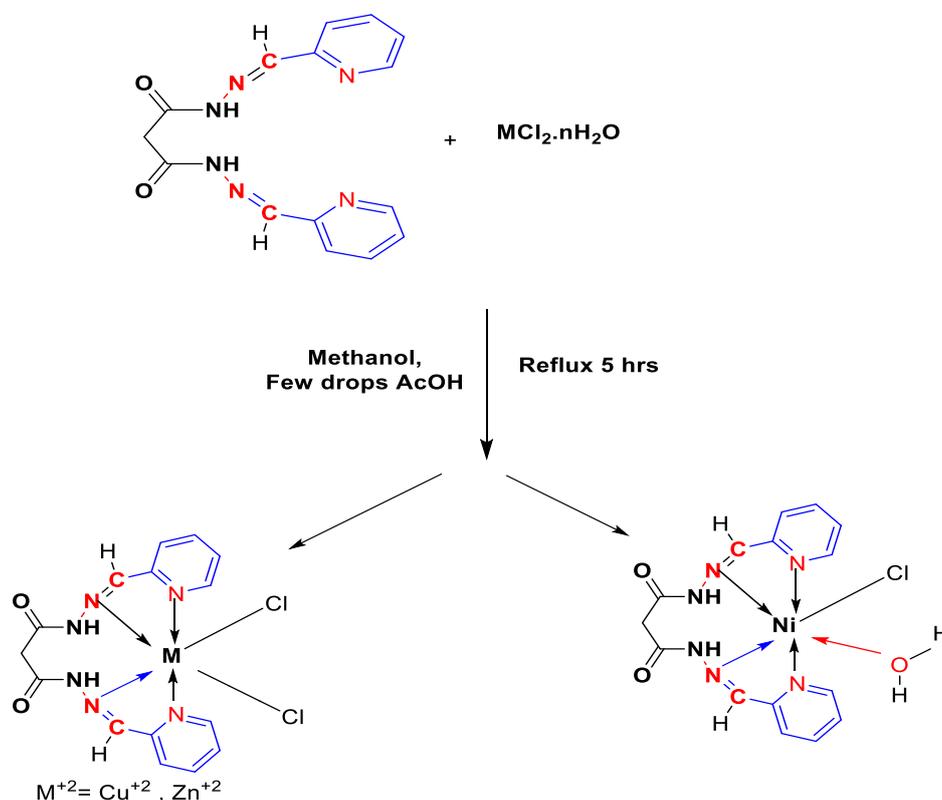


Scheme 2. Synthesis of Schiff base ligand.

Preparation of metal Complexes

With stirring, the produced ligand (0.2 g, 0.6 mmol) was dissolved in 10 ml of methanol. According to Scheme 3, metal chloride [Cu^{2+} , Ni^{2+} , and Zn^{2+}] (0.6 mmol) was dissolved in 10 ml of methanol and added

to the ligand solution in 1:1 molar ratio. After 5 hours of reflux heating, the mixture's color changed as shown in Table 1. After the precipitate was filtered out, it was washed with methanol, and dried at room temperature for 48 hours, the yields were good to very good 71–79%.



Scheme 3. Synthesis of Metal Complexes.

Results and Discussion

The tetradentate ligand was produced in excellent yield when one mole of Malonic acid dihydrazide and two moles of 2-pyridine carboxaldehyde reacted. Table 1. provides an overview of the produced ligand's physical characteristics and micro elemental

analyses, as well as its metal complexes. The recommended structural formula and the results are well correlated. The close agreement between the calculated and observed results of the elemental analyses has proven that ligand and complexes form.

Table 1. The physical properties of the prepared compounds.

Compound	Ligand	Ni ⁺²	Cu ⁺²	Zn ⁺²
Formula	C ₁₅ H ₁₄ N ₆ O ₂	[Ni L Cl (H ₂ O)]Cl	[Cu L Cl ₂] (H ₂ O)	[Zn LCl ₂](H ₂ O)
M.wt	310.32	458.03	462.78	464.64
Color	White	Green	Black`	Brown
m.p. °C	214-216	220-224	256-259	230-233
Yield %	86%	79%	73%	71%
C% Calcd,	58.06	39.34	38.93	38.77
Exprt	57.11	40.08	40.02	39.67
H% Calcd,	4.55	3.52	3.48	3.47
Exprt	5.23	4.97	4.12	3.85
N% Calcd,	27.8	18.35	18.16	18.09
Exprt	26.91	18.50	17.48	17.72
M% Calcd,		12.82	13.73	14.08
Exprt		13.77	12.95	15.29
Cl% Calcd,		15.48	15.32	15.26
Exprt		19.11	14.89	14.61

UV-Visible for the Ligand and Its Complexes

Figs. 1-4 shows the UV/Vis spectrums in range of (200-1100) nm for the prepared ligand and its complexes after they were dissolved in DMF. The electronic spectrum of the ligand exhibited strong absorption at 314nm and 331nm that are attributed to ($\pi \rightarrow \pi^*$), ($n \rightarrow \pi^*$) respectively¹¹. The electronic spectrum of Ni(II) complex showed three peaks at 987, 598, and 449 nm assigned to ${}^3A_2g \rightarrow {}^3T_2g(F)$, ${}^3A_2g \rightarrow {}^3T_1g(F)$ and ${}^3A_2g \rightarrow {}^3T_1g(P)$ respectively¹². Ni(II) complex magnetic moment value were equal to (2.8)B.M, which confirmed its high spin octahedral geometry, Table 2. The electronic spectrum of Cu(II) complex showed two peaks at 436nm and 778 nm assigned to ${}^2B_1g \rightarrow {}^2A_1g$, ${}^2B_1g \rightarrow {}^2E_g$ respectively¹³. Moreover, the magnetic moment (1.4 B.M) corresponds to one unpaired electron, which offers possibility of an octahedral geometry, Table 2. The complex of Zinc (II) was diamagnetic as expected for (d^{10}) ion, since the UV-Vis spectra of the band position were compared with that of the ligand only¹⁴. Measurements of conductivity reveal electrolyte dynamics¹⁵. According to Table 2, all of the complexes have

octahedral geometry¹¹⁻¹⁴. Table 3 contains a complete list of the electronic spectra's data.

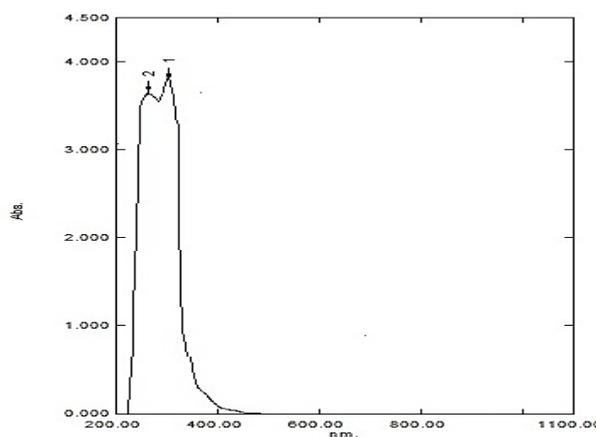


Figure 1. UV/Vis Spectrum of ligand.

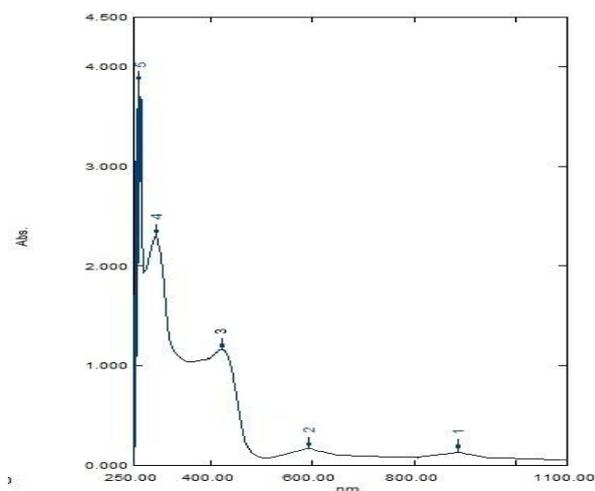


Figure 2. UV/Vis Spectrum of Ni(II) Complex.

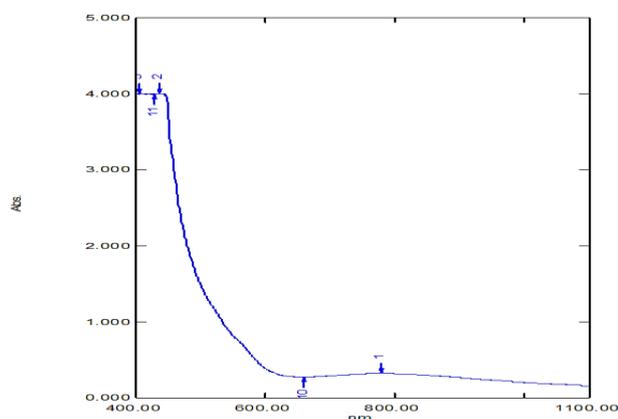


Figure 3. UV/Vis Spectrum of Cu(II) Complex.

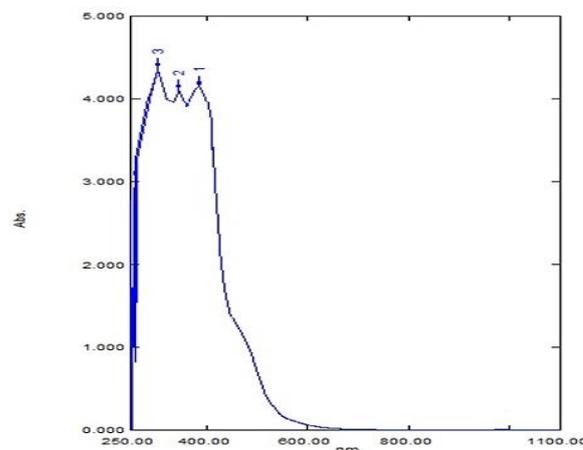


Figure 4. UV/Vis Spectrum of Zn(II) Complex.

Molar Conductivity Measurements

The molar conductance for all complexes were measured in DMF solvent ranged from 65-90 $\text{ohm}^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$, indicating that the Ni complex is electrolytic in nature while the Cu(II) and Zn(II) complexes are not. Table 2 shows these findings.

Table 2. Magnetic moments, and molar conductivity for Schiff base L and its Complexes.

Complexes	μ_{eff} (B.M)Cal	Magnetic moment	Molar Cond. $\text{Ohm}^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$	Type
[NiLCl(H ₂ O)]Cl	2.71	Paramagnetic	90	Electrolyte
[CuLCl ₂](H ₂ O)	1.47	Paramagnetic	60	Non-electrolyte
[ZnLCl ₂](H ₂ O)	Di	diamagnetic	65	Non-electrolyte

Table 3. Electronic spectra, for Schiff base ligand and its Complexes.

compound	electronic arrangement	λ_{max} (nm)	Absorption (cm^{-1})	bands	Assignments
L	-	314	31847.1		$\pi \rightarrow \pi^*$
C ₁₅ H ₁₄ N ₆ O ₂	-	331	30211.4		$n \rightarrow \pi^*$
[[NiLCl(H ₂ O)]Cl	d ⁸	978	10224.9		$^3A_{2g} \rightarrow ^3T_{2g}(F)$
		598	16722.4		$^3A_{2g} \rightarrow ^3T_{1g}(F)$
		449	22271.7		$^3A_{2g} \rightarrow ^3T_{1g}(P)$
[CuLCl ₂](H ₂ O)	d ⁹	778	22935.7		$^2B_{1g} \rightarrow ^2A_{1g}$
		436	12853.4		$^2B_{1g} \rightarrow ^2E_g$
[ZnLCl ₂](H ₂ O)	d ¹⁰	311	32154.3 – 29069.7		$\pi \rightarrow \pi^*$
		344			CT

Studies of the Ligand's Infrared Spectrum and Its Complexes

The ligand shows bands at 3014 cm^{-1} and 3431 cm^{-1} , respectively, attributed to $\nu(\text{C-H})$ and (N-H) bands, respectively^{16,17}. FT-IR spectrum of free ligand band shows absorption at 1695 cm^{-1} for $\nu\text{C=O}$, in addition to a strong band at 1664 cm^{-1} that can be attributed to the stretching band of the azomethine group. After donating nitrogen electrons to the partly full d-orbitals of the metal ions(II), the coordination of the metal ions to the nitrogen azomethine causes a shift-down in the frequency of the (C=N) value^{18,19}. This is because the electron density on the azomethine lowers. The complexes' IR spectra display distinctive bands in the range of $1641\text{--}1608\text{ cm}^{-1}$ that demonstrate how the metal ions coordinate to the L

through the nitrogen atom of the azomethine²⁰⁻²². There is a broad band at $1413\text{--}1363\text{ cm}^{-1}$ for the complexes, indicating coordination of nitrogen of the C-N pyridine to the metal atoms²²⁻²³. The coordinated water molecules (O-H) are responsible for the wide absorption band in the 3450 cm^{-1} areas of the Ni(II) complex spectrum²⁴. Scheme 3 and Table 4 provide more information about the trait. As shown in Figs. 5-8, new stretching modes were found in the far-infrared spectra of the complexes that weren't present in the spectrum of ligand at $445\text{--}462\text{ cm}^{-1}$ and $347\text{--}352\text{ cm}^{-1}$, which are attributed to (M-N) and (M-Cl), respectively. These modes provide evidence for the formation of bonds between the metal ions (II) and the nitrogen azomethine and chloride.

Table 4. FT-IR data of Ligand and its metal complexes (cm^{-1}).

Compound	L_2	Ni^{+2}	Cu^{+2}	Zn^{+2}
N-H stretch	3431	3429	3442	3419
H ₂ O Coord	-	3450	-	-
CH Ar	3014	3072	3043	3026
CH Aph	2879	2943	2985	2993
C=O	1695	1695	1695	1693
C=N	1664	1641	1610	1608
N-H in plane	1556	1471	1477	1469
C-N	1413	1359	1363	1363
N-H out of plane	642	642	648	624
H ₂ O Coord	-	777-561	-	-
M-O	-	520	-	-
M-N	-	474	470	462
M-Cl	-	320	347	352

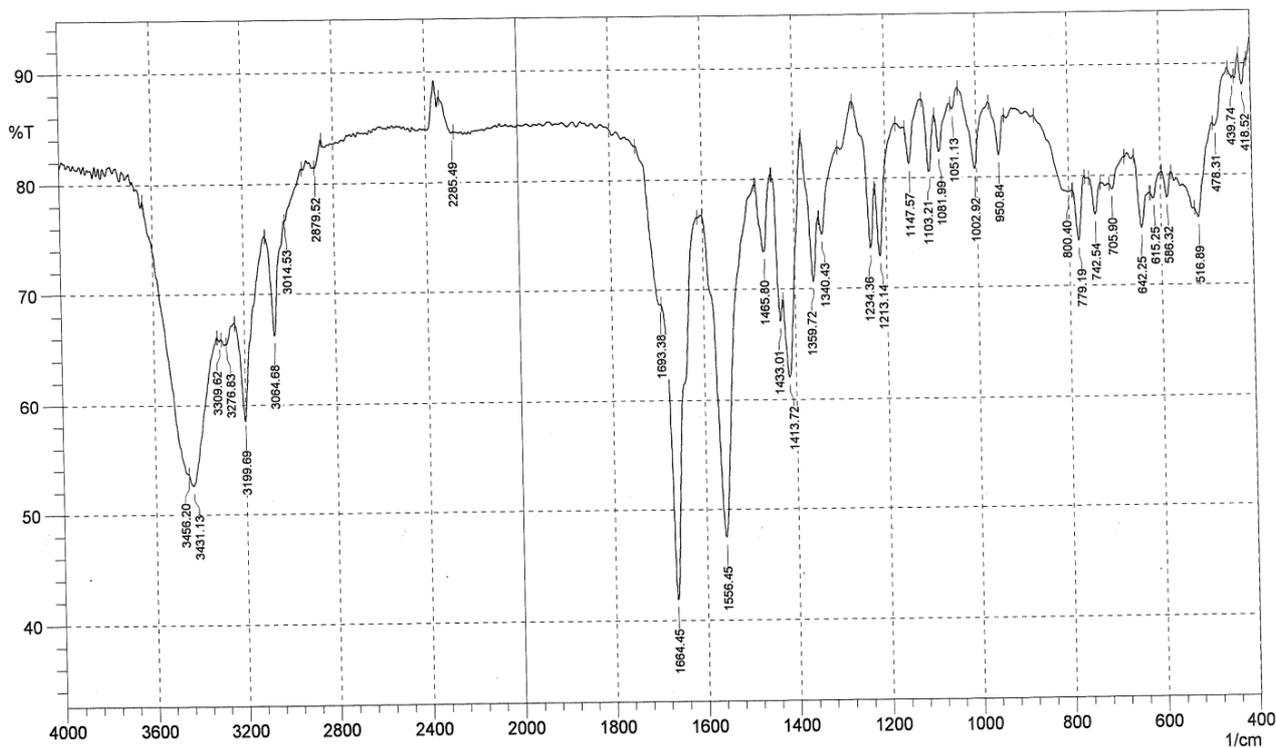


Figure 5. FTIR-Spectrum of ligand.

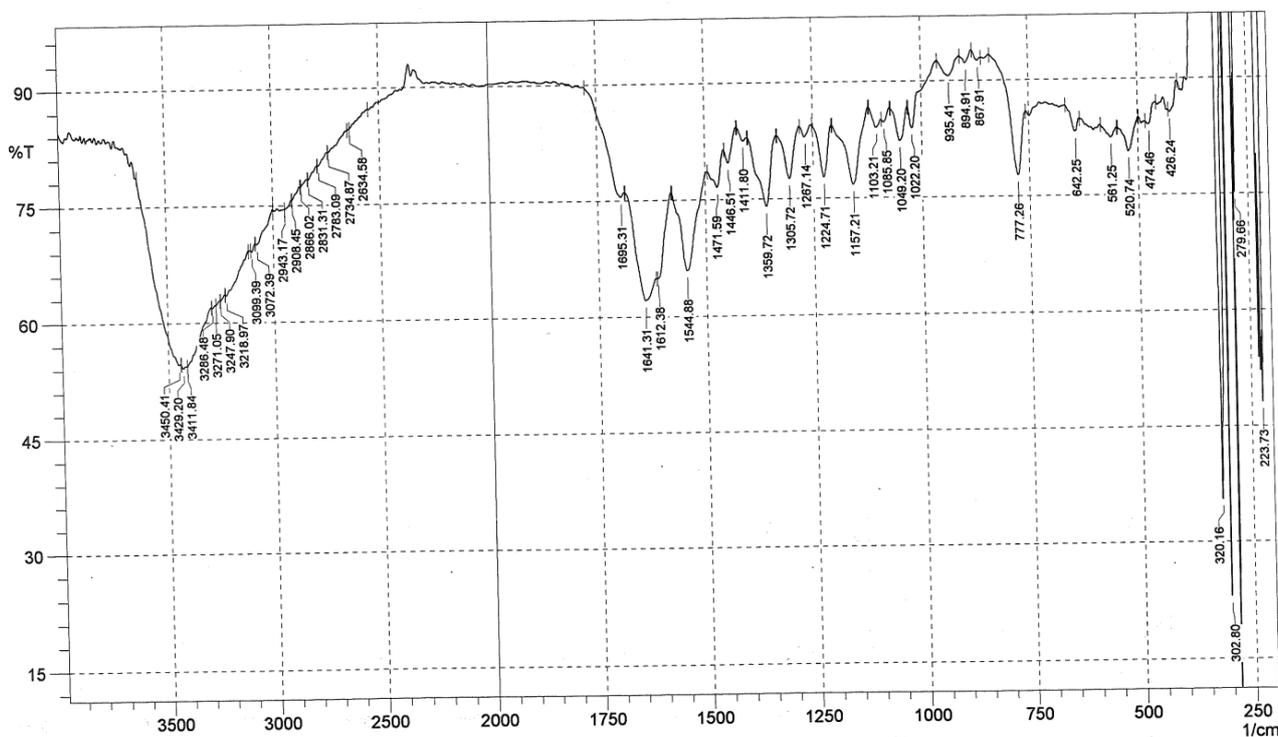


Figure 6. FTIR-Spectrum of Ni(II) Complex

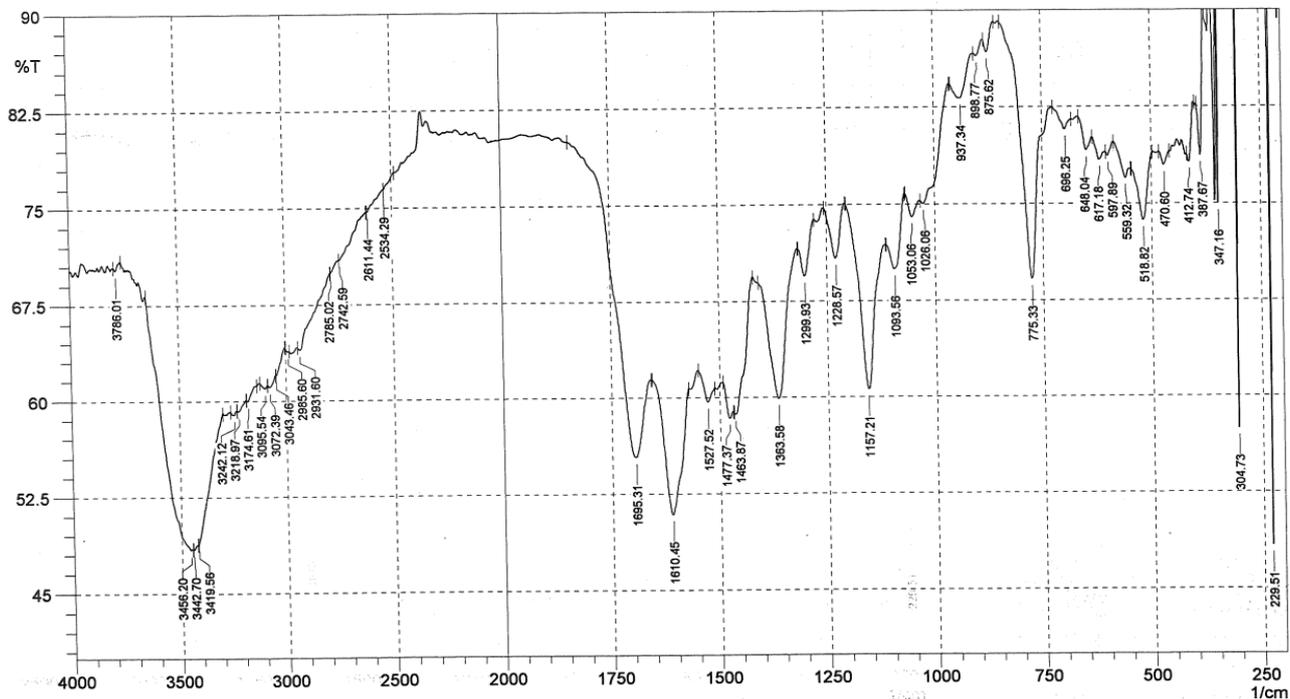


Figure 7. FTIR-Spectrum of Cu(II) Complex.

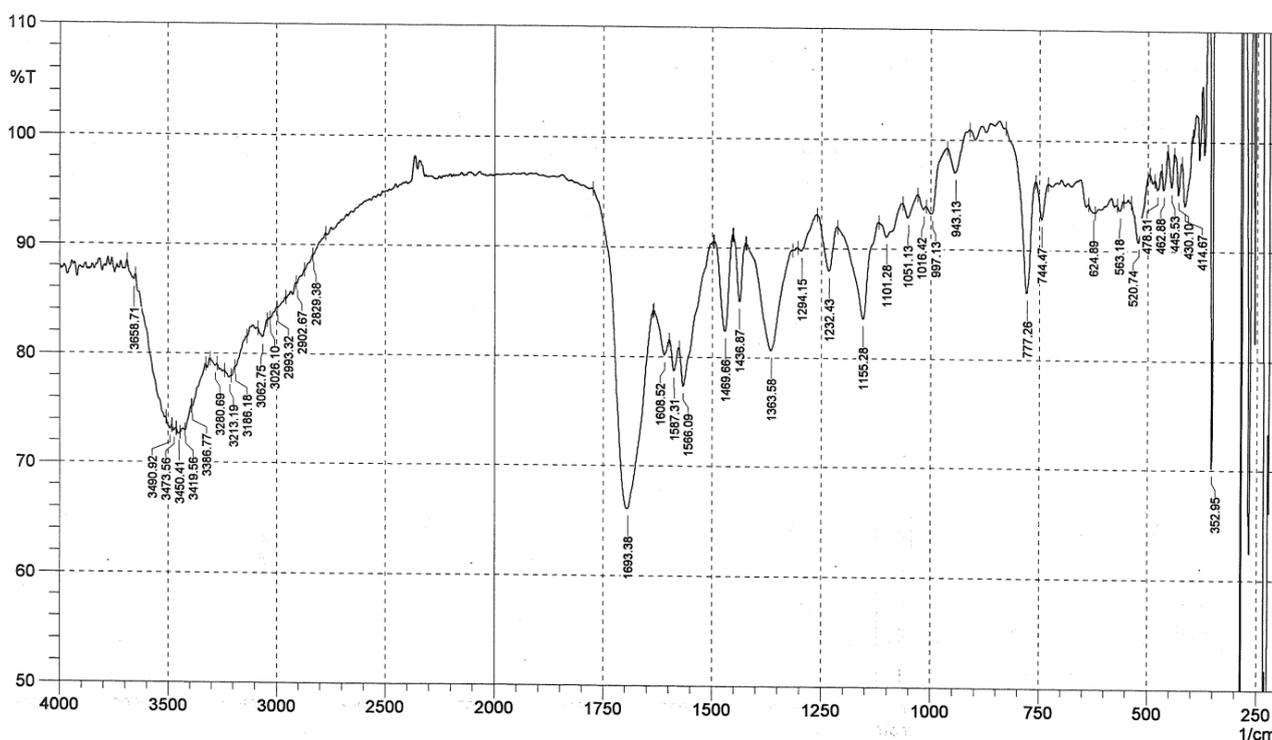


Figure 8. FTIR-Spectrum of Zn(II) Complex.

Proton Nuclear Magnetic Resonance Spectroscopy ($^1\text{H-NMR}$):

The $^1\text{H-NMR}$ of the ligand in dimethyl sulfoxide (DMSO-d_6) is displayed in Fig. 9 using

tetramethylsilane (TMS) as the internal reference standard. All required peaks for proving the chemical structure of the synthesized ligand were shown by the $^1\text{H-NMR}$ of the ligand. At a chemical shift of 3.07 ppm, the ligand showed a singlet peak that is

associated with the aliphatic CH₂ group. This peak has changed to a greater chemical shift because it is close to two carbonyl groups, which leads to the deshielding of electrons around the corresponding protons. A singlet peak is visible at a chemical shift of 7.94 ppm for the proton of the azomethine group (HC=N). With the exception of one proton that was changed to a greater chemical shift and produced an obvious double doublet peak at 8.63 ppm, the four

protons of the heteroaromatic unit exhibit multiplet peaks in the range of 7.5 ppm to 7.8 ppm. Due to the proton's connection to an unsaturated carbon atom close to a very electronegative nitrogen atom in the aromatic system, this peak is significantly displaced. At a chemical shift of 10.56 ppm, the NH of the hydrazine group finally exhibits a singlet peak. Thus, Table 5 contains a summary of the ¹H-NMR data of the ligand.

Table 5. ¹H NMR and ¹³C NMR spectra data of synthesized ligand.

Compound	¹ H-NMR	¹³ C-NMR
L	δ = 10.56 ppm (S, 2H, 2NH), 8.63 ppm (dd, 2H, 2Ar-H next to N), 7.94 ppm (S, 2H, 2HC = N), 7.80-7.77 ppm (m, 4H, 4Ar-H), 7.51 ppm (m, 2H, 2Ar-H), 3.07 ppm (S, 2H, CH ₂).	δ (ppm) = 167.11, 153.14, 148.11, 142.40, 137.61, 123.01, 119.09, 47.90.

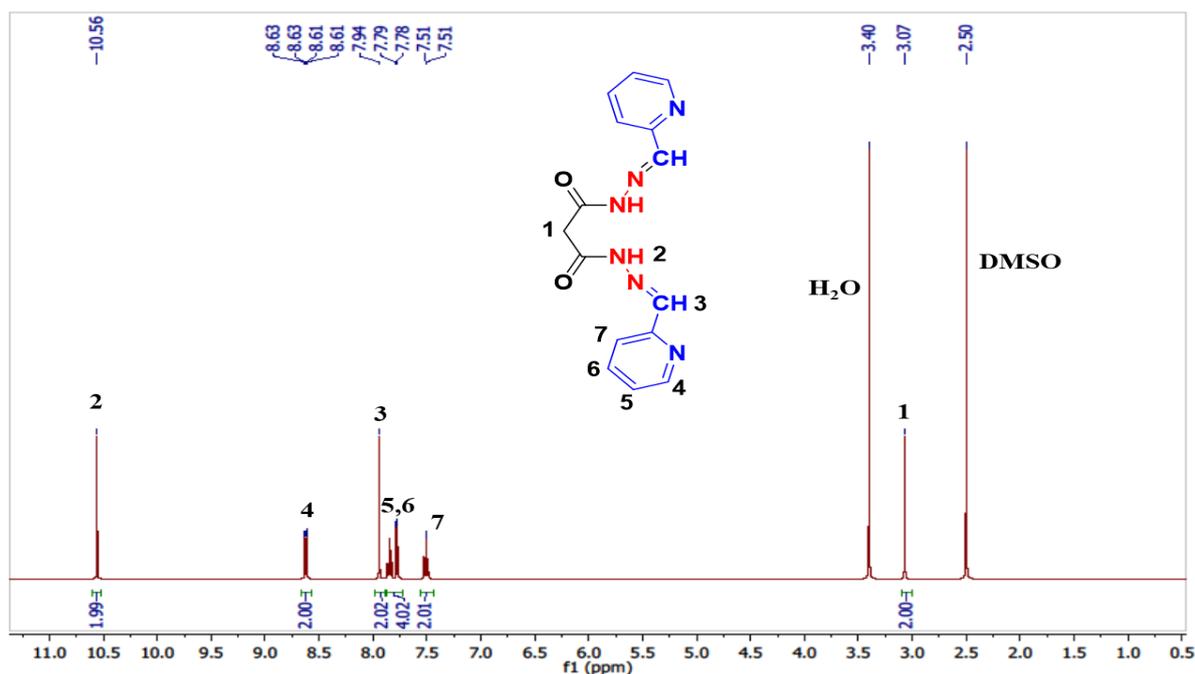


Figure 9. ¹H-NMR spectrum of synthesized ligand.

Carbon Nuclear Magnetic Resonance Spectroscopy (¹³C-NMR):

A ¹³C NMR spectrum is used to establish the chemical structure of the synthesized ligand by identifying chemical shifts that correspond to each of its carbons. Observing the synthetic ligand's eight distinct carbon atom habitats in its chemical

structure. The chemical structure of the produced materials is confirmed by the ¹³C NMR spectroscopy, which showed eight distinct peaks with strong boundaries at matching chemical shifts, as shown in Fig. 10. The aliphatic CH₂ carbon atom has a peak in the spectrum at a chemical shift of 47.90 ppm. Due to the proximity of two carbonyl groups, which results in the de-shielding of electrons

around the corresponding carbon atom, this peak has shifted to a greater chemical shift. On the other hand, because it is an unsaturated carbon atom adjacent to oxygen, the carbon atom of the carbonyl group (C=O) exhibits a peak at a chemical shift of 167.11 ppm. According to our hypothesis, the heteroaromatic unit's five carbon atoms exhibit three peaks at 119.09, 123.01, and 137.61 ppm, and two carbon atoms that underwent a greater chemical shift

exhibit two peaks at 148.11 and 153.14 ppm. Because they are an unsaturated carbon atom close to a very high electronegative nitrogen atom in the aromatic system, these peaks are significantly shifted. Last but not least, the azomethine group's carbon atom (HC=N) exhibits a peak at a chemical shift of 148.11 ppm. Thus, Table 5. provides an overview of the ^{13}C -NMR data of the ligand.

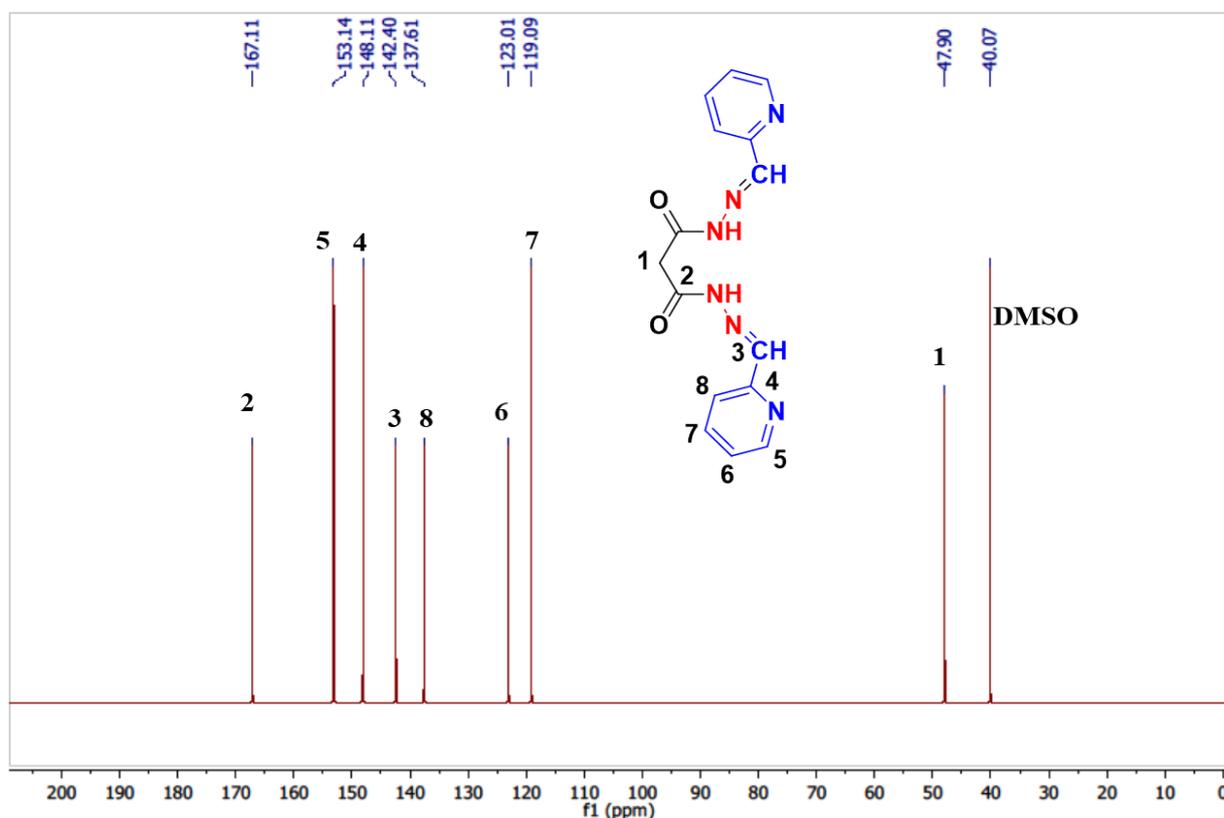


Figure 10. ^{13}C NMR spectrum of synthesized ligand.

Characterization of Schiff Bases Ligand by Mass Spectroscopy:

The molecular weight of the produced compounds is calculated using the mass spectrum, and the fragmentation that belongs to the compounds under investigation is identified. The mass spectra of the

produced Schiff bases ligand shown in Fig. 11. were in accordance with the suggested structural formula, $\text{C}_{15}\text{H}_{14}\text{N}_6\text{O}_2$. The predicted m^+ value (310.12) as shown in Fig. 15 is matched by the molecular ion peak, which was discovered at m/e 310, validating their formula weight for the ligand. As it was successively fragmented, new unique peaks for the ligand were visible in the mass spectra.

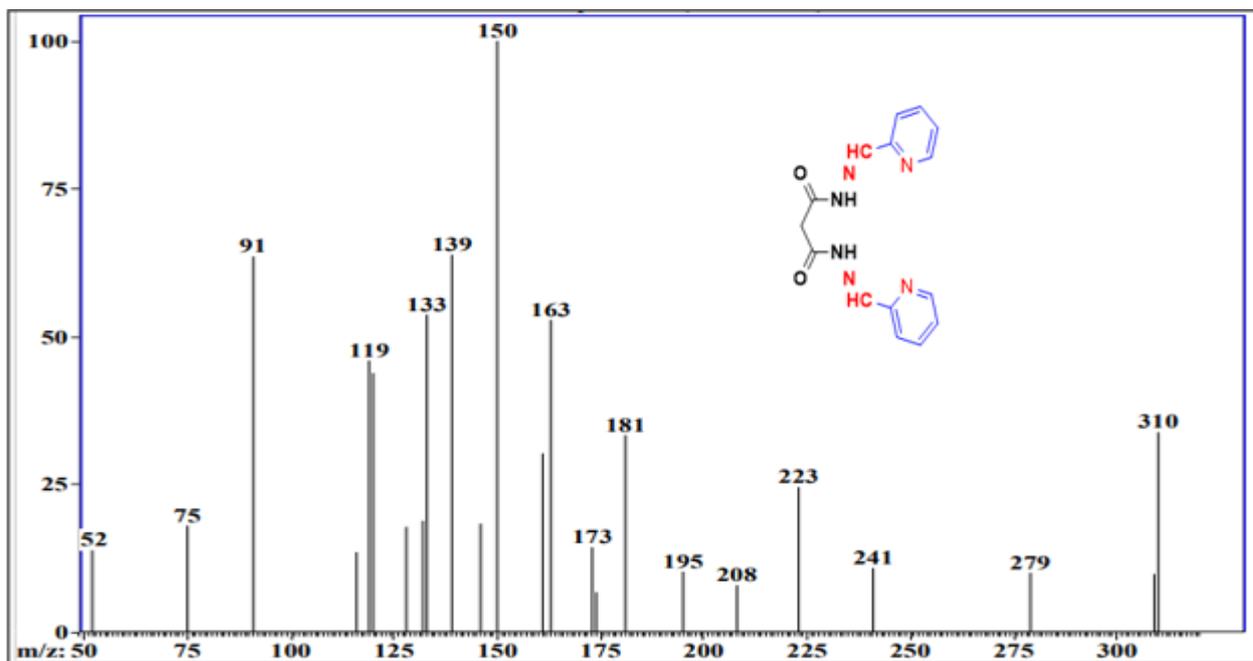


Figure 11. Mass spectrum of L.

Microbiological Analysis of Synthesized Ligand and Its Complexes

Gram-negative (*Staph* and *Escherichia coli*) and Gram-positive (*Bacilla* and *pseudomonas*) bacteria were used to investigate the ligand in vitro antibacterial efficacy. According to Table 6, the antibacterial activity data unmistakably demonstrated that the produced ligand and its complexes were biologically active. The results showed that several of these chemicals had positive effects on the examined organisms. The ligand

displayed the highest activity among its complexes against all tested bacterial species, while its complex Cu(II) displayed the highest activity against *Bacillus*, Zn(II) complex displayed the highest activity against *Staph* bacteria. Antibacterial properties of ligand and its related complexes are shown in Table 6 and Fig. 12. Antifungal activity against different fungus strains was also tested on the produced ligand and its complexes (*Candida*). According to the antifungal activity data, synthesized ligand has the maximum activity against *Candida* in its complexes²⁵⁻²⁹.

Table 6. Anti-Bacterial Activity of synthesized ligand and Its Complexes.

Compounds	Staph	E.Coli	pseudomonas	Bacilla	Candida
Ligand	14	17	17	17	16
Cu ⁺²	16	15	16	20	17
Zn ⁺²	18	18	17	15	22
Ni ⁺²	15	15	9	16	16

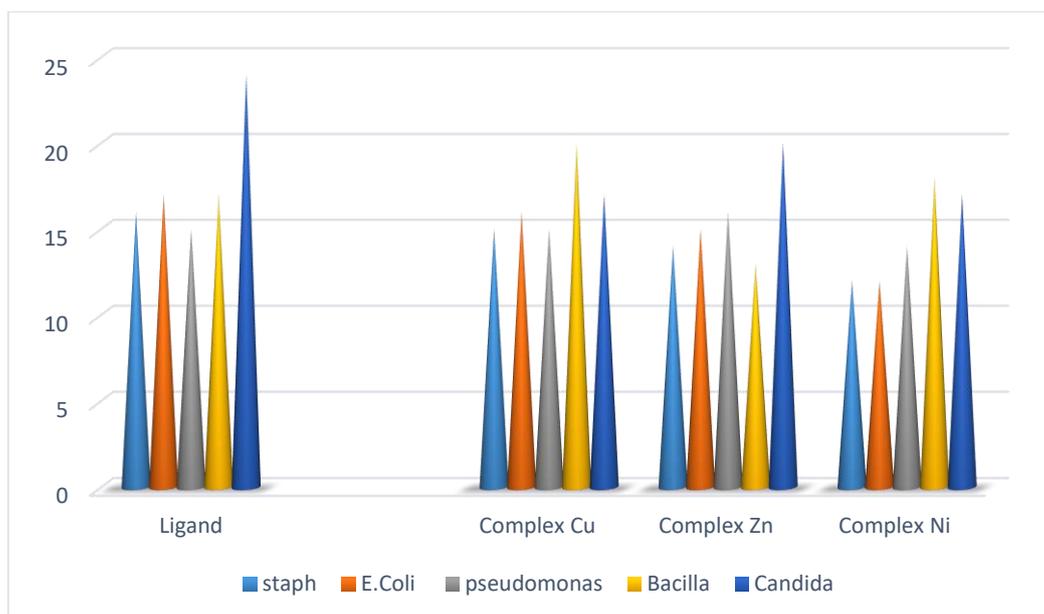


Figure 12. Anti-Bacterial Activity of synthesized ligand and Its Complexes.

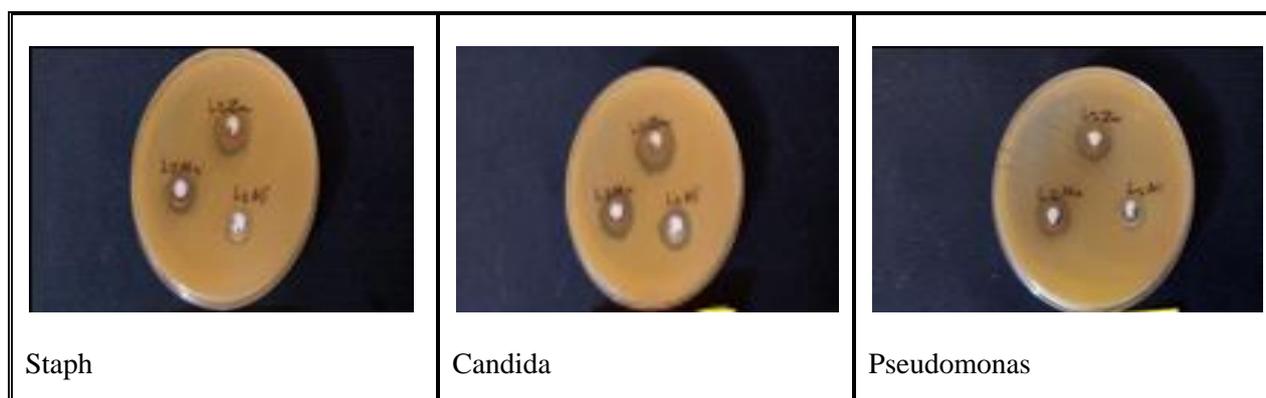


Figure 13. Biological Activity of synthesized ligand and Its Complexes.

Conclusion

A tetradentate ligand, the generated Schiff base molecule attached to the metal ion via the nitrogen of pyridine and the nitrogen of azomethine, according to all spectrum data from this experiment. The analytical findings also revealed that all of the complexes formed had a 1:1 M:L ratio, which is compatible with a mononuclear structure. The complexes in DMF solution were all shown to be non electrolytes for Cu^{+2} and Zn^{+2} complexes while the Ni^{+2} complex is an electrolyte with octahedral

structures by spectral and elemental analyses, as well as magnetic moment and molar conductivity. All of the complexes' biological activity against two different bacterial and fungal species. When investigated, *Escherichia coli*, *pseudomonas*, *staphylococcus aureus*, *Bacilli*, and *Candida* all showed effective inhibition. While the complex of Nickel didn't give any good inhibitory results against *pseudomonas*.

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Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been

Authors' Contribution Statement

N. Sh. conceived this idea and supervised the project.
R. G. H. carried out the experiment, wrote the manuscript, and performed the analysis. All authors

- included with the necessary permission for re-publication, which is attached to the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

discussed the results and contributed to the final manuscript.

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تحضير وتشخيص ودراسة النشاط البيولوجي لبعض المعقدات الجديدة مع قاعدة شيف المشتقة من ثنائي هيدرازيد حمض مالونيك مع 2-بيريدين كربوكسالدهيد

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الخلاصة

تم تحضير ثلاث معقدات جديدة Ni (II) و Cu (II) و Zn (II) باستخدام الليكند المحضر الجديد من تفاعل حامض مالونيك ثنائي هيدرازيد مع 2-بيريدين كربوكسالدهيد. حيث شخّصت المعقدات لمحضرة وكذلك الليكند باستخدام تقنيات مختلفة مثل FT-IR و UV-Vis و Mass و ¹H-NMR و ¹³C-NMR وتحليل العناصر CHN وتقدير محتوى الكلور والموصلية المولارية والحساسية المغناطيسية والامتصاص الذري لتشخيص هذه المركبات. لكل معقد محضر جديد من النيكل والنحاس والزنك، كشفت نتائج التشخيص عن معقدات ذات شكل هندسي ثماني السطوح سداسي التناسق. تمت دراسة تأثير المواد المحضرة على الفعالية البيولوجية لاثنتين من البكتيريا موجبة الغرام *Staphylococcus aureus* و *Bacillus subtilis* واثنتين من البكتيريا سالبة الجرام *Escherichia coli* و *Pseudomonas aeruginosa*، بالإضافة إلى *candida fungus* اثبتت جميع المركبات المحضرة قابلية تثبيطه جيدة باستثناء معقد النيكل، الذي فشل في إحداث أي تأثيرات مثبطة فعالة ضد *pseudomonas*.

الكلمات المفتاحية: النشاط البيولوجي، حامض مالونيك ثنائي هيدرازيد، المعقدات الفلزية، 2-بيريدين كربوكسالدهيد، قاعدة شف.