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Synthesis and Characterization of Vanillin Schiff Base Complexes with Paracetamol and Divalent Metal Ions: Antimicrobial Activity Study

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Antimicrobial, Complexes, Schiff base, Vanillin, Paracetamol, physiocochemical tools.

ABSTRACT

The work presented in this research deals with the synthesis and physico-chemical characterization of Schiff base ligand (HL) created from vanillin with p-aminoazobenzene containing (N, O) as donor atoms. The synthesis ligand (HL) was characterized by the CHN, (FT-IR), (UV-Vis), (^{1}H,^{13}C-NMR) and mass spectroscopy, in addition the melting point were used to characterize the Schiff base. A series of mixed metal ligands complexes were formed by using Schiff base ligand (HL) as primary ligand and Paracetamol (PAR) as a secondary ligand with five divalent metal ions; Ni, Cu, Zn, Cd(II) and Hg. The formed complexes were characterized by using some analytical and standard spectroscopic methods; molar conductivity, magnetic susceptibility, FT-IR, electronic and absorption atomic spectroscopy. Via the magnetic susceptibility and (UV-Vis) measurements supported by molar conductivity suggested an octahedral geometry for all the complexes. The antimicrobial activity of the formed complexes and ligands were tested against bacteria Staphylococcus aureus and *E.Coli*, and antifungus *Candidalbica*.

Introduction

agents due to their ability to coordinate with biologically active ligands [1-3]. The interaction between metal ions and pharmaceutical ligands significantly influences the pharmacological behavior of drugs, as metal ions can participate in vital biological processes by binding to enzymes, proteins, and nucleic acids within living systems [4-7]. Such coordination often enhances the stability, solubility, and bioavailability of the resulting metallodrug, leading to improved therapeutic efficacy and reduced side effects [8]. Among commonly studied ligands, paracetamol—also known as acetaminophen (Fig. 1)—is a widely used analgesic and antipyretic drug employed in the treatment of fever and various types of pain, including post-surgical and cancer-related pain [9, 10]. It is also a principal component in numerous formulations for treating influenza and the common cold [11-13]. The molecular structure of paracetamol enables it to coordinate with transition metal ions, forming complexes that may exhibit enhanced biological activity compared to the parent compound. Schiff bases, characterized by the azomethine (-C=N-) functional group, have attracted substantial interest due to their remarkable versatility and wide range of biological and industrial applications [14]. These compounds are known for their antimicrobial, anticancer, and antioxidant activities and play important roles in catalysis, coordination chemistry, and pharmaceutical research [15, 16]. Schiff bases derived from aromatic aldehydes such as vanillin are particularly significant, as they provide an oxygen and nitrogen donor system capable of forming stable chelates with transition metals, thereby modulating the physicochemical and biological properties of the resulting complexes. The development of metallo-Schiff base complexes has provided a promising platform for the design of new antibacterial and antifungal agents. Chelating ligands containing donor atoms such as nitrogen and oxygen exhibit a broad spectrum of biological activity, attributed to their ability to form coordinate bonds with various transition metal ions [17, 18]. Mixed-ligand complexes, involving Schiff bases as primary ligands and biologically relevant molecules such as nicotinamide as secondary ligands, have been extensively investigated for their structural diversity and therapeutic potential [19]. For instance, complexes of Cr(III), Fe(III), Co(II), Ni(II), Cu(II), Cd(II), and Hg(II) with Schiff base and nicotinamide have been synthesized and characterized using physicochemical and computational tools, demonstrating notable antibacterial properties supported by DFT calculations and molecular docking analyses [20-22]. In light of these findings, the present study aims to synthesize and characterize coordination compounds derived from vanillin-based Schiff bases and paracetamol with selected transition metal ions. The physicochemical properties of the complexes were investigated through spectroscopic and analytical techniques, and their antimicrobial activities were evaluated against selected bacterial and fungal strains [23]. This study seeks to elucidate the relationship between metal–ligand coordination and biological activity, contributing to the design of new potential antimicrobial agents [24, 25].

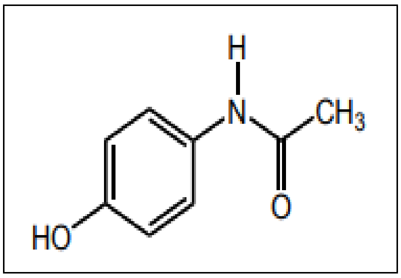


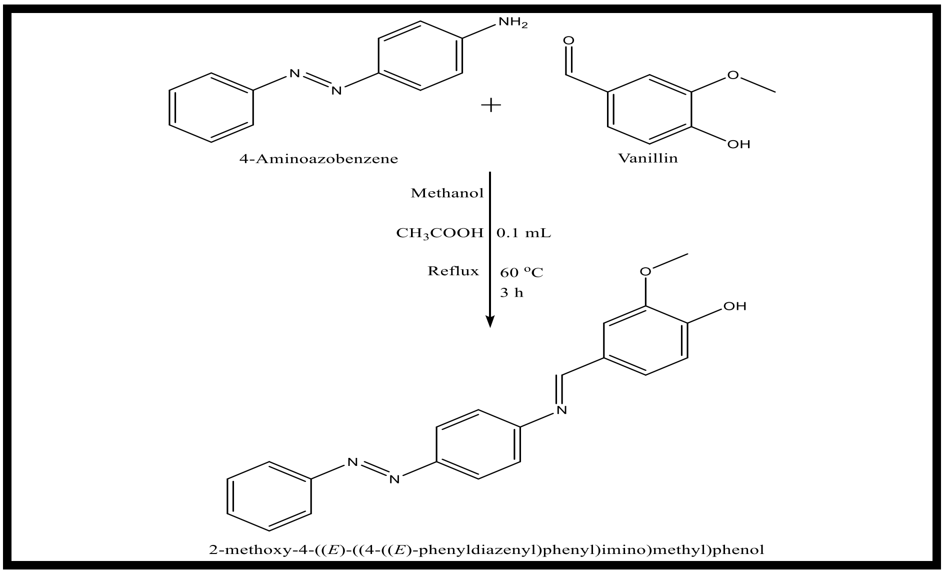
Figure 1. Structure of Paracetamol

Materials and Methods

All the chemicals were obtained from Sigma–or BDH and utilized without assistance purification. Vanillin, p-aminoazobenzene, DMSO and CH_3OH were Analar grade (BDH). FT-IR spectra were recorded in 400–4000cm^{-1} region with 8300- Shimadzu spectrophotometer. Metal determination with spectrophotometer (A.A-160). The mass spectrum was recorded by MS Model: 5973 spectrometer, Elemental microanalysis CHN- 2400 elemental analyzer. proton and carbon NMR spectra were recorded for (HL) in DMSO solvent, by using a device (INOVA-500-MHz) in δ (ppm). UV spectra (10^{-3}M) by (Shimadzu U.V160-A), Λm 10^{-3}mol/L in DMSO solvent were reached by Ino.Lab.720 digital conductivity. Magnetic susceptibility of the mixed ligand complexes was measured using a Sherwood Scientific auto magnetic susceptibility balance at 25 ℃ [26-28].

Synthesis of Schiff base

In 100 mL flask, the Schiff base ligand (HL) was prepared by condensation of vanillin (3mmol, 0.456 gm) was dissolved in (15 mL) methanol. After that p-aminoazobenzene (3 mmol, 0.591 gm) was dissolved in (25 mL) methanol and added to the mixture followed by addition of acetic acid (1 mL) with constant stirring. The reaction mixture was refluxed for 3 h at 60 C° until the completion of reaction and progress of reaction were monitored by TLC Scheme 1. The reddish grey color precipitated compound was filtered, washed with hot methanol and recrystallized to get a pure sample and dried in $CaCl_2$ [29, 30].



Scheme 1. Synthesis route of Schiff base (HL)

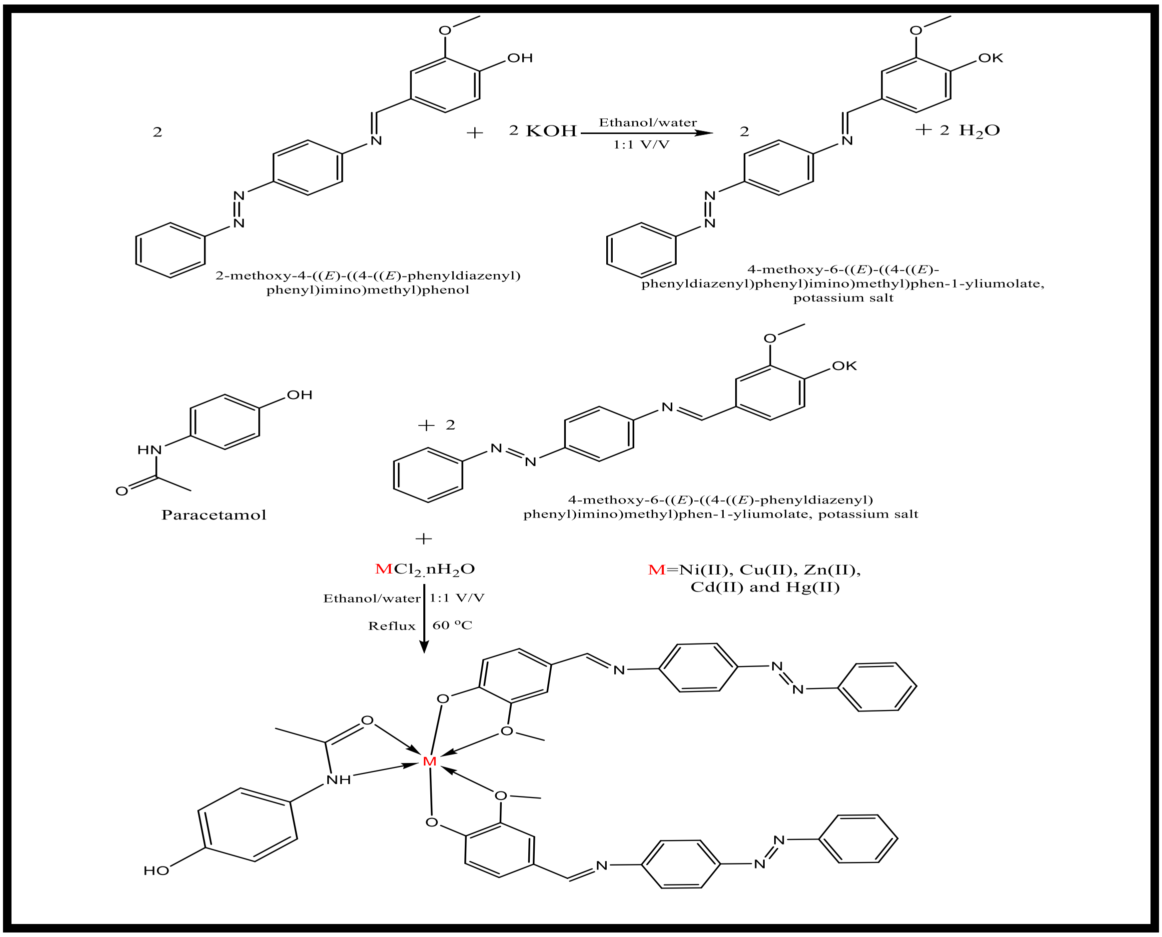
Synthesis of the mixed complexes of Schiff base and paracetamol

Synthesis of the mixed complexes (1–5) were syntheses by reacting the (L) and paracetamol with the Ni (II) (1), Cu(II) (2), Zn(II) (3), Cd(II) (4) and Hg(II) (5) ions as per the literature method (10), as shown in Scheme 2.

RESULTS and Discussion

Characterization of the Schiff base (HL)

The yield of the synthesized (HL), was 84% (solid, color: reddish grey, m.p. 160-162°C). The formula weights, elemental analysis of CHN data and melting points are given in (Table 1). FTIR (KBr, cm^{-1}) Fig. 2, 3375 ν (O–H), 1604 ν (C=N), 1535 ν (C=C), 1022 *ν* (C-O-C). 1145 *ν* (OCH_3) (11,12). UV-Vis, 10^{-3} mol L^{-1} in DMSO, λ max nm: 281, 345 and 392 assigned to ($\pi\rightarrow\pi^*$), ($n\rightarrow\pi^*$) and ($n\rightarrow\pi^*$) transitions respectively Fig. 3. ^{1}H NMR (ppm *d6*-DMSO, 400MHz), 9.89 ppm δ (s, 1H, OH) phenol, displays 8.56 ppm δ (s, 1H, CgH), 7.97 and 7.95 ppm δ (d, 1H, CfH), 7.91 and 7.89 ppm δ (d, 1H, CeH), a multiple in the region δ (m, 1H, Ca,Cb,Cc,Ck,Cm and Ch-H) 7.63-6.92 ppm corresponding to aromatic protons , Besides the above peaks, displays 3.87 ppm δ (s, 3H, CH_3), Fig. 4 (13,14). The ^{13}C-NMR peaks for the azomethine carbon atom of the coordinated Schiff base ligand were respectively observed at δ=161.84 ppm, and other signals are listed in Fig. 5.



Scheme 2. The synthesis route of HL and PAR complexes

Table 1. Some physical properties and elemental analysis of the (HL)

Comp.	M.wt g/mol	Color	M.P °C	Found% (calcu)%		
				C	H	N
HL	331.38	Reddish grey	160-162	72.33 (72.49)	4.93 (5.17)	12.49 (12.68)

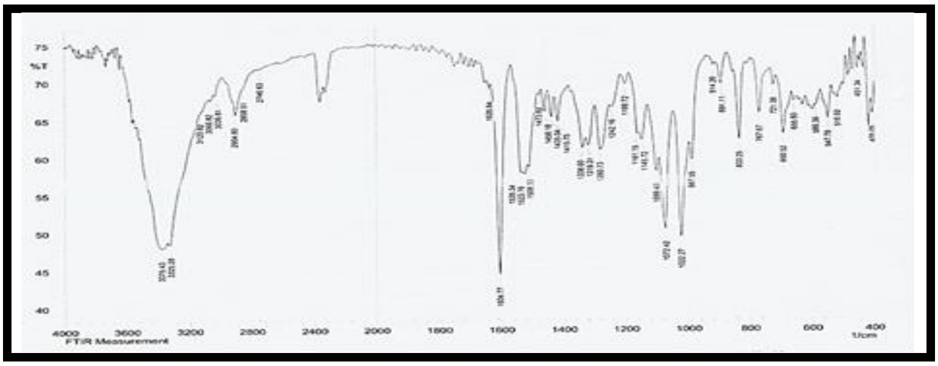
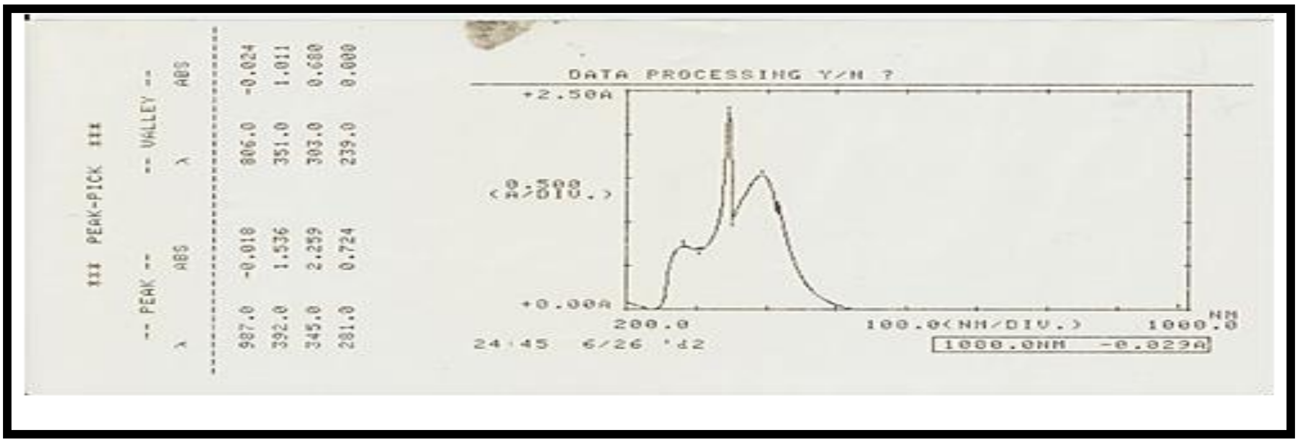


Figure 2. FT-IR spectrum of (HL)



PEAK-PICK

-- PEAK -- λ	ABS	-- VALLEY -- λ	ABS
987.0	-0.018	806.0	-0.024
392.0	1.536	351.0	1.011
345.0	2.259	303.0	0.680
281.0	0.724	239.0	0.000

Figure 3. Electronic spectrum of (HL)

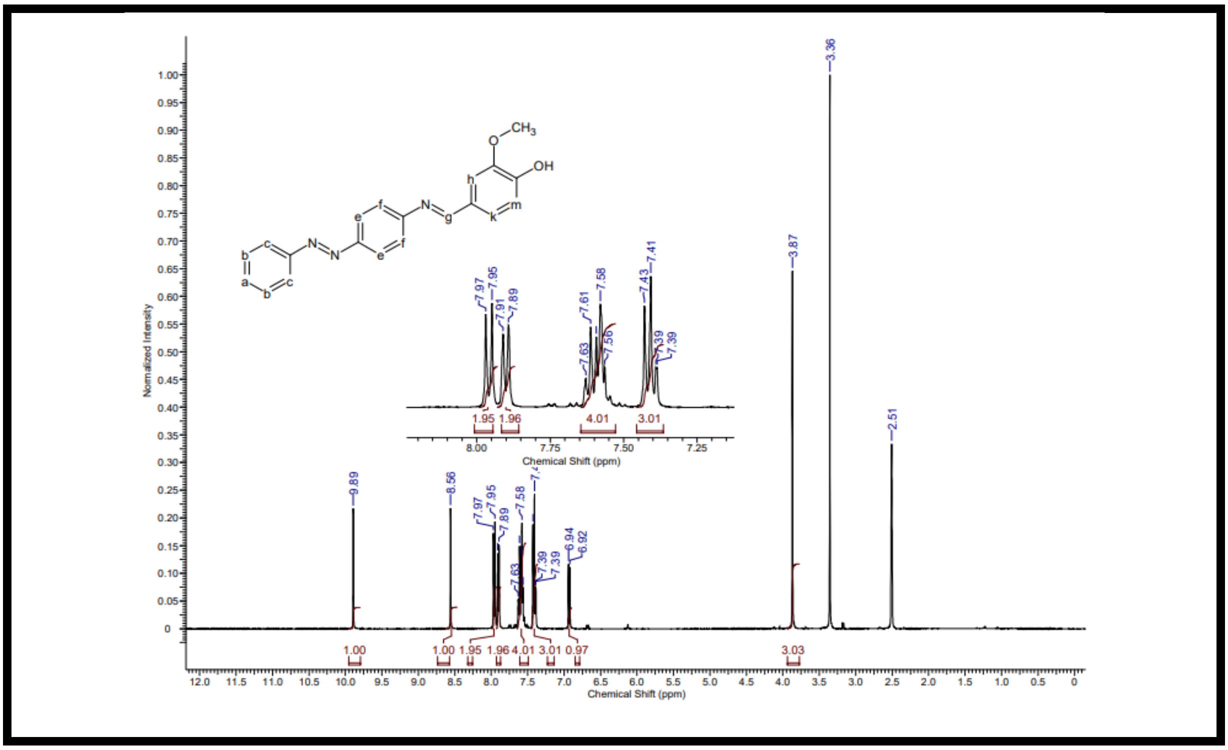


Figure 4. ¹H-NMR spectrum of the Schiff base ligand (HL)

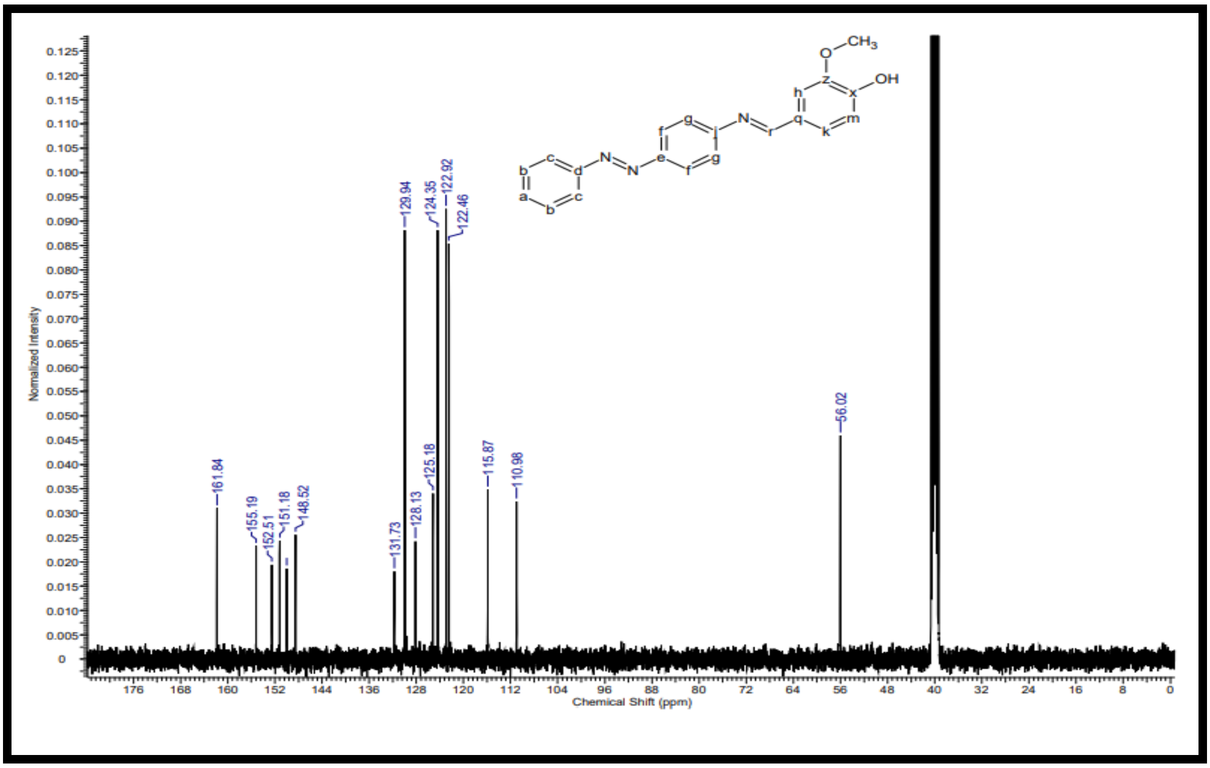


Figure 5. ^{13}C-NMR spectrum of the Schiff base ligand (HL)

The mass spectrum of HL, Fig. 6 showed the parent ion peak at $[C_{20}H_{17}N_3O_2]^{\bullet+}$ = 331.37 (m/z) which is consistent with the molecular weight of the Schiff base. The others fragments and their relative abundances and fragmentation pathways data shown in (Scheme 3) strongly confirmed the formation and the structure of Schiff base ligand [31].

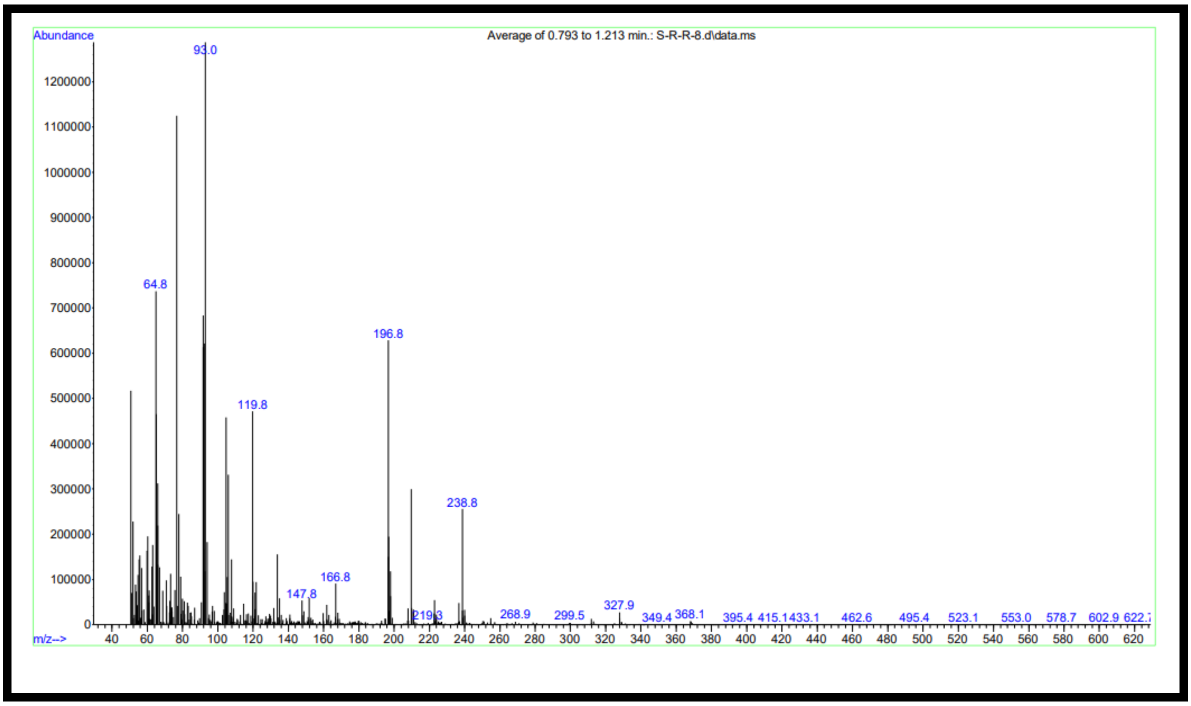
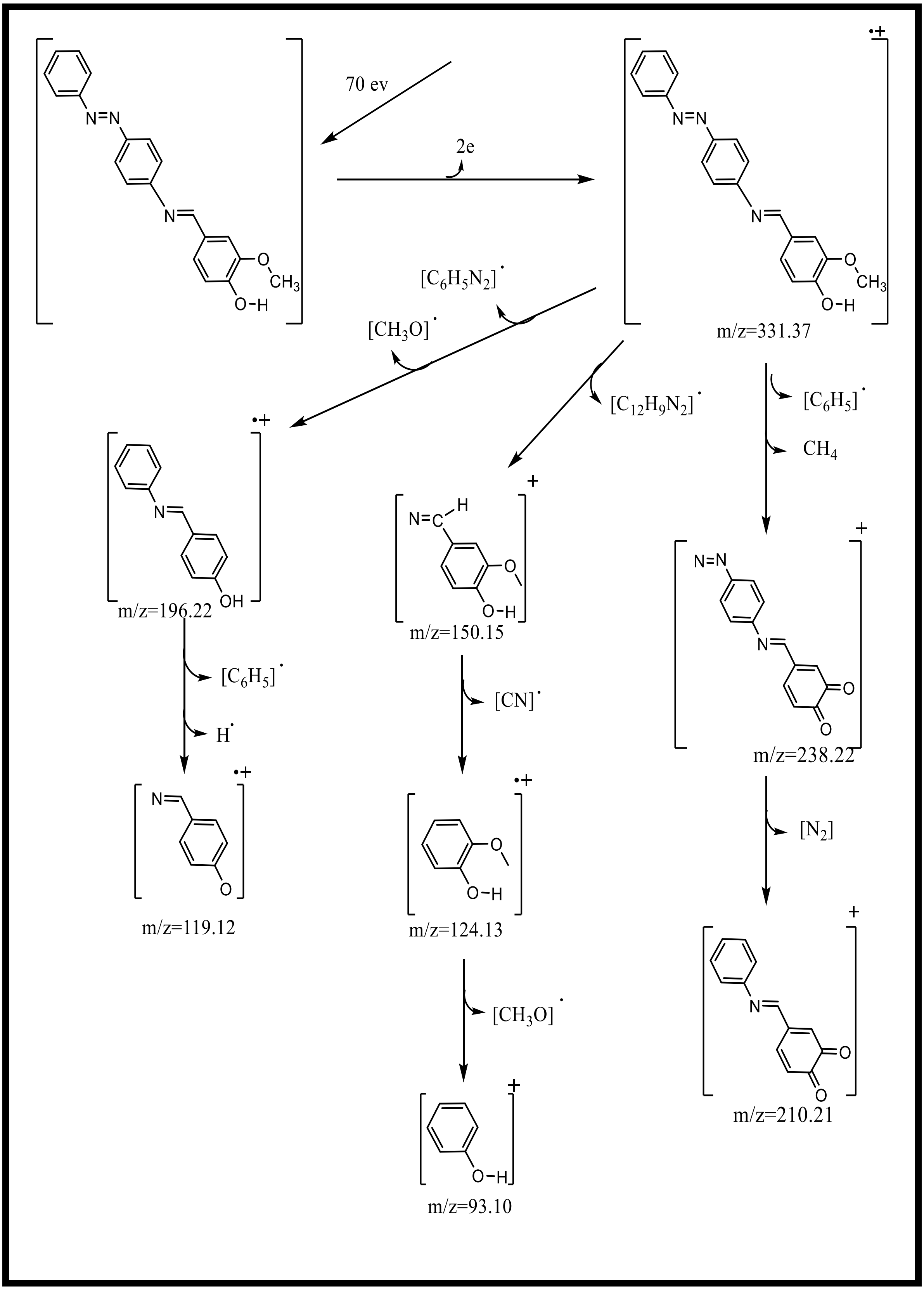


Figure 6. Mass Spectrum of HL



Scheme 3. Proposed mass spectral fragmentation pattern of the Schiff base (HL)

Characterization of [L-Metal-PAR] Complexes

All the complexes were destined reacting the metal chlorides $MCl_2.nH_2O$, and the ligands by utilizing 1:2:1 mole ratio, i.e., metal: two moles of L: PAR. The synthesis of $[M(L)_2(PAR)]$ complexes may be represented as shown in the overall equation below:

$$2(HL) + 2KOH \rightarrow 2(LK) + 2H_2O$$

$MCl_2.nH_2O+2L+(PAR) \rightarrow [M(L)_2(PAR)] +2KCl+nH_2O$ Where;

L = Schiff base ($C_{20}H_{17}N_3O_2$) accrued from condensation of vanillin and p-aminoazobenzene as a primary ligand, PAR as a secondary ligand.

In Table 2, the melting points (m.p) of the complexes were higher than that of the ligands, demonstrating that the complexes are steadier than the ligands thermally. The solubility of the complexes was examined in different solvents appeared that all complexes are dissolvable in all solvents. The test for chloride particle with $AgNO_3$ arrangement was negative (Nil%) demonstrating that there's no (Cl^-) outside to the coordination circle of the central metal. The calculated and exploratory values of metal percentage (M%) in each complex are in ensile agreement. The formula weights, atomic absorption spectroscopy, and melting points are given in (Table 2), The molar conductance Λm values for the complexes were found between 1.44–7.31(Ω^{-1} cm^2 mol^{-1}) in DMSO, which demonstrates their non-electrolytic nature (16).

Table 2. Some physical properties and metal% of the [L_2-Metal-PAR]

Comp.	Color	M.W	Yield %	m.p C°	M% (exp)
$[Ni(L)_2(PAR)]$	Dark brown	870.59	81	>250	6.74(6.59)
$[Cu(L)_2(PAR)]$	Light brown	875.44	84	>250	7.26(6.94)
$[Zn(L)_2(PAR)]$	Light brown	877.27	78	>250	7.45(7.1)
$[Cd(L)_2(PAR)]$	Brown	924.31	79	>250	12.16(12.38)
$[Hg(L)_2(PAR)]$	Brown	1012.48	84	>250	----

FTIR spectra

The important frequencies in cm^{-1} of $[M(L)_2(PAR)]$ complexes are shown in (Table 3). The band at 3325 and 3201 cm^{-1} stretching vibration is due to υ (–OH) hydroxyl group overlapping with υ(N–H) secondary amine stretching vibration in PAR. On complexation –N-H stretching at 3201 cm^{-1} was shifted to higher frequency in range 3224-3390 cm^{-1} were indicated metal chelated through the amine Nitrogen. The absorption bands at 516-578 cm^{-1} and 424-462 which assigned to ν (M-O) and ν (M-N) respectively (17).

The FT-IR spectra showed that the PAR acts as a bidentate ligand through N- and O-carbonyl atoms (18-22), and the Schiff base ligand (L) is coordinated to the metal ions as bidentate ligand through oxygen-($O-CH_3$) atom and Ionization of the hydroxyl group (23).

Table 3. The FT- IR spectral data of [M(L)$_2$(PAR)] complexes

comp.	O-H	N-H	C-H	C=O	C=N	C=C	N=N	M-O	M-N
[Ni(L)$_2$ (PAR)]	3360	3224	3034 2939	1640	1604	1577	1411	551	462
[Cu(L)$_2$ (PAR)]	3441	3336	3045 2920	1658	1593	1560	1411	516	451
[Zn(L)$_2$ (PAR)]	3533	3379	3062 2927	1640	1597	1592	1411	547	424
[Cd(L)$_2$ (PAR)]	3560	3387	3058 2908	1666	1604	1581	1411	551	432
[Hg(L)$_2$(PAR)]	3433	3390	3090 2981	1640	1604	1570	1411	578	459

Electronic spectra and magnetic moment

All the electronic spectra of the mixed PAR- Schiff base metal (II) complexes shown similar absorption spectra as the Schiff base which is either moved to the red or blue locale (Table 4).

The electronic spectrum for the paracetamol in DMSO solvent (10^{-3}M) was characterized by one absorption peak at 291nm (34364 cm^{-1}) (εmax= 2065 molar^{-1}cm^{-1}) assigned to ($\pi \rightarrow \pi^*$) intra-ligand transitions [32]. The observed magnetic value of Ni(II) complex was 3.88 µB, Cu(II) complex was 1.69 µB. which revealed an octahedral geometry(24), around the central metal ions. Zn(II), Cd(II) and Hg d^{10} electronic configuration complexes are diamagnetic nature [33].

The electronic spectrum of the [Ni(L)$_2$(PAR)] complex gave three bands at (270 nm, 37037 cm^{-1}) is due to ($\pi \rightarrow \pi^*$), second and third peaks, at (345 nm, 28985 cm^{-1}) and (416 nm, 24038 cm^{-1}) are due to charge transfer [34].

The electronic spectrum of [Cu(L)$_2$(PAR)] complex gave three bands at (270 nm, 37037 cm^{-1}) is due to ($\pi \rightarrow \pi^*$), second peak, at (416 nm, 24038 cm^{-1}) is due to charge transfer and third peak is due to (d-d) transition, $^2B_1g \rightarrow {}^2B_2g$ = (730 nm, 13698 cm^{-1}) respectively [35].

[Zn(L)$_2$(PAR)] complex gave three bands at (272 nm, 36764 cm^{-1}) is due to ($\pi \rightarrow \pi^*$), second and third peaks, at (305 nm, 32786 cm^{-1}) and (396 nm, 25252 cm^{-1}) are due to charge transfer [9].

[Cd(L)$_2$(PAR)] complex gave three bands at (276 nm, 36231 cm^{-1}) is due to ($\pi \rightarrow \pi^*$), second and third peaks, at (305 nm, 32786 cm^{-1}) and (393 nm, 25445 cm^{-1}) are due to charge transfer [36].

[Hg(L)$_2$(PAR)] complex gave two bands at (276 nm, 36231 cm^{-1}) is due to ($\pi \rightarrow \pi^*$), second peak, at (393 nm, 25445 cm^{-1}) are due to charge transfer [37].

An octahedral geometry was proposed for all complexes based on its unearthly information and explanatory conductance, which displayed coordination number six and may be defined as [M(L)$_2$(PAR)] *Fig.* 7.

Table 4. Electronic spectral data of the [M(L)$_2$(PAR)] complexes and (HL) ligand

comp.	nm	Є max L.mol^{-1}.cm^{-1}	υ' cm^{-1}	Assignments
HL ($C_{20}H_{17}N_3O_2$)	281	742	35587	$\pi \rightarrow \pi^*$
	345	2259	28985	$n \rightarrow \pi^*$
	392	1536	25510	$n \rightarrow \pi^*$
[Ni(L)$_2$(PAR)]	270	810	37037	$\pi \rightarrow \pi^*$
	345	1938	28985	Charge transfer
	416	1440	24038	Charge transfer
[Cu(L)$_2$(PAR)]	270	567	37037	$\pi \rightarrow \pi^*$
	416	943	24038	Charge transfer
	730	19	13698	$^2B_{1g} \rightarrow {}^2B_{2g}$
[Zn(L)$_2$(PAR)]	272	845	36764	$\pi \rightarrow \pi^*$
	305	859	32786	Charge transfer
	396	1111	25252	Charge transfer
[Cd(L)$_2$(PAR)]	276	843	36231	$\pi \rightarrow \pi^*$
	305	857	32786	Charge transfer
	393	1099	25445	Charge transfer
[Hg(L)$_2$(PAR)]	270	780	37037	$\pi \rightarrow \pi^*$
	393	1383	25445	Charge transfer

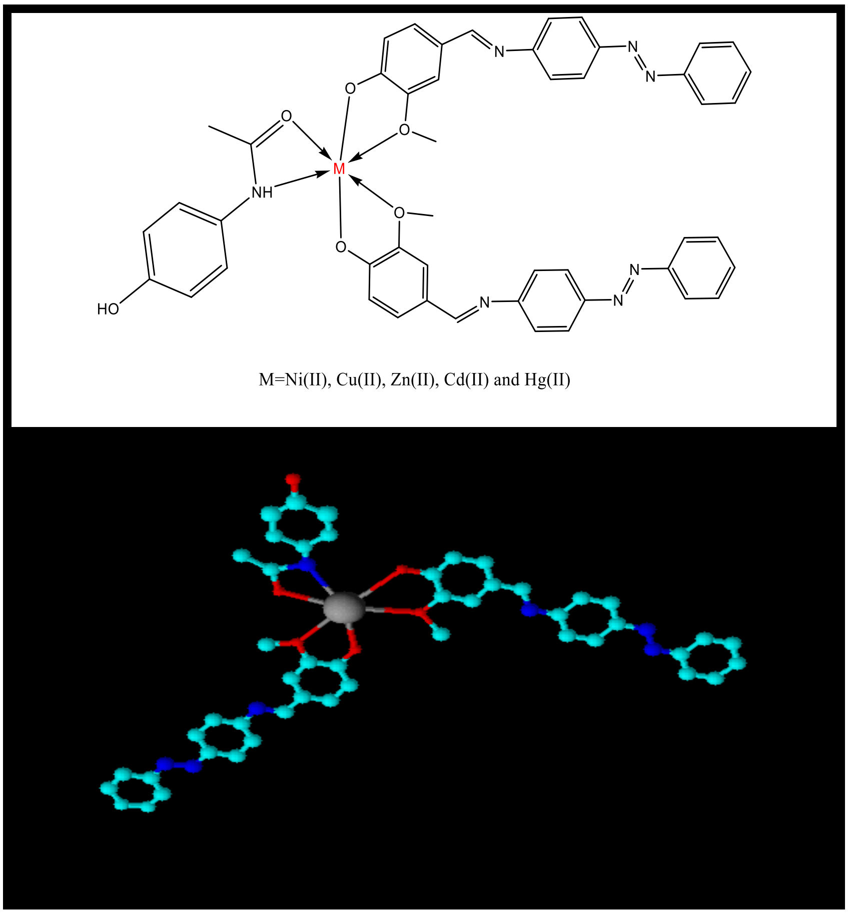


Figure 7. Proposed structure of [M(L)$_2$(PAR)] complexes

Biological Activities

The tests were carried out on one Gram-positive (+) and one Gram-negative (-) bacterial strain concurring to the standard method [28]. The all complexes, are similar and there are no major differences in their biological activity. The results were represented using bar graphs *Fig.* 8, 9 and 10. The zones of inhibition (Plates Figures 4) were measured in millimeters (mm); high activity 11-15, very high ≥16 activity and low activity (4) for DMSO. All the compounds showed a significant antibacterial activity against the tested bacteria, the ligands were found to be active against the bacterial strains and some complexes were more significant than the two ligands [38, 39]. The compounds were assessed on one strain of finding that all the test complexes initiated antifungal movement against the *candida* species, Bar Figs. 11 and 12 values shown a really comparable antifungal movement by all the test compounds, there are numerous components increment the movement are bond length between the metal, conductivity, dipole minute , dissolvability [40]**.**

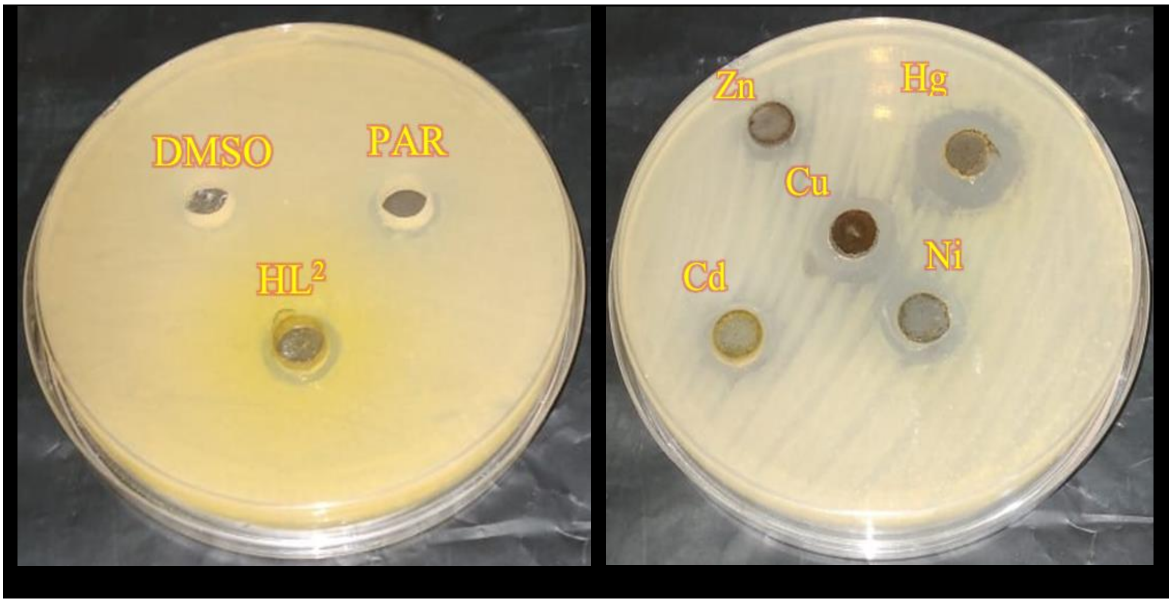


Figure 8. Plates -(ZI) antibacterial activity of the [M(L)$_2$(PAR)] complexes against Staphylococcus aureus

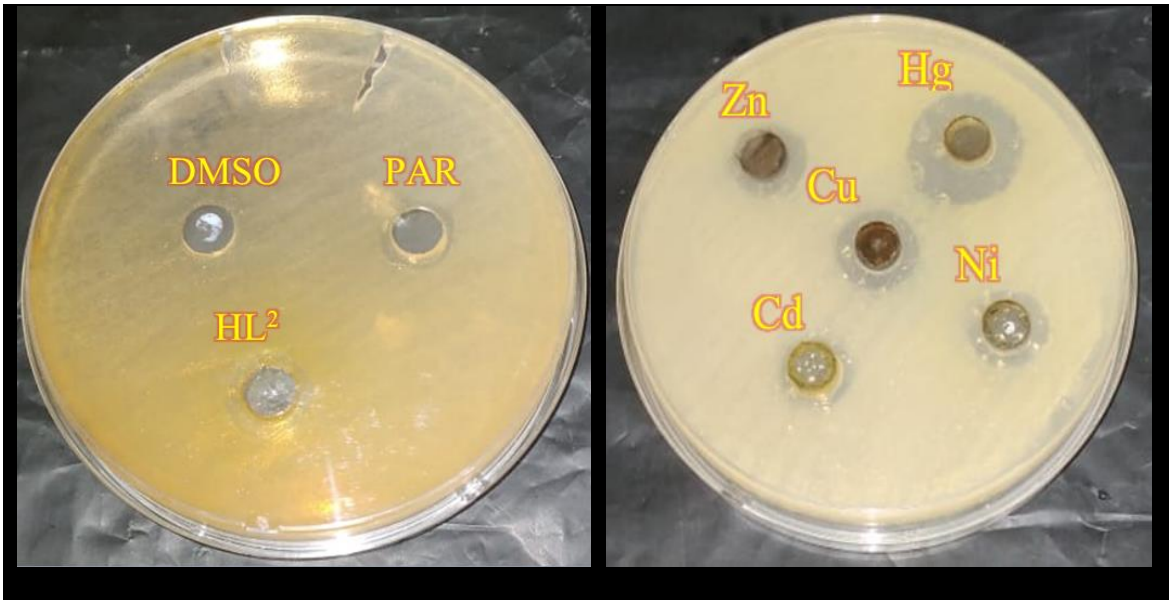


Figure 9. Plates -(ZI) antibacterial activity of the [M(L)$_2$(PAR)] complexes against E. Coil

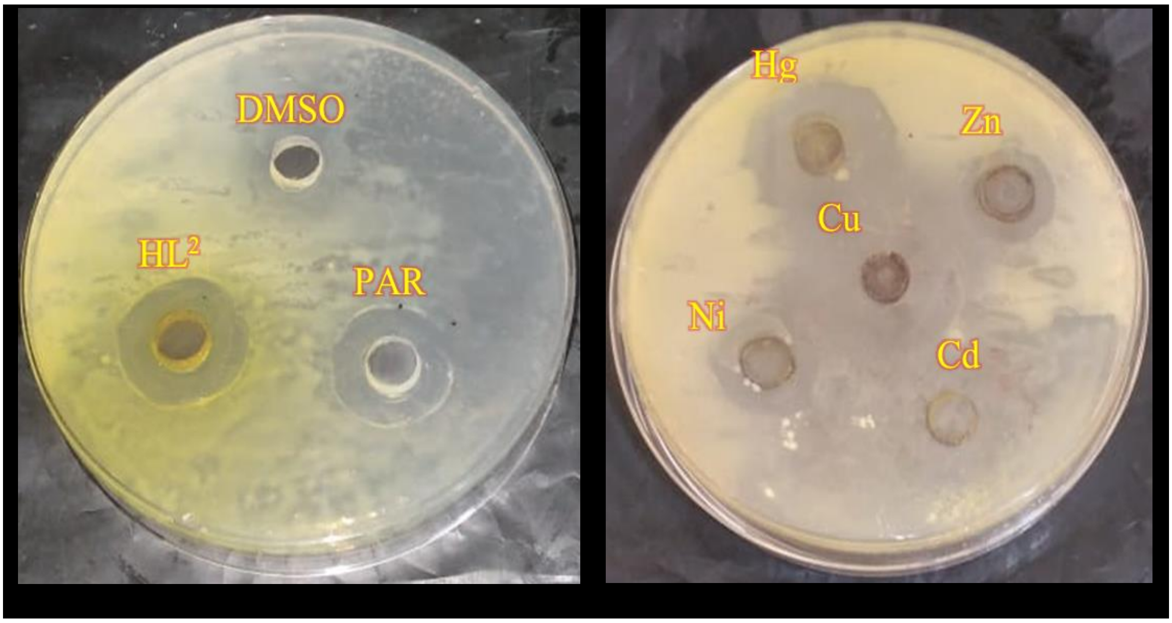


Figure 10. Plates -(ZI) antibacterial activity of the [M(L)$_2$(PAR)] complexes against *Candida albicans*

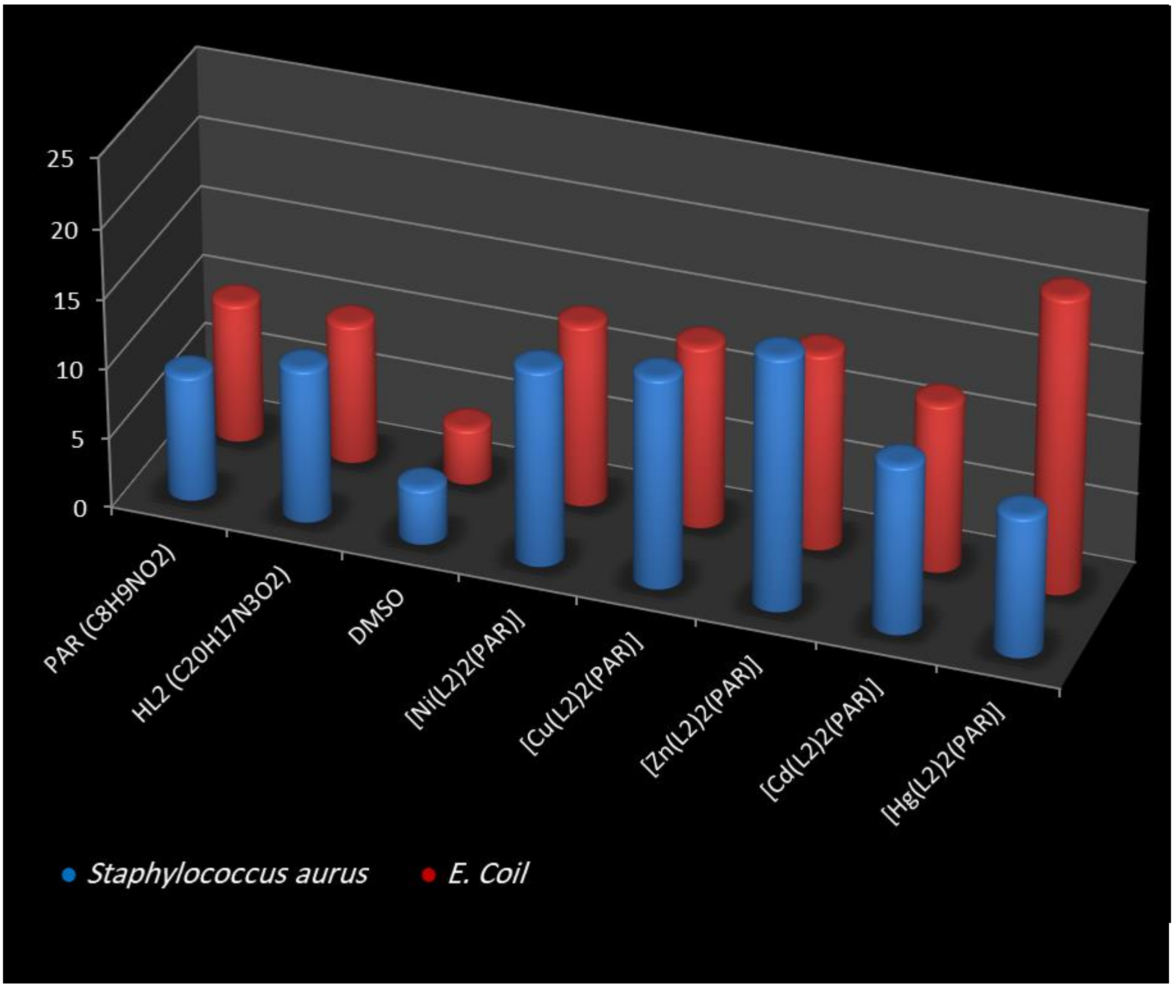


Figure 11. Bar graphs (ZI) of [M(L)$_2$(PAR)] against *Staphylococuse* and *E.coli* strains

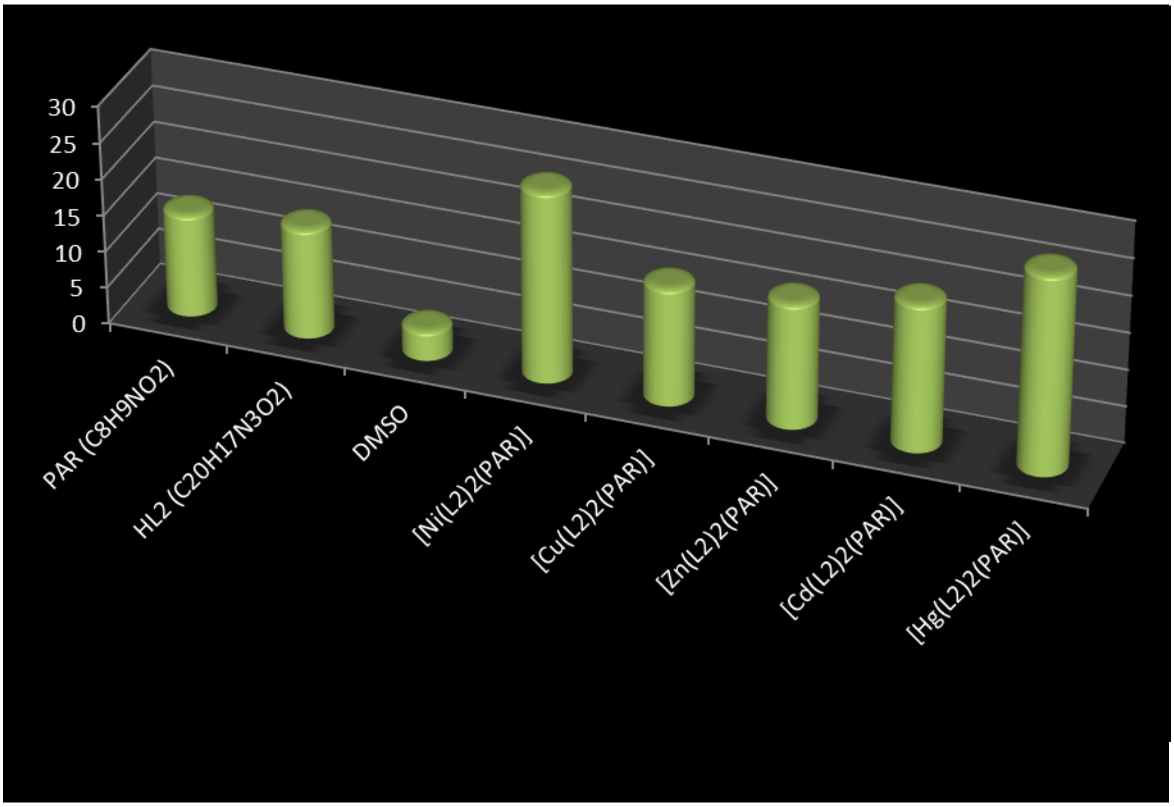


Figure 12. Bar graphs (ZI) of [M(L)$_2$(PAR)] against Candida albicans

Conclusion

In this study, a Schiff base (vanillin with p-aminoazobenzene). They formed stable mixed ligand complexes, [L-M-(PAR)] system with transition metal ions such as Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) were synthesized. The activity of the synthesized mixed L- PAR complexes match the effectiveness of some anti-microbial strains.

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ETHICS

The authors affirm that all ethical considerations were carefully observed, and they remain committed to addressing any ethical issues that may arise following the publication of this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Author contributions: S.R.A. developed the theoretical formalism and performed the analytical calculations. T.H.A. carried out the numerical simulations. M.M.E. contributed to data analysis and manuscript preparation. S.M.B. supervised the project and finalized the manuscript.

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