

RESEARCH ARTICLE

Synthesis and Characterization of New Ligand for β -enaminone and its Mixed Ligand Complexes with Some Metal Ions and Evaluation of their Biological Activity

Hassan J. Kadhom, Ahmed T. Numan, Eman M. Atiyah*

Department of Chemistry, College of Education for Pure Sciences, Ibn- Al-Haitham, University of Baghdad, Baghdad, Iraq

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ABSTRACT

The synthesized ligand (3-(2-amino-5-(3,4,5-tri-methoxybenzyl)pyrimidin-4-ylamino)-5,5-dimethylcyclohex-2-enone) [H_1L_1] was characterized via fourier transform infrared spectroscopy (FTIR), 1H , ^{13}C – NMR, Mass spectra, (CHN analysis), UV-vis spectroscopic approaches. Analytical and spectroscopic techniques like chloride content, micro-analysis, magnetic susceptibility UV-visible, conductance, and FTIR spectra were used to identify mixed ligand complexes. Its (ML_13ph) mixed ligand complexes [$M= Co(II), Ni(II), Cu(II), Zn(II),$ and $Cd(II)$; (H_1L_1) = β -enaminone ligand= L_1 and (3ph) = 3-aminophenol= L_2]. The results demonstrate that the complexes are produced with a molar ratio of $M: L_1:L_2$ (1:1:1). To generate the appropriate complex, a tetradentate β -enaminone ligand with N_3O donor atoms is coordinated to $Co(II), Ni(II), Cu(II), Zn(II),$ and $Cd(II)$ ions. The synthesized ligand and its mixed ligand complexes have been tested against various pathogenic fungi and bacteria for antifungal and antibacterial activities. In this case, when compared with conventional antibiotic ciprofloxacin, the biological activity regarding such compounds was good.

Keywords: 3-aminophenol, Biological activity, Mixed ligand complexes, Octahedral.

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INTRODUCTION

The use of β -enaminone derivatives as synthons for synthesizing diverse biologically active compounds, including antibacterial, anti-epileptic, anticonvulsant, anti-inflammatory, anti-tumor, and other therapeutic agents is essential.¹⁻⁸ As a result, there is a lot of interest in the synthesis of this type of compounds. Many catalysts have used direct condensation of the amines with β -dicarbonyl compounds as a suitable synthesis method to produce β -enaminones.⁹ Since it is a significant organic intermediate, enaminones are utilized in synthesizing many heterocyclic and biological activity analogs, as well as in pharmaceutical research. With regard to coordination chemistry, enaminones have been thought to be effective chelating ligands for transition metals.¹⁰⁻¹³ The biological characteristics of 5,5-dimethyl-1,3-cyclohexanedione (Dimedone) and its derivatives include anti-cancer inorganic, anti-histaminic, antioxidant, and anti-coagulant. Its usage in green organic processes is one of its principal uses. Also, found in macrocyclic metal complexes, acridine-based compounds, and tetrahydro quinolone diones, quinazoline derivatives, xanthenes, and substituted antimicrobial agents.¹⁴⁻¹⁶ Polydentate or

bidentate ligands comprise a minimum of two distinct forms of chemical functional groups that are able to bind to metal atoms. The development regarding such ligands is gaining popularity at the moment because the various characteristics related to every donor atom confer distinct reactivity to their metal complexes.¹⁷ Mixed ligand complexes are biologically significant because they are often more efficient compared to free ligands.¹⁸ Concerning biological systems, the stability of mixed chelates is critical since various toxicological and metabolic activities depend on them. The stability of metal-ligand complexes has been linked to their antimicrobial activities in numerous studies.^{19,20} In addition, the mixed ligand complexes are useful for simulating metal ion roles, detoxification mechanisms, and drug design. New mixed ligand complexes have been investigated regularly to obtain biologically active compounds.²¹ In this work, $Co(II), Ni(II), Cu(II), Zn(II),$ and $Cd(II)$ mixed ligand complexes of ligand [H_1L_1] and 3-aminophenol were attempted to synthesize. Spectroscopic approaches were used for characterizing all of the complexes, and their biological activity was investigated.

*Author for Correspondence: emanchem12@gmail.com

EXPERIMENTAL

Materials and Methods

Every utilized chemical has been of an analytical grade and utilized with no additional purifications. Reagents have been utilized with no additional purifications as well. The FTIR spectra has been evaluated as (KBr disc) with the use of the "Shimadzu FTIR-8400-S", FTIR spectro-photometer. The $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ have been performed with the use of the Bruker 400MHz NMR spectrophotometer. Mass spectral measurement has been achieved on Finnigan MAT LCQTM mass spectrometer. Electronic spectra have been recorded in the dimethylsulfoxide (DMSO) on "Shimadzu UV-visible160 A UV-Vis. Spectrophotometer". Elemental micro-analyses (CHN) have been carried out with the use of the Leco932 US Elemental Analyzer. Atomic absorption has been evaluated with the use of the "Varian-AA775 Atomic Absorption spectrophotometer". The chloride has been determined using the potentiometer titration approach on a (686Titro processor-665 Dosimat-Metrohm). The evaluations of the conductivity have been carried out in the DMSO for 10^{-3} M of the complexes with the use of the (Philips PW9526 Digital Conductivity meter) at the room temperature. Magnetic moment (μ_{eff} BM) for prepared complexes has been measured at the room's temperature with the use of the BM. Ultimately, the melting points have been obtained through the use of the "Stuart Melting Point Apparatus."

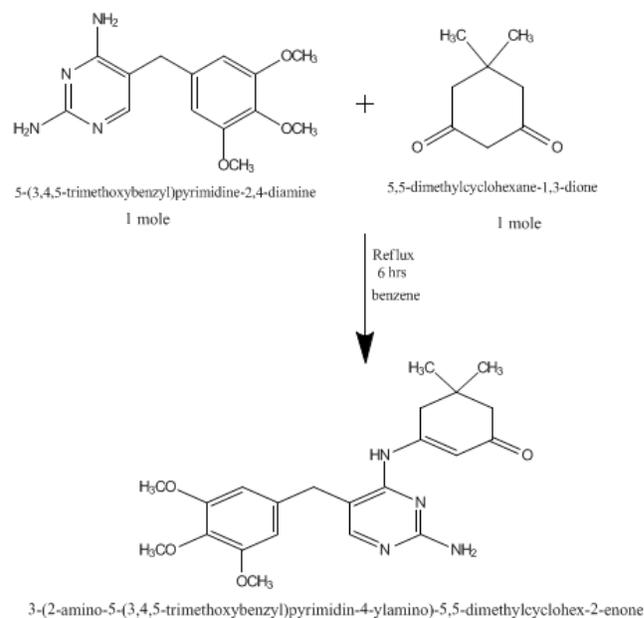
Synthesis of ligand (H_1L_1)

A 5,5-di-methylcyclohexane-1,3-dione (0.21g, 1mmol) solution in dry benzene (10ml) has been added slowly to 5-(3,4,5-trimethoxybenzyl) pyrimidine-2,4-diamine (0.25g, 1mmol) solution in dry benzene (10ml). Allowing the mix to stir continually till it has been entirely dissolved has resulted in a light-yellow solution. The solution was refluxed for 6hrs till a light-yellow precipitate developed, and the solution was monitored using total leukocyte count (TLC). Also, the reaction mix has been allowed to cool to lab temperature

before being filtered for obtaining a light-yellow product which has been isolated as well as washed many times with benzene before being allowed to dry to provide a yellow precipitate. Yield (63%), weight (0.223 gm), m.p (170-172) $^\circ\text{C}$, Scheme 1 depicts the ligand synthesis method, Table 1 depicts certain physical parameters and micro-analysis of (H_1L_1) and its complexes findings.

Synthesis of Mixed Ligand Metal Complexes

For 10 minutes, the metal solution of $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ (0.118 g, 1 mmole) in 10 mL of ethanol was stirred. The metal solution contains the ligand solution (0.25 g, 1 mmole) in 10 mL of ethanol. Lastly, after adjusting the pH to (9-8) with a few drops of KOH solution, a solution of 3-aminophenol (0.054 g, 1 mmole) in 10 mL of the ethanol was added to the above metal



Scheme 1: Synthesis route of ligand (H_1L_1)

Table 1: The micro-analysis of results and a few physical characteristics for ligand(H_1L_1) and the prepared complexes

Compounds	M. wt g.mol^{-1}	MP ($^\circ\text{C}$)	Colour	Yield %	Elemental analysis found (Calc.)				Molar conductivity (S.cm^2 molar^{-1})
					C	H	N	M	
H_1L_1	412.48	(170-172)	Light yellow	63	64.54 (64.06)	6.53 (6.84)	13.19 (13.58)	-	-
$[\text{Co}(\text{L}_1)(3\text{ph})]$	578.53	(216-218)	Light green	66	58.21 (58.13)	5.69 (5.75)	12.20 (12.11)	10.03 (10.19)	11.42
$[\text{Ni}(\text{L}_1)(3\text{ph})]$	578.29	(192-194)	Light green	69	58.33 (58.15)	7.51 (5.75)	12.01 (12.11)	9.90 (10.15)	6.95
$[\text{Cu}(\text{L}_1)(3\text{ph})]$	583.14	(192-194)	Dark nutty	71	57.24 (57.67)	5.63 (5.70)	13.19 (12.01)	10.42 (10.90)	11.88
$[\text{Zn}(\text{L}_1)(3\text{ph})]$	585.00	(164-168)	Pale yellow	72	57.22 (57.49)	5.31 (5.69)	11.19 (11.97)	10.80 (11.18)	7.05
$[\text{Cd}(\text{L}_1)(3\text{ph})]$	632.00	(204-206)	Dark yellow	65	53.02 (53.21)	5.11 (5.26)	11.19 (11.08)	17.10 (17.79)	9.75

solution. The mix was then heated in reflux for two hours. The mix was filtered after that, and the precipitate was rinsed with excess ethanol before being dried at room temperature for 24 hours. The result was a blue solid. Weight (0.33 g), m.p. (216–218°C), yield (66%) For the preparation of Cu(II), Ni(I), Zn(II), and Cd(II) complexes, a procedure comparable to that used for the preparation of (Co) complex was used. The physical characteristics and elemental mixed ligand analysis of complexes are given in Table 1. Figure 1 shows the proposed structures of complexes. Table 1 lists some physico-chemical ligand (H_1L_1) and prepared complexes characteristics. Elemental analyses have been in agreement with a formula of the ligand(H_1L_1) and the prepared complexes that are listed in Table 1.

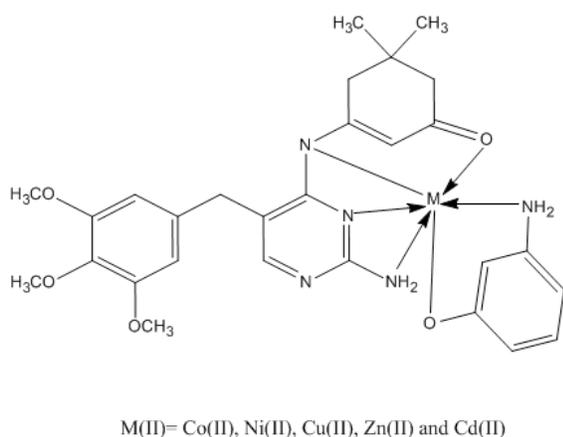


Figure 1: Proposed structures of complexes

RESULTS AND DISCUSSION

FTIR Spectra

The free ligands' FTIR spectra reveal distinct bands because of the functional groups $\nu(O-H)$, $\nu(NH_2)$, $\nu(C=O)_{di}$, $\nu(N-H)$, and $\nu(C=N)_{ring}$. Table 2, and Figures 2 and 3 show that the IR spectra related to the mixed ligand complexes showed bands with suitable shifts because of the complex formation. The lack of a peak around 3290 cm^{-1} in all complexes shows that (N-H) group was deprotonated during complex formation.²² For complexes, the $\nu(C=O)_{di}$ vibration at 1633 cm^{-1} in the free ligand (H_1L_1) is shifted and identified around ($1681\text{-}1662\text{ cm}^{-1}$), specifying coordination of the ligand's oxygen atom to metal atom,²³ and the $\nu(C=N)_{ring}$ for free ligand vibration at (1591 cm^{-1}) is shifted and indicated around ($1643\text{-}1597\text{ cm}^{-1}$), specifying coordination of ligand's nitrogen atom. Also,

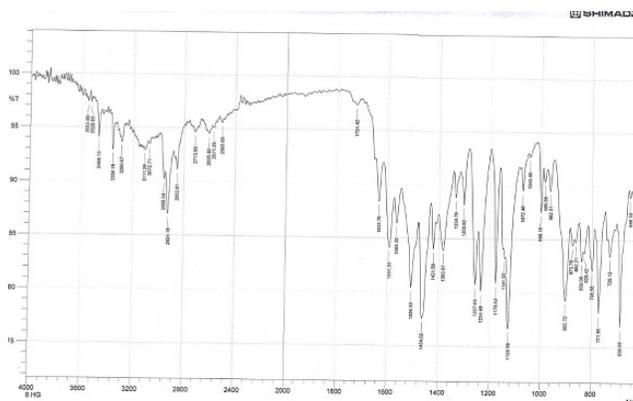


Figure 2: FTIR Spectrum of ligand (H_1L_1)

Table 2: FTIR data of ligands (H_1L_1) and (3ph)(cm^{-1}) and their complexes

Compounds	$\nu(NH_2)$	$\nu(N-H)$	$\nu(O-H)$	$\nu(C=O)_{di}$	$\nu(C-H)$ Arom.	$\nu(C-H)$ alph.	$\nu(C=N)$ ring	$\nu(M-N)$	$\nu(M-O)$
H_1L_1	3358 3468	3290	-	1633	3072	2955 2924 2852	1591	-	-
3ph	3294 3460	-	3535	-	3028 3128	-	-	-	-
$[Co(L_1)(3ph)]$	3321 3406	-	-	1678	3163	2870	1643	497 482 466	447 428
$[Ni(L_1)(3ph)]$	3321 3406	-	-	1681	3159	2958	1643	586 509 462	435 401
$[Cu(L_1)(3ph)]$	3298 3206	-	-	1662	3143	2958	1627	505 474 462	447 401
$[Zn(L_1)(3ph)]$	3302 overlap	-	-	1662	3086	2954	1597	586 528 493	451 405
$[Cd(L_1)(3ph)]$	3302 overlap	-	-	1662	3086	2954	1597	586 528 492	451 401

the spectra of ligand (3ph) show a band at (3535cm^{-1}) that could be due to the $\nu(\text{OH})$ group and a strong band at (1257cm^{-1}) that could be due to the $\nu(\text{C}-\text{O})$ stretching vibration, as previously reported for such ligand type (3ph). The vibrations of $\nu(\text{C}-\text{O})$ are altered to higher frequency values, implying that metal ion coordination takes place through the phenolic meta-oxygen atom, as has been shown for all of the transition metal complexes of *m*-hydroxy (3ph).²⁵ The observation resulted in the conclusion which complexes are formed through the deprotonation of the $\nu(\text{OH})$ group of the (3ph) moiety, implying that the hydroxyl proton is displaced via $\text{M}(\text{II})$ ion, resulting in covalent $\nu(\text{M}-\text{O})$ bonding with the ligand (3ph).²⁶ They should have $\nu(\text{NH}_2)$ in the range of ($3468-3294\text{cm}^{-1}$) at the isoelectric point.²⁷ The IR spectra regarding the present complexes revealed distinctive bands in the range of ($3406-3206\text{cm}^{-1}$), which are lower than those of the free $\nu(\text{NH}_2)$. As a result, it may be deduced that the ligands' nitrogen (H_1L_1) and (3ph) are involved in coordination. At lower frequencies, the complexes showed new bands about ($586-462\text{cm}^{-1}$) and ($451-401\text{cm}^{-1}$),

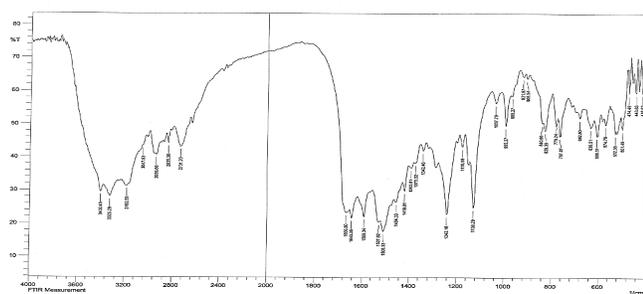
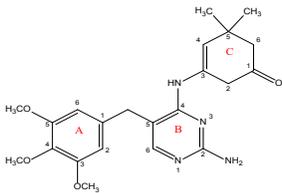


Figure 3: FTIR spectrum of Cu complex

Table 3: ^{13}C -NMR data for ligand evaluated in DMSO-d_6 and chemical shift in ppm

Compounds	Chemical shifts (s) ppm	Assignments
	195.91	(C=O)
	172.81	(C_3 -NH)in ring C
	162.07	(C_2 - NH_2) in ring B
	158.52	(C_4, C_6)in ring B
	153.17	(C_3, C_5)in ring A
	136.11	C_6 in ring A)
	130.33	C_1 in ring A)
	105.86	C_5 in ring B)
	103.74	(C_2, C_6)in ring A
	101.42	C_2 in ring C)
	60.43	OCH_3
	56.27	$2(\text{OCH}_3)$
	50.62	(C_6) in ring C
	42.59	(C_4) in ring C
	(40.48- 39.48)	DMSO-d_6 solvent
	33.40	CH_2 alph.
	32.71	(C_5) in ring C
	28.41	2CH_3

(H_1L_1)



respectively, which are ascribed to $\nu(\text{M}-\text{N})$ and $\nu(\text{M}-\text{O})$ vibration modes.²⁶ Furthermore, the $^1\text{H}, ^{13}\text{C}$ -NMR spectrum in DMSO-d_6 revealed signals corresponding to different carbon and proton, confirming the structure of the ligand (H_1L_1) as indicated in Tables 3 and 4.

NMR Spectra

$^1\text{H}, ^{13}\text{C}$ -NMR spectrums, and the assignments for ligand (H_1L_1) are exhibited in Tables 4 and 5 and Figures 4 and 5.

An EI-Mass spectrum of ligand (H_1L_1)

The electrospray (+) mass spectrum of (H_1L_1) exhibits a parent ion peak at ($M/Z = 412.49$) that agrees with $[\text{M}^+]$; other fragments' relative abundance as well as a pattern of fragmentation can be seen in Table 5, Figure 6.

Electronic Spectra, Magnetic Moments, and Conductivity Measurement

Table 1 shows the molar conductance values related to mixed ligand complexes in DMSO with a standard reference with the use of $1 \times 10^{-3} \text{ mol}^{-1}$ solutions at room temperature, which

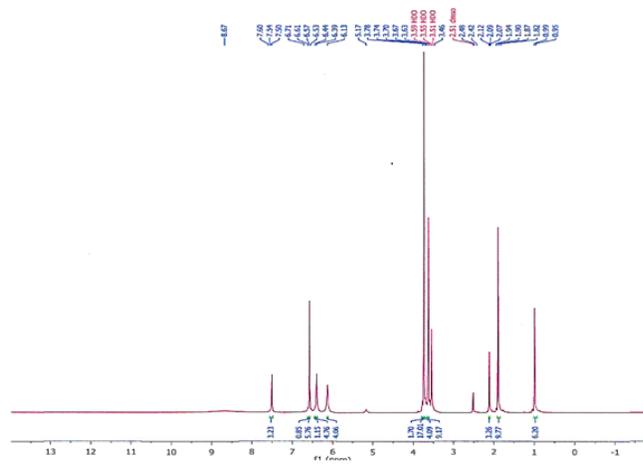


Figure 4: ^1H -NMR ligand (H_1L_1) spectra

Table 4: ^1H -NMR data for ligand evaluated in DMSO-d_6 and chemical shift in ppm

Compounds	Chemical shift(s)ppm	Assignments
	8.67	(s,1H,NH)for (NH) of enaminone
	6.71	(m,2H, NH_2)
	(6.61,6.71)	(s,2H,Ar-H)
	6.70	(s,1H,CH in ring B)
	5.17	(m,2H, CH_2 in ring C)
	3.78	(m,2H, CH_2)
	3.63	((m,9H, OCH_3)
	2.51	DMSO-d_6 solvent
	2.42	(s,1H, CH_2 in ring C)
	2.21	(s,1H, CH_2 in ring C)
	0.99	(m.6H, CH_3)

s=singlate, m=multiplate

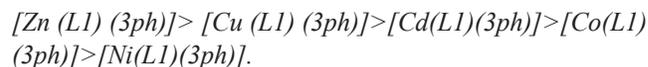
transition, respectively of a Co-complex with distorted octahedral geometry. The magnetic moment (μ_{eff}) for such a complex was 4.5 BM for each Co ion.³⁰ The absorption spectrum regarding nickel complex showed a band at about 10121 cm^{-1} attributed to (${}^3A_2g \rightarrow {}^3T_2g$) transition of a Ni complex with distorted octahedral geometry. The magnetic moment (μ_{eff}) for such a complex was 3.5 BM for each Ni ion.³¹ The absorption spectrum regarding copper complex showed a band at about 11737 cm^{-1} attributed to (${}^2Eg \rightarrow {}^3T_2g$) transition of a Cu complex with distorted octahedral geometry. The magnetic moment (μ_{eff}) for such a complex was 1.73 BM for each Cu ion.³²

The absorption spectrums related to Zn and Cd complexes, showing absorption bands at about 22522 and 22624 cm^{-1} as a result of the (charge transfer) transition, respectively of Zn and Cd complexes with distorted octahedral geometry, which were found to be diamagnetic as expected for d^{10} system, where d-d transitions are excluded.^{33,34}

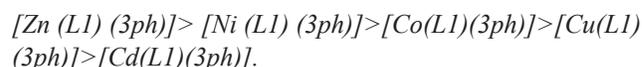
Biological Activity Studies

The biological activity related to ligand [H_1L_1] as well as its complexes have been screened against four bacteria types,

(*Bacillus subtilis*, *S. Aureus*) gram-positive bacteria and (*E. coli*, *K. pneumonia*) gram-negative bacteria and it also evaluation of the antifungal activities by *Rhizosporim*.³⁵⁻³⁷ Ciprofloxacin was used in the biological study as a standard drug. Those types were utilized for determining the inhibiting impact on the growth of such organisms. The antibacterial activity of mixed (H_1L_1) complexes showed the order:



The antifungal activity of mixed (H_1L_1) complexes showed the order:



Zinc complex showed more antibacterial activity than other complexes against (*Staphylococcus Aureus*, *Bacillus subtilis*) (Gram-positive Bacteria) and (*K. Pneumonia*, *E. Coli*) (Gram-Negative Bacteria), and it also antifungal activity by *Rhizosporim*. The data on the biological activity of synthesized compounds are provided in the Table 7 and reported in Figures 7 and 8.

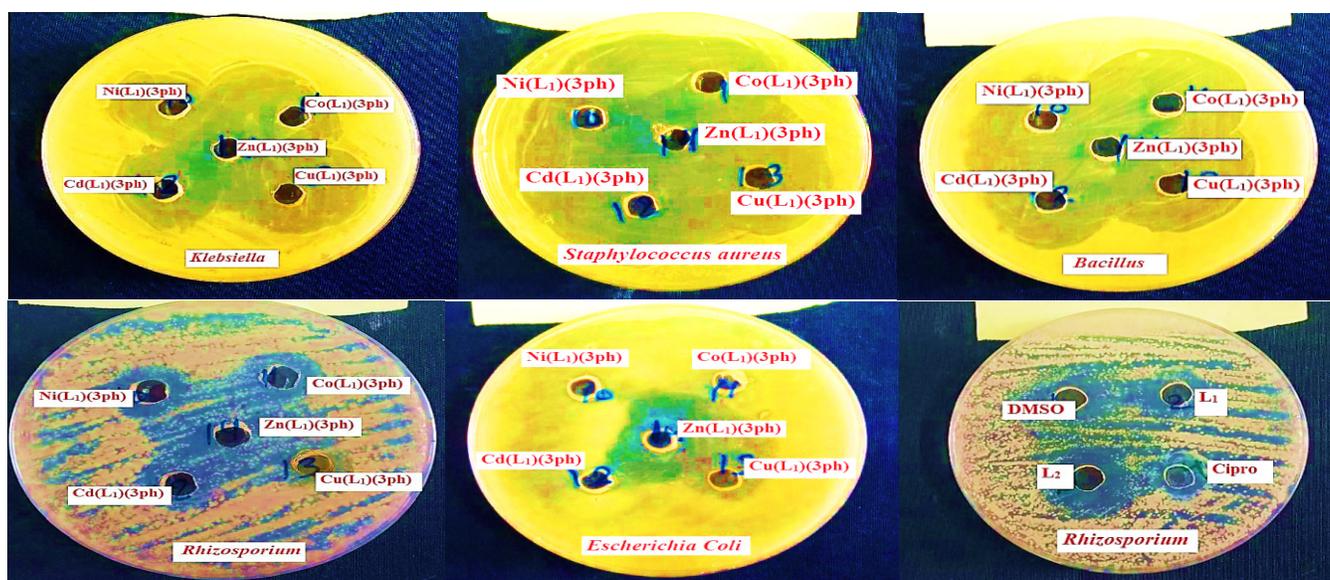


Figure 7: The effects of antibacterial activity and antifungal activity of the ligand and their complexes

Table 7: Diameter of the Inhibition Circle in (mm) for biological activity after 24hr. Incubation at 37 °C for the compounds

Compounds	Gram-negative (G-)		Gram-negative(G+)		Rhizosporim
	<i>Staphylococcus Aureus</i> (G+)	<i>Bacillus ubtilis</i> (G+)	<i>Klebsiella Pneumonia</i> (G-)	<i>Escherichia Coli</i> (G -)	
DMSO	-	-	-	-	-
Cipro	40	40	44	43	34
(H_1L_1)	13	30	28	35	14
[Co(L ₁)(3ph)]	30	35	32	-	17
[Ni(L ₁)(3ph)]	33	30	25	11	19
[Cu(L ₁)(3ph)]	33	40	35	20	16
[Zn(L ₁)(3ph)]	48	48	40	22	20
[Cd(L ₁)(3ph)]	34	30	30	13	15

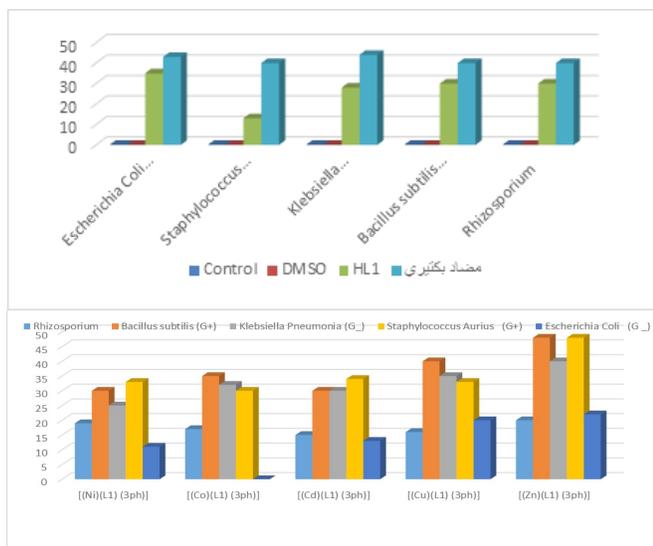


Figure 8: Biological activity for ligand and mixed ligand complexes

CONCLUSION

Microanalysis, FTIR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, and mass spectra all validated the structure of the ligand (H_1L_1). Spectroscopic approaches and other research were used to efficiently synthesize and characterize a new series of mixed ligand complexes. Also, it was discovered that when the ligand was in contact with metal ions, it behaved naturally. Around the metal center, all of the complexes had octahedral geometry. The produced metal complexes have been non-electrolytes in nature, according to spectroscopic studies utilized for verifying the chemical composition of the products (along with the geometry of the complexes and molar conductance). Based on the findings above, the synthesized complexes have significantly higher biological activity against microorganisms compared to the free ligand.

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