Syntheses, and Characterization of Complexes Containing Beta-lactam Group with some Transitional Elements and Study their Biological Activity

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Abstract

In this study, a novel azo-azomethine ligand [6[2-hydroxy-4-((3-nitrophenyl)diazenyl)-1-phenyl]imine penicillanic acid] [HNDIP] is synthesized from [2-hydroxy-4-((3-nitrophenyl)diazenyl) benzaldehyde]. And reflux with 6-aminopenicillin acid, this ligand was identified by UV-Vis, FTIR, 1H-NMR, C13NMR, and mass, and it was used to prepare new complexes with [Cu(II), Ni(II), Co(II), Zn(II), and Fe(II)] metal ions. These complexes were identified by FTIR, UV-Vis, molar conduct, magnetic sensitivity, and atomic absorption for all complexes, the reaction ingredients were observed to be ratio 1:2 (metal: ligand). The ligand, a tridentate with a single negative charge, was coupled with metal ions to form claw complexes, resulting in an octahedral shape. Finally, antibacterial effectiveness was determined for the ligand and complexes against two distinct bacteria strains (Pseudomonas and klebsiella). It was discovered that the ligand and its complexes have high inhibitory activity against bacteria (Pseudomonas and Klebsiella). As a result, the chemicals created may be feasible substitutes for routinely used drugs.

Key Words: Azo-azomethine, ß-lactam, 6-aminopenicillin Acid, Biological Activity.

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Introduction

Azo-azomethine Ligand, is an acceptor ligand capable of stabilizing metal ions and coordinating compounds (I.N. Witwit, 2016). Numerous compounds with aromatic and heterocyclic rings were examined, including phenyl derivatives, pyridine, pyrimidine, triazole, and indole, among others (A. İnan et al 2018, E. Ispir et al 2019). Due to the fact that the azo-azomethine class is highly effective (N = N-CH = N) (M. Almáši et al 2020), a large number of them have been synthesized and studied as chelating ligands (R.S. Mahmood et al 2020). Where Azo-azomethine metal complexes act as intermediates and catalysts in biological formation. (M.S. Kasare et al 2019).

Penicillin was one of the first and most widely used ß-lactam antibiotics (G.A. Estrada et al 2015). In 1928, Fleming discovered penicillin (A. Fleming et al 1929) and the penicillins' four-membered ß-lactam ring led to several advances in antimicrobial and pharmacological properties (N.C. Cohen 1983, A.D. Deshpande et al 2004). Where Antimicrobial resistance is a problem due to misuse and abuse (L.M. Bush et al 1995).

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There is controversy over beta-lactams which form a covalent complex and where hypersensitivity reactions range from 1 to 10% (N.S. Egorov 1985, L.M. Lima et al 2020) and the first antibiotic to beta-lactam is 6-aminopenicillin acid. This acid has important biological effects (P. Nag et al 2020). To the acylase hydrolysis of penicillin "V" (D.J. Fu et al 2020) or penicillin G (P.Nicoletti et al 2020) to produce semi-synthetic penicillins and phenylacetic acid as a by-product. (R.H. Jasim et al, B. Qusai et al 2017, S.R. Ayakar et al 2019, J.C. Wu et al 2000)

(Y.H. Sabah) use reaction of 6-amino penicillanic acid (6-APA) with terephthaladehyde, glyoxal, and vanillin The results showed that the prepared ligands compounds have octahedral shape ratio [2:1], [2:1] and [1:1] metal to ligand [M:L]. (M. Ali Dahi et al 2020). (B.Q.Ali, R.H. Jasim, and M.H. Hamid) use the reaction of 6-amino penicillanic acid (6-APA) with Salicyldehyde, Benzyldehyde, and O-Nitrobenzyldehyde The results showed that the prepared ligands compounds have tridentate, and bidentate ligands, octahedral shape (B.Q.Ali et al 2016). (I.Ali, M.H.Said, W.AL-Wazn). The reaction of 6-amino pencillanic acid with Schiff base "(Z)-3-((3-hydroxybenzylidene) amino) phenol)" has formed a novel Azo–azomethine ligand (HL) "(7-((Z)-(2-hydroxy-4-((Z)-((3-hydroxyphenyl) imino) methyl) phenyl) diazenyl)-3, 3- dimethyl-6-oxo-2-thiabicyclo [3.2.0] heptane-4-carboxylic acid The results showed that the prepared ligands compounds have tridentate ligand, octahedral shape ratio [2:1] metal to ligand [M:L] (I. Ali et al 2021). In this study, new ligands synthesis (HNDIP)] obtained from [2- hydroxy-4-((3-nitrophenyl) diazenyl) benzaldehyde] and reflux with 6-aminopenicillin acid were produced with complexes of some transition metal ions Zn (II), Cu (II), Ni (II), Co (II), Fe(ll) refers to the synthesis, characterization, and study of salts ligands with antibiotics of ß-lactam (6APA) and chelating ligands formation. Refers the results of spectral and analytical data, To demonstrate that the ligand is a tridentate molecule with a single negative charge and that the claw complexes have an octahedral shape, the ligand and complexes were screened for antibacterial activity against two different types of bacteria (Pseudomonas and klebsiella). The biological activities of the chelates were carried out and compared with the standard known drugs. The formation of these compounds was explained through spectroscopic techniques.

Experimental

Materials and Methods

The starting materials used for the synthesis of azo dyes and Schiff base were purchased high purity.

1. Preparation of 2-hydroxy4 ((3nitrophenyl) diazenyl) benzaldehyde (HNDB)

The Procedure of Diazonium Salt

A mixture from hydrochloric acid (5ml), distilled water (15ml), and (0.014mole, 2 gm) of 4-nitroaniline was collected into a conical flask (200 ml). The mixture was cooling into the ice bath to 0_5 C. Then sodium nitrate (096 gm, 0.014mol) in distilled water (10ml) was added dropwise to the mixture with kept the temperature at 0_5 C.

- *The Procedure of Azo Dyes*

Diazonium solution was added drop-wise to coupling component solution which prepared by mixing (0.014 mol, 1.70 g, 1.5 ml) salicylaldehyde and (0.014mol, 0.56 g) of sodium hydroxide in (20ml) distill water. The precipitate than Filtered color orange.

- *The Procedure of Schiffs Ligand Base*

The ligand was produced by dissolving 6-Aminopenicillanic acid (0.49 gm, 0.0002 moles) in 20ml absolute ethanol (basic medium) and then trying to add it to (0.5gm, 0.0002 mole) of (HNDB) the resulting mixture was refluxed for 2hrs, after, dried, and returned recrystallized from absolute ethanol.

2. Preparation of Complex

For the preparation of complexes, a ligand (0.18 g) (HNDIP) Solution was mixed with a mole of (0.02g, 0.04g, 0.05g, 0.04g, 0.04g) of (Zn, Cu, Fe, Co, Ni) Respectively in 15 ml of absolute ethanol. The mixture was refluxed For 1h, then cooling to room temperature, the Colored complexes got precipitated slowly.

3. Microbiological Investigations

The culture medium was prepared by dissolving twenty grams of Muller-Hinton agar in 500 milliliters of distilled water. with constant stirring, after which the medium was placed in an autoclave for 1 hour and then left to cool to 40°C until it solidified. The bacteria were grown using sterile

swabs left for 30 minutes, after which a drill was made in the culture medium using a sterile cork drill. The laboratory prepared solution was placed inside the pits and the dishes were placed in the incubator for 24 hours, after which the diameter of the inhibition area was measured.

Table 1. Physical properties of the synthesized compounds:

Compd	M.P (C)	Color	Yield (%)	Solubility				
				H_2O	C_2H_6O	DMSO	$C_4H_{10}O$	C_6H_6
L	85-93	Orange	75%	-	+	+	-	÷
$[Cu(L)_2]$	110	Dark brown	60%	-	+	+	-	÷
$[Co(L)_2]$	170	Corrosion	90%	-	+	+	-	÷
$[Ni(L)_2]$	170	Dark red	70%	-	+	+	-	÷
$[Zn(L)_2]$	135	Red	60%	-	+	+	-	÷
$[Fe(L)_2]$	180	Blak	80%	-	+	+	-	÷

Results and Discussion

^{1}H-NMR and ^{13}C-NMR Spectra of the Schiff base Ligand

The ^{1}H-NMR spectrum of the ligand Fig(1). The DMSO-d6 solvent was showed a signal at (2.5ppm) and the first signal at δ=(1.3,1.5 ppm) due to two(CH3) groups and signals in the range (6.7-7.6 ppm), (Jabbars. Hadi et al 2014) due to aromatic protons (G.K. Karaoglan et al 2007). The other signals at δ=(8.7 ppm), due to the N=CH group. The ^{13}CNMR Additionally, the ligand's spectrum was recorded DMSO-d6 solvent. Fig (2) The ^{13}CNMR spectrum of ligand showed the azomethine carbon peak at (160) ppm. (M.N. Ibrahim et al 2011) The carboxylic (C=O) group peak showed at (169) ppm. The carbonyl group peak showed at (172) ppm and the peak of aromatic carbon is located at (111-130) ppm (O.O. Gungor et al 2020).

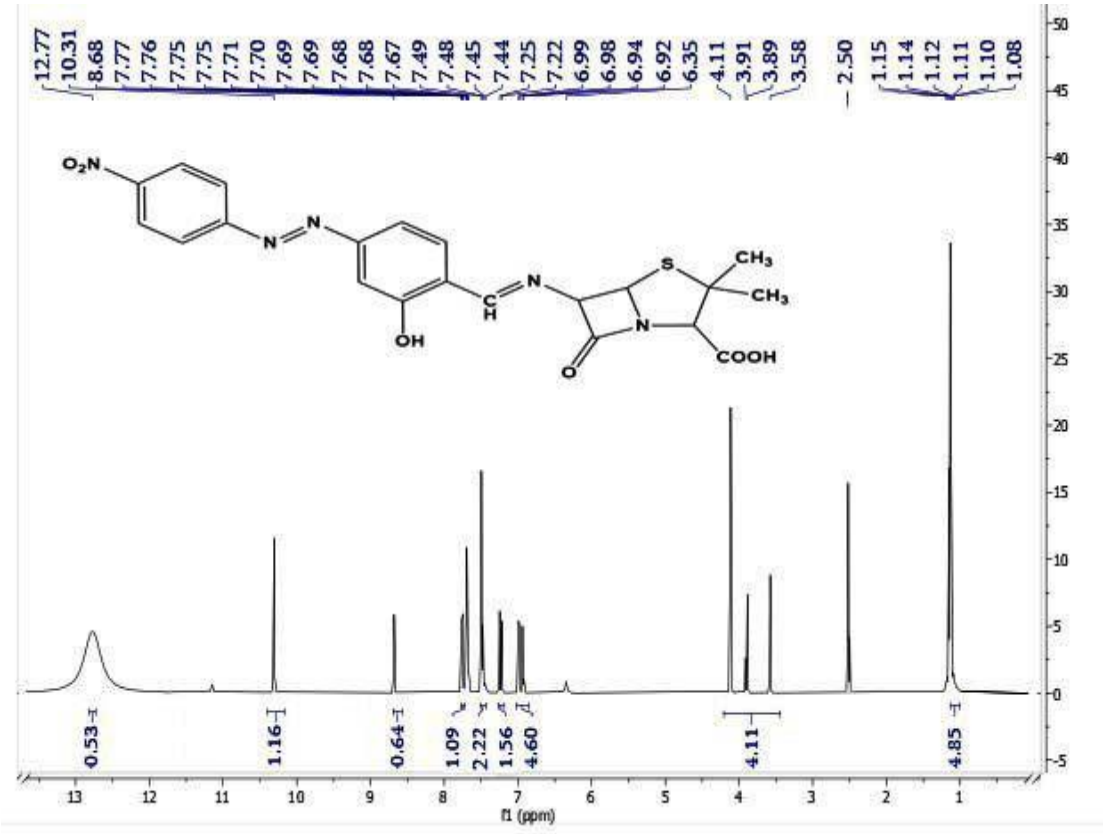


Fig. 1. ^{1}HNMR Spectra of ligand

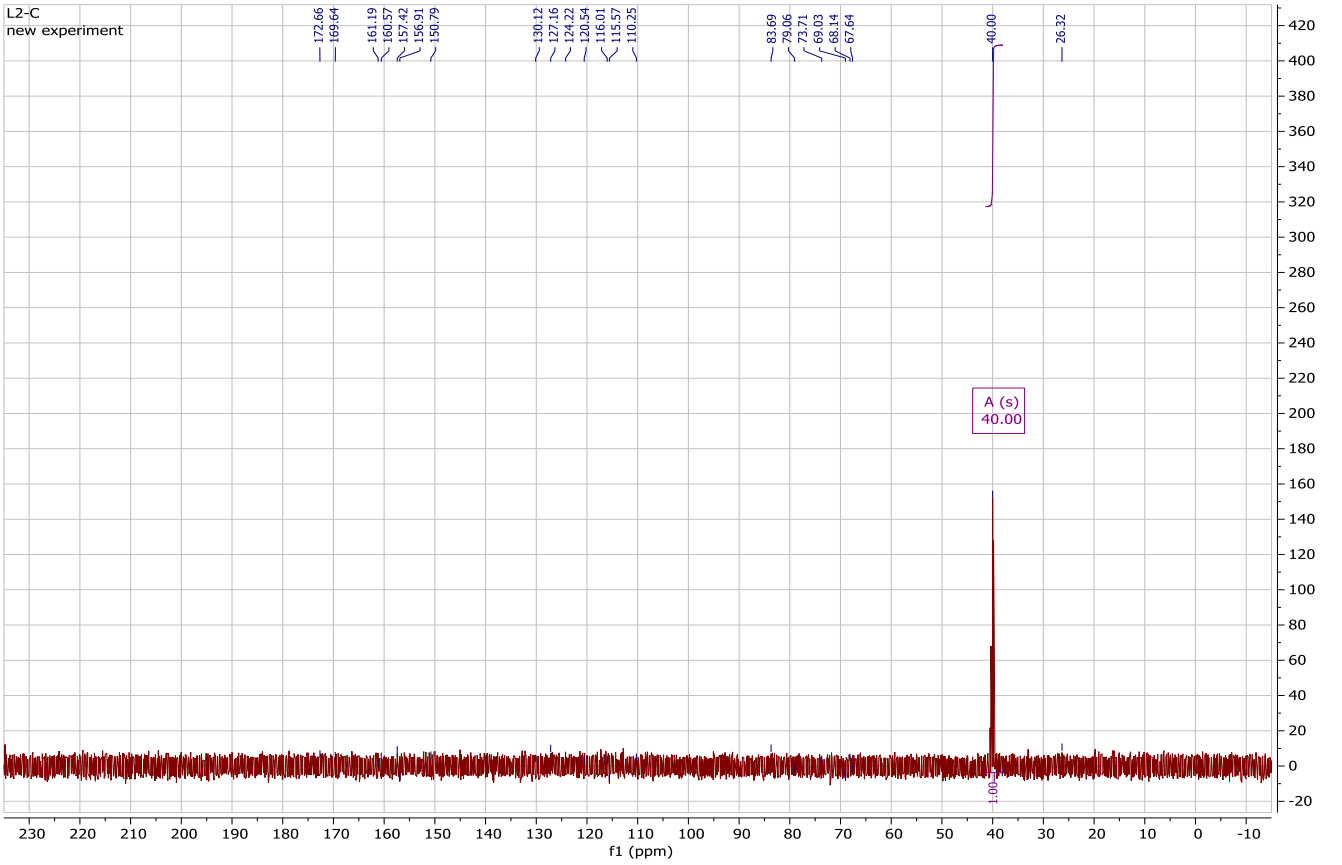


Fig. 2. ^{13}CHNMR Spectra of ligand

- *Mass Spectra of Ligand*

Mass spectrometry has been successfully used to investigate molecular (Prakash A et al 2010). A free ligand's mass spectrum is depicted in fig(3). A peak on the spectrum represents the parent ion centered at (468) fragmentation for ligand are summarized in Scheme (1) and table (2).

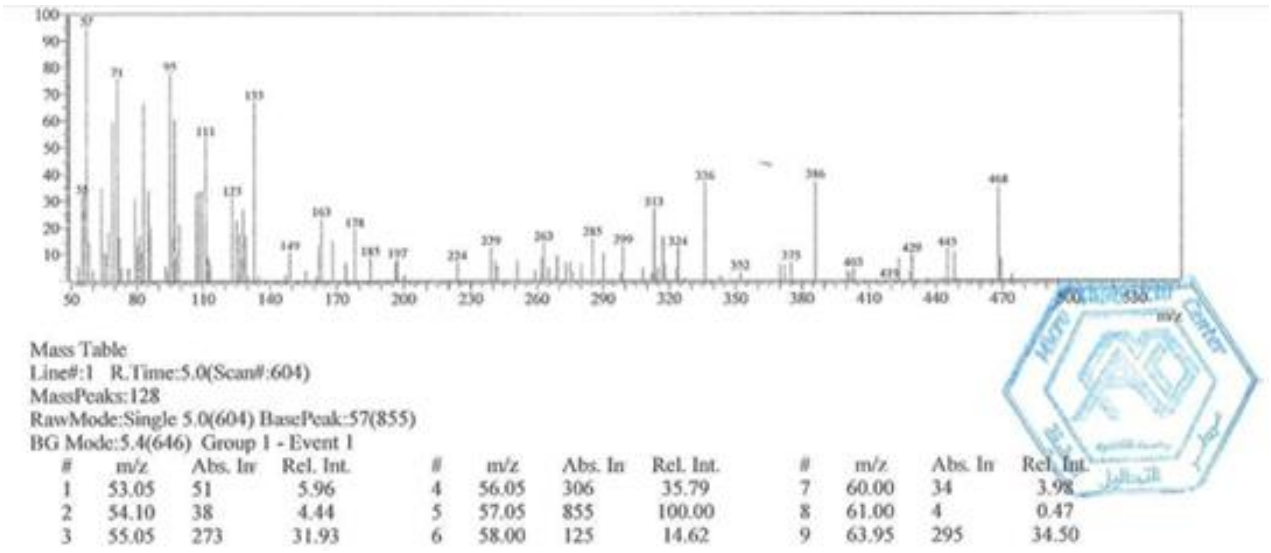
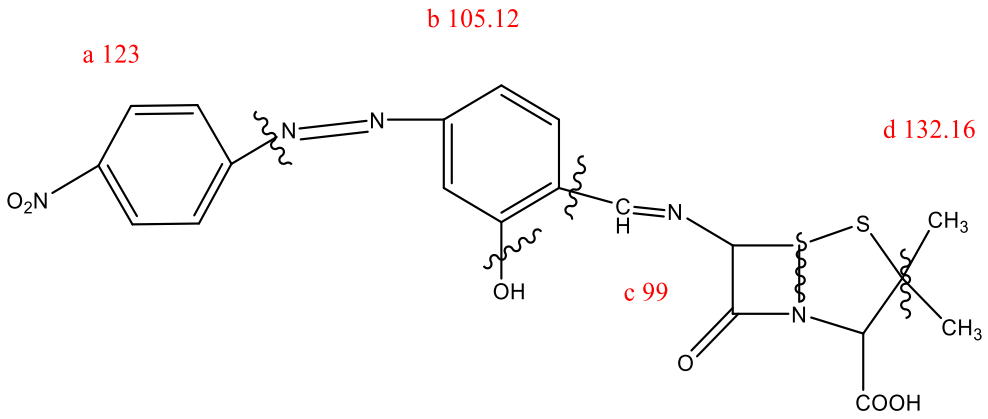


Fig. 3. Mass Spectra of ligand



Scheme 1. Mass Spectrum of ligand

Table 2. Show to fragmentation for ligand

	m/z	Abs.n	Rel .Int
1	53.05	51	5.96
2	54.10	38	4.44
3	55.05	273	31.93
4	56.05	306	35.79
5	57.05	855	100.00
6	58.00	125	14.62
7	60.00	34	3.98
8	61.00	4	0.47
9	63.95	295	34.50

- *FT-IR spectral Data*

The spectrum of the below compound Fig (4-9) was shown characteristic bands at (3367) cm^{-1} assigned to (OH) and the band at (1774)cm^{-1} (M.K. Mahmmod et al 2012)] assigned for the carbonyl group (lactam) (C=O). At (1627) cm^{-1} assigned to (C=N), Other bands assigned for (C-H) aromatic, (N=N), (C=C) aromatic (C-O) respectively (J. Mitchell 1994). Table (3) shows the change in (O-H), (C=N), and carbonyl group (C=O).

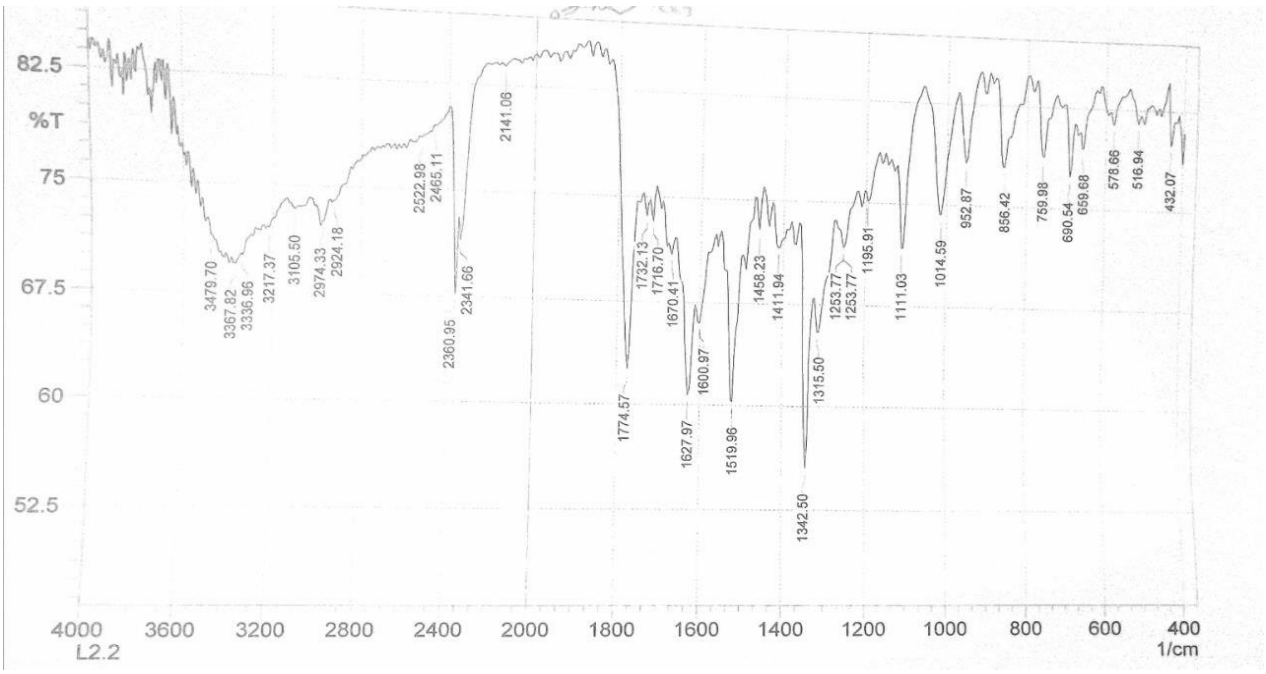


Fig. 4. FT-IR spectrum of ligand

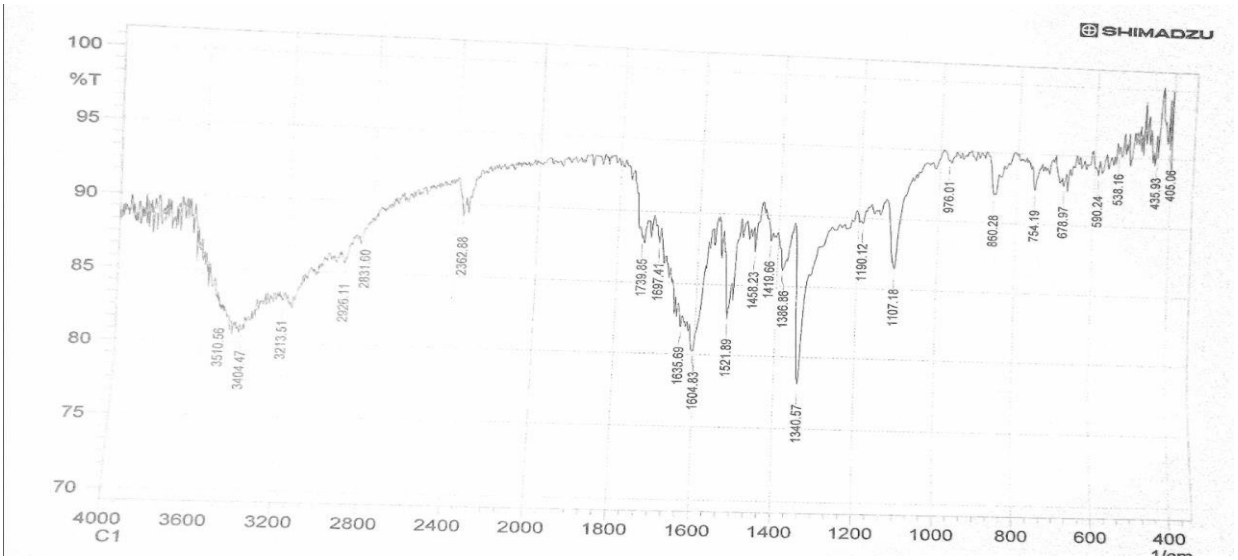


Fig. 5. FT-IR spectrum of $[Cu\ (L)_2]$

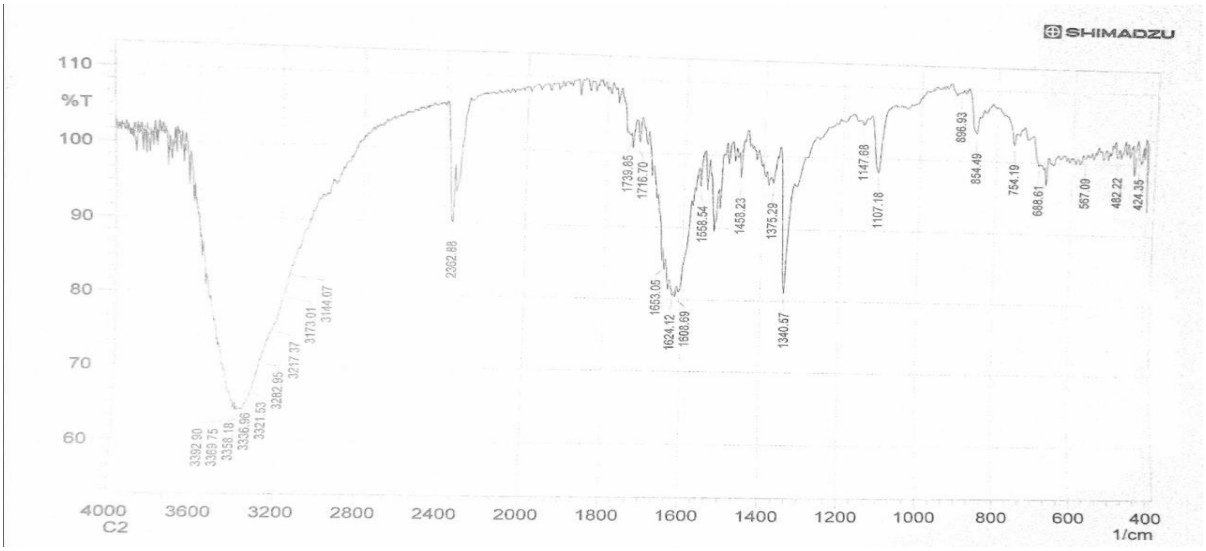


Fig. 6. FT-IR spectrum of $[Co(L)_2]$

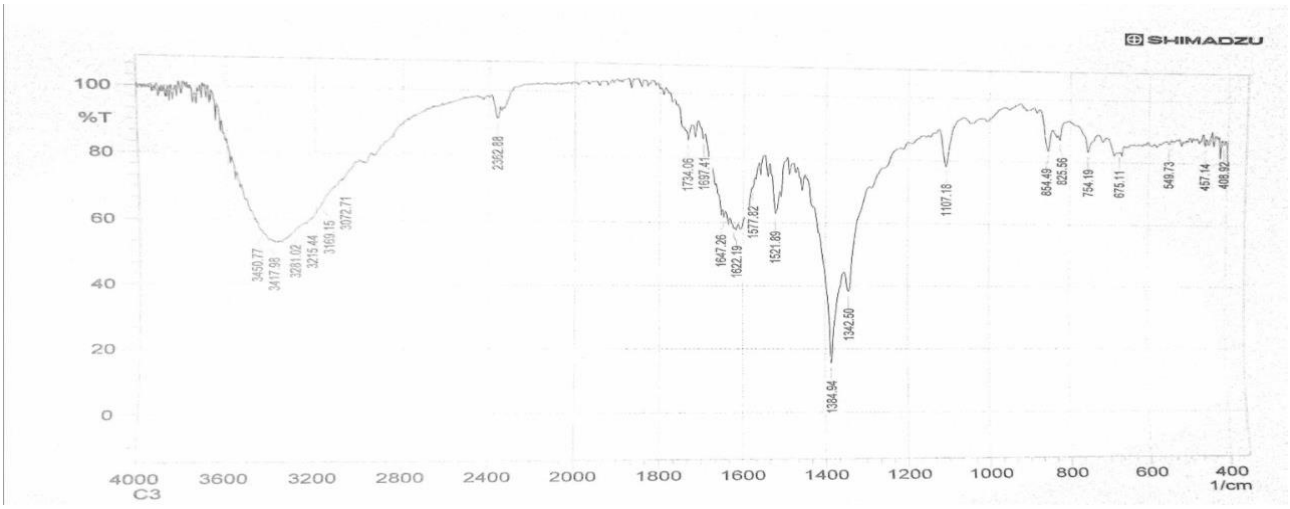


Fig. 7. FT-IR spectrum of $[Ni(L)_2]$

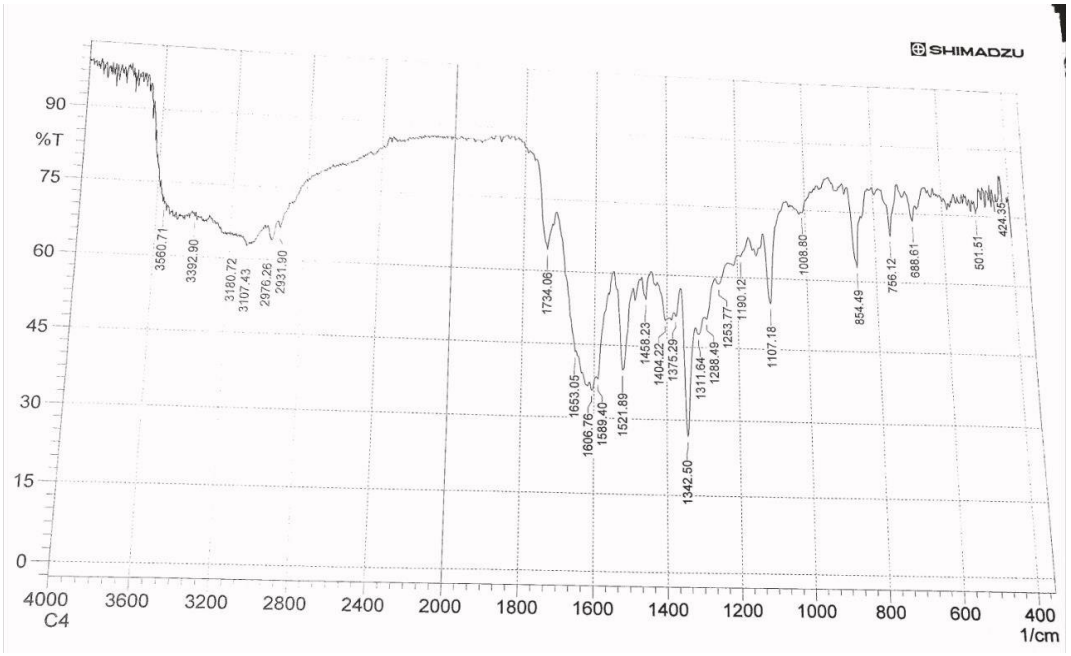


Fig. 8. FT-IR spectrum of $[Zn(L)_2]$

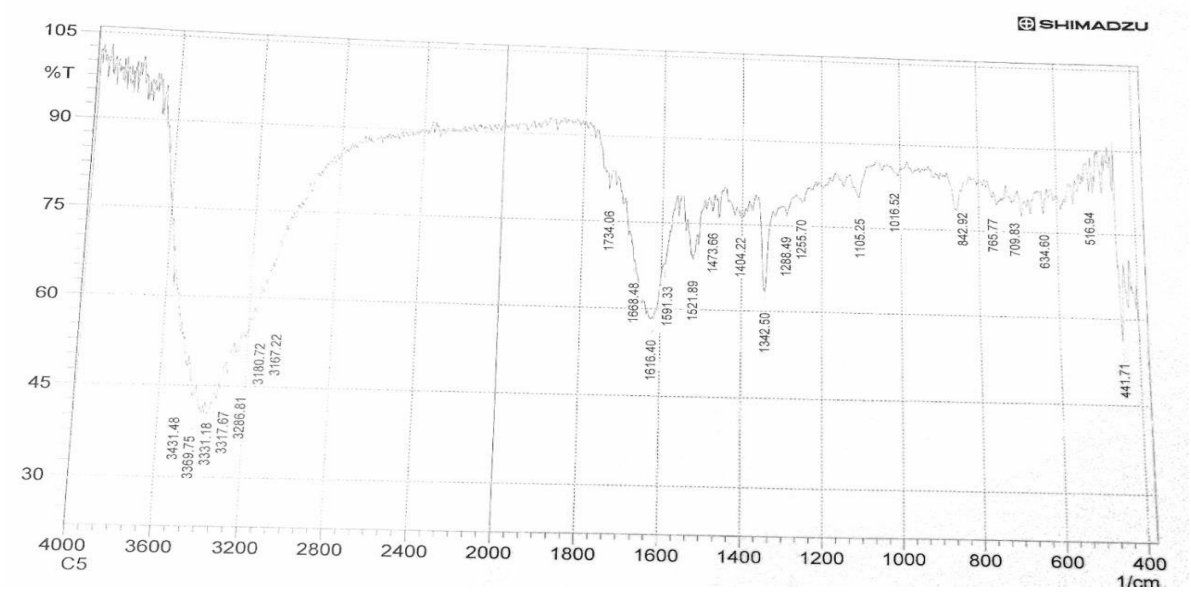


Fig. 9. FT-IR spectrum of $[Fe(L)_2]$

Table 3. FT-IR spectral data

	L	$[Cu(L)_2]$	$[Co(L)_2]$	$[Ni(L)_2]$	$[Zn(L)_2]$	$[Fe(L)_2]$
O-H	3367	3404	3369	3417	3392	3369
C-H_{AR}	3105	3100	3110	3072	3107	3110
C=O_{lac}	1774	1739	1739	1734	1734	1734
C=N	1627	1635	1624	1622	1635	1616
N=N	1458	1458	1458	1458	1458	1458
C=C	1519	1521	1519	1521	1521	1519
C-O	1253	1253	1253	1253	1253	1255
C-N	1111	1107	1107	1107	1107	1105

AR= Aromatic, Lac= lactam

- *Spectra of Electronic Elements*

In ethanol absolute solution, the electronic spectrums of the ligand and complexes were determined. The UV-Visible spectrum of the ligand contains absorption peaks at wavelengths 250 nm, which correspond to the aromatic ring's π-π* transition and the 440 nm n-π* transition for the nonbonding pair of an electron in the nitrogen azomethine group, respectively (M. Wang et al 2003, A.B.D. Nandiyanto et al 2019). A spectrum of complexes exhibits peaks in the UV-Vis, due to the (C.T) (Saha.S et al 2015)]. Table 4 Fig (10-15).

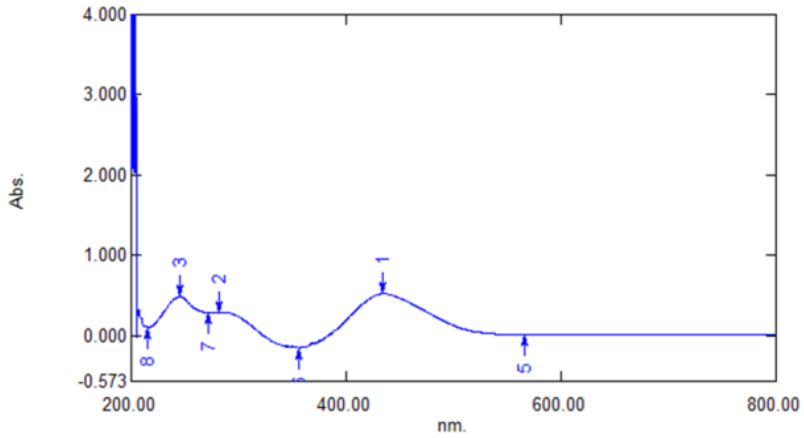


Fig. 10. UV-Vis spectrum of ligand

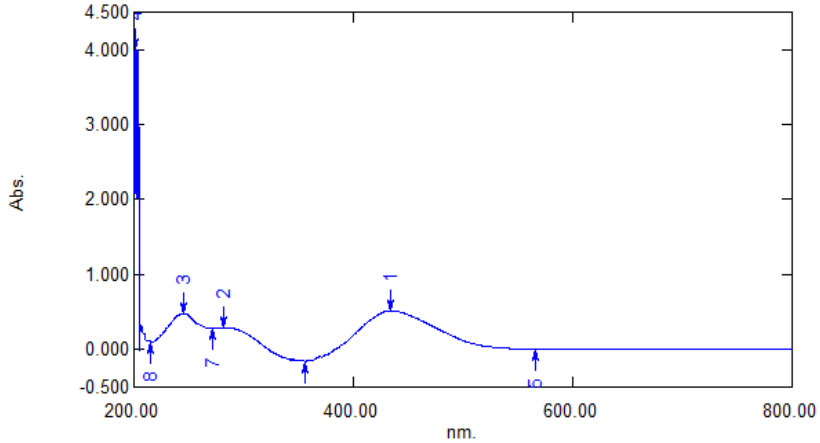


Fig. 11. UV-Vis spectrum of $[Cu(L)_2]$

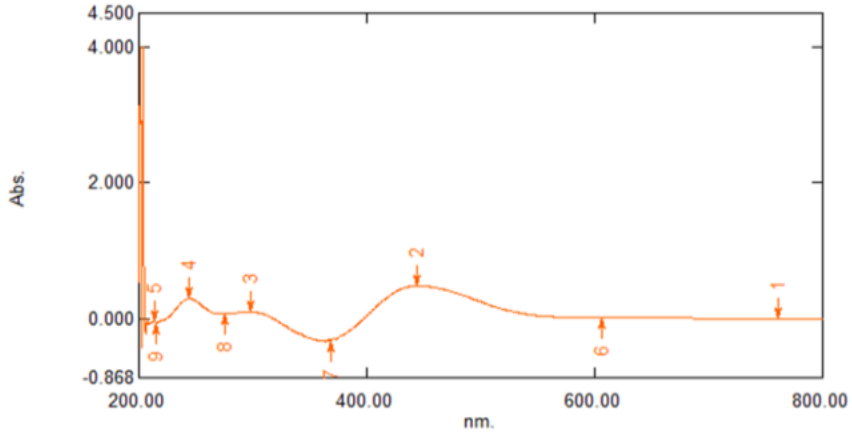


Fig. 12. UV-Vis spectrum of $[Co(L)_2]$

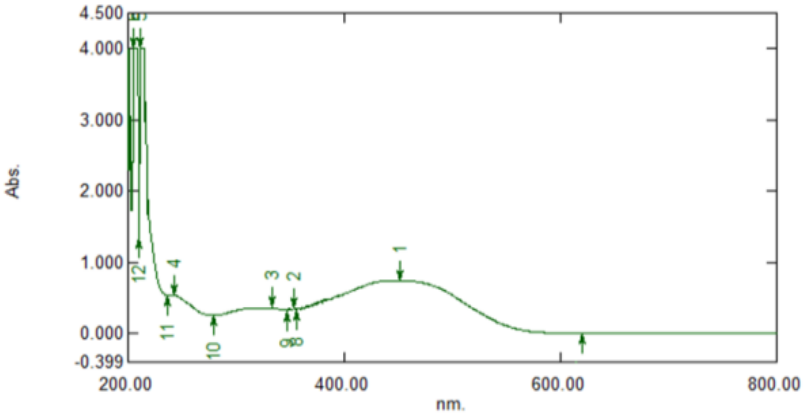


Fig. 13. UV-Vis spectrum of $[Ni(L)_2]$

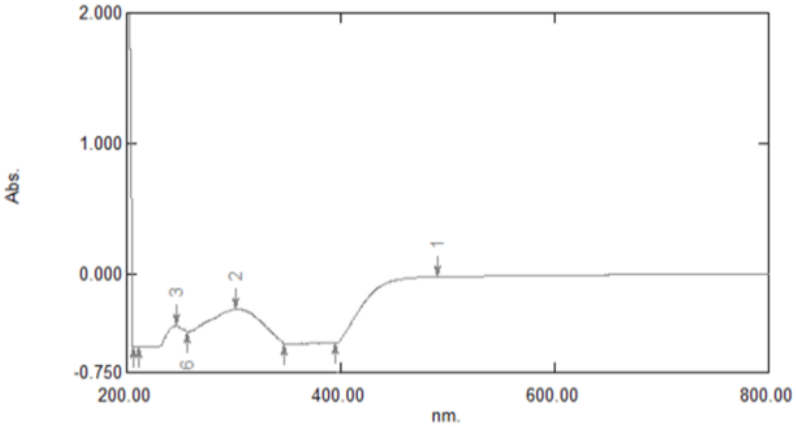


Fig. 14. UV-Vis spectrum of $[Zn(L)_2]$

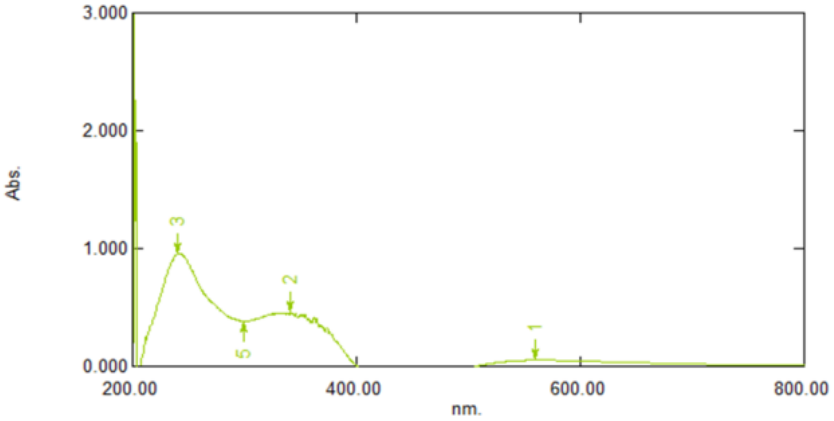


Fig. 15. UV-Vis spectrum of $[Fe(L)_2]$

Table 4. Electronic spectra

Complexes	Absorption Band nmλ	Assignment
L2	250 ,440	π-π*, n-π*
[Cu(L2)	260 ,445	C.T
[Co(L2)	255 ,460	C.T
[Ni(L2)	259,450	C.T
[Zn(L2)	310,495	C.T
[Fe(L2)	255,350	C.T

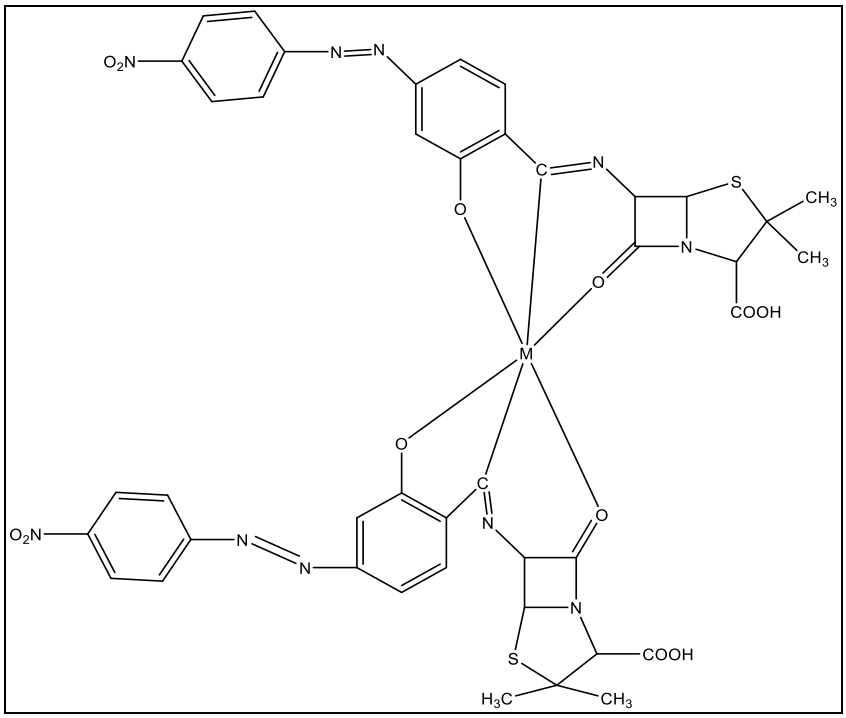
- *Magnetic Susceptibility and Molar Conductivity for Coordination Complexes*

The magnetic susceptibility properties of all complexes were measured and compared to the literature (Radhakrisnan. PK 1985). It was discovered that the vacuum formed by these complexes is octahedral in shape (M.S. Iqbal et al 1993), while the molar connectivity of each

complex recipe is ionic (neutral) (R.T. Mahdi et al 2014). Table 5 illustrates the magnetic susceptibility and molar connectivity and atomic absorption of each complex.

Table 5. Magnetic susceptibility and conductivity at the molar level for coordination complexes

Compound		Malar conductivity s	Xg *10^{-6}	μ_{eff}	Shape	Atomic absorption	
						Cal	Found
C1	Cu(L)2	12	1.3	2.1	Oct	6.2	5.5
C2	Co(L)2	0.7	1.24	2.1	Oct	5.8	4.9
C3	Ni(L)2	17	4.1	3.3	Oct	5.8	5.0
C4	Zn(L)2	20	-	-	Di	6.4	5.8
C5	Fe(L)2	0.5	12.7	5.6	Oct	5.5	5.1



Scheme 2. Structure of complex
M= (Cu^{+2}, Co^{+2}, Ni^{+2}, Zn^{+2}, Fe^{+2})

Scheme (2) illustrates the structure of the complexes and shows that the prepared ligand is a trident chelating and the preparation ratio is 1:2, [matel: ligand] and that the proposed geometric shape is octahedral, non-electrolytic and the measurement of the atomic absorption of the complexes, practical results were close to the theoretical results.

- *Biological Activity for the Ligand and Complexes*

They are many factors that influence the biological activities of ligands and metal ion complexes such as type of ligand, type of metal ion-electron configuration of metal ion, the transition series, and geometry of complexes (Alias. M et al 2014). The biological activity of the ligands and their complexes were studied by using the inhibition method for types of bacteria. Two types of bacteria, Pseudomonas and klebsiella. The compounds show inhibition diameter to the types of complexes, which show inhibition diameter against bacteria, the results indicate that the complexes show more activity than the ligand under similar conditions this may be due to the that the chelation considerably reduces the polarity of the ion mainly because of partial sharing of its positive charge with the donor groups and possible electron delocalization over the whole chelate ring Table 5 Fig. (16-17).

Table 5. Biological activity for the ligand and complexes

Compound	Pseudomonas	Klebsiella
C1	11	20
C2	21	14
C3	15	13
C4	16	3
C5	10	15
C6 L	15	10

Fig. 16

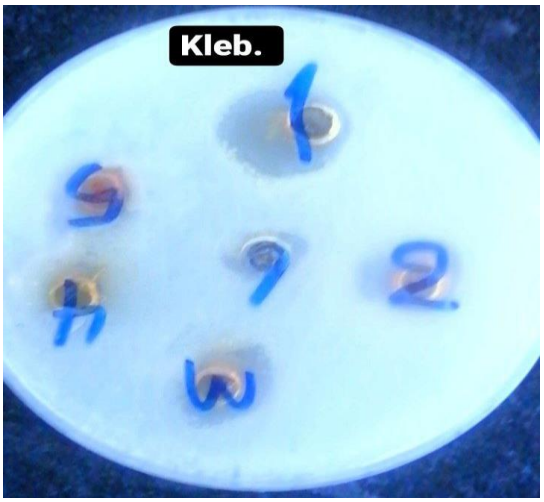


Fig. 17

Conclusions

The prepared ligand and its complexes demonstrated a high level of inhibitory activity against the bacteria (Pseudomonas and Klebsiella). As a result, the prepared compounds may be useful as substitutes for the commonly used antibiotics to treat this bacteria.

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