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Synthesis, characterization, biological activities of Schiff base metal(II) complexes derived from 4-hydroxy-3,5-dimethoxybenzaldehyde and 3-aminoquinoline

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A new Schiff base ligand (E)-2,6-dimethoxy-4-((quinolin-3-ylimino)methyl)phenol (HL) and its Cu(II), Co(II), Ni(II) and Zn(II) metal complexes have been synthesized and characterized by various spectroscopic (UV-visible, IR, NMR and mass), SEM and magnetic susceptibility measurement. The ligand (HL) have been synthesized by condensation of 4-hydroxy-3,5-dimethoxybenzaldehyde and 3-aminoquinoline. Based on electronic spectral data and magnetic susceptibility measurement the tetrahedral geometry is proposed for all the complexes. The ligand and metal complexes are screened for their antimicrobial activities against bacteria (*Staphylococcus aureus, Escherichia coli)* and antifungal activity against the fungi (*Candida albicans)*. Further, the ligand and its Cu(II) complex are also screened for anticancer activity on human breast (MCF7) cancer cell lines by the MTT assay method. Interestingly, Cu(II) complex shows better anticancer activity than the free Schiff base ligand. The *in vitro* anti-inflammatory and anti-diabetic activities of the ligand and Cu(II) complex are studied. The Cu(II) complex show higher inhibition activity than that of the free ligand.

Keywords: Schiff base, Biological activity, Anti-inflammatory, Anti-diabetic, Anticancer

Schiff base complexes are considered to be among the most significant stereochemical model in the main group and transition metal coordination chemistry due to their perspective accessibility and structural assortment. Schiff bases have been widely working as ligands because of the high stability of the coordination compounds and their good solubility in common solvents[1]. In the preparation of Schiff base, an aromatic amine reacts with carbonyl compound by nucleophile addition. Dehydration of the resultant hemiaminal produces an imine carbon-nitrogen double bond which provides a consequence contribution in various development of chemical sciences[2]. The general structural characteristic of these compounds is the azomethine group with a general formula RHC=N-R'. Schiff bases are accounted to have biological activities like antibacterial, antifungal, antitumor, antiviral, anti-HIV and anti-influenza-A virus activities[3-6]. In particular, aminoquinoline is found to inhibit acetylcholine and butyrylcholinesterases[7]. Additionally, they have extensive relevance in the field such as homogenous and heterogeneous catalysis. Schiff bases find significant role in bioinorganic chemistry and redox enzymes systems[8]. Schiff bases are potential anticancer drugs and when administered as their metal complexes, the anticancer activities of the complexes are enhanced compared to the free ligand. In recent times, hydroxy substituted Schiff bases have received substantial attention due to good anticancer activity[9]. Considering the numerous applications of Schiff bases in various fields of chemistry, there has been tremendous interest in evolving proficient methods for their synthesis. Many methods and procedures have been brought in for the preparation of imines in the literature since the pioneering work of Hugo Schiff. Based on the above facts and its applications, the primary aim of our present work is to synthesize Schiff base transition metal complexes derived from 4-hydroxy-3,5-dimethoxybenzaldehyde and 3-amino quinoline and its various metal(II) salts. The analytical and spectral characterizations of synthesized ligand and its metal(II) complexes are examined and their biological activities are explored.

Materials and Methods

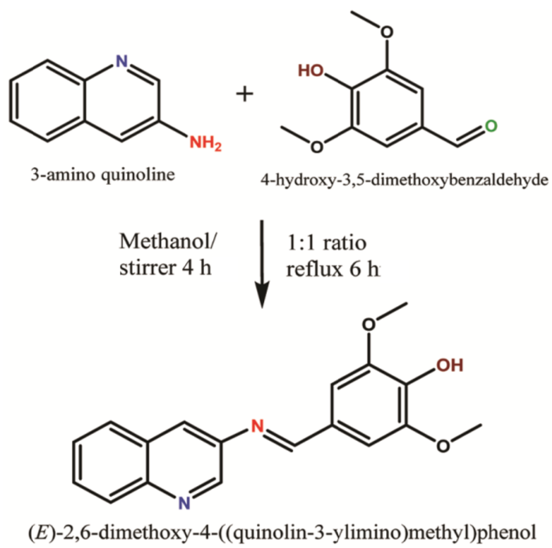
All the reagents and chemicals were purchased from TLC and used for our work without further purification. The metal acetate salts like $M(CH_3COO)_2$. nH_2O (M = Co & Ni, (n=4); Cu, (n=1); Zn, (n=2)) were purchased from Sigma Aldrich. AR grade solvents were utilized for synthesis and recrystallization. The elemental analysis

(C, H, N) was performed using an elemental analyzer namely FEI Quanta-250 FEG apparatus. Melting points of newly synthesized compounds were noted by Electro Thermal 9100 apparatus using open capillaries and are uncorrected. IR spectra of ligand and its metal complexes were recorded as KBr pellets on a Bruker Tensor 27 spectrophotometer in the conventional range of 4000 – 400 cm^{-1}. UV-visible spectra were recorded using JASCO V 650 spectrophotometer in the range of 200 – 800 nm. Magnetic susceptibility measurements on powder samples were carried out by the Goy method. Mass spectra were determined by JEOL D-300(EI) Mass spectrometer. ^{1}H and ^{13}C NMR spectra of ligand and its metal(II) complexes were recorded on the spectrometer model Bruker 300 Hz spectrometer using d6-DMSO as solvent.

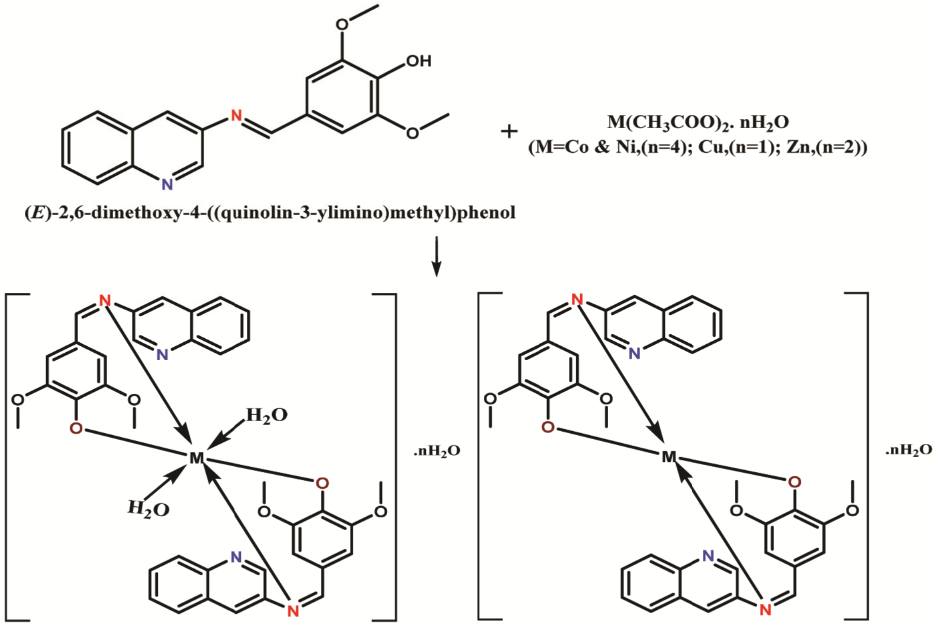
Synthesis of ligand and metal complexes

The ligand (E)-2,6-dimethoxy-4-((quinolin-3-ylimino)methyl)phenol (HL) was prepared using 4-hydroxy-3,5-dimethoxybenzaldehyde and 3-aminoquinoline. 1 mmol of 4-hydroxy-3,5-dimethoxybenzaldehyde (0.182 g) dissolved in 20 mL of methanol. Then it was added dropwise into a 1 mmol methanolic solution of 3-aminoquinoline (0.144 g). The mixture was stirred continuously and refluxed for 3 h at 60–70 °C, then the product obtained was filtered and dried (Scheme 1). The ligand was dissolved in 30 mL methanol and added to 30 mL methanolic solution of metal salt. The metal-ligand molar ratio was (1:2). The mixture was refluxed for 2 h, then cooled and the complex was separated by filtration and dried as per the reported procedure[10]. The synthesis of metal complexes is shown in Scheme 2.

Schiff base (HL) and their Cu(II), Co(II), Ni(II) and Zn(II) complexes synthesized were stable at room temperature. The synthesized ligand and its metal complexes were characterized by elemental analysis and spectral analysis. The biological activity of the ligand and its metal complexes were also studied.



Scheme 2 — Synthesis of Schiff base ligand (L)



Scheme 1 — Synthesis of Schiff base metal complexes (ML) M= Co(II), Ni(II) (n=4); Zn(II) (n=1) (a) and Cu(II) (n=2) (b)

Table 1 — Analytical data of the Schiff base ligand and its mononuclear metal complexes

Compounds	M.W.	Colour	M. P.	Molar conductance (Ω^{-1} cm^2 mol^{-1})	Elemental analysis			
					C	H	N	M
Ligand(L) $C_{18}H_{16}N_2O_3$	308	Yellow	130	--	70.11	5.23	9.08	
[Cu(L)]$C_{40}H_{38}CuN_4O_{11}$	814	Brown	260	42.36	58.99	4.70	6.88	7.80
[Co(L)] $C_{40}H_{44}CoN_4O_{14}$	863	Dark green	232	56.65	55.62	5.14	6.48	6.83
[Ni(L)] $C_{40}H_{44}NiN_4O_{14}$	863	Green	245	50.42	55.63	5.14	6.49	6.80
[Zn(L)] $C_{40}H_{40}ZnN_4O_{12}$	834	Yellowish orange	216	51.98	57.59	4.83	6.72	7.84

Results and Discussion

Elemental analyses and molar conductivity

The results of elemental analyses with suggested molecular formula and physical properties of the Schiff base ligand and its metal(II) complexes are listed in Table 1. The Schiff base ligand and its metal(II) complexes are insoluble in most organic solvents, except DMF and DMSO. Molar conductance was measured at 1× 10^{-3} M for each complex in DMSO at room temperature. The mononuclear metal complexes exhibit low value in the range of 14 – 28 Ω^{-1} cm^2 mol^{-1} indicate that the complexes are non-electrolytic[11] as given in Table 1.

IR spectra

The IR bands of ligand and its complexes are listed in Table 2. The ligand azomethine (C=N) group shows a strong band at 1595 cm^{-1} and it is shifted to a lower frequency in the region 1577 – 1582 cm^{-1} in all the metal complexes indicating the azomethine nitrogen atom involved in coordination to the metal ion. The hydroxyl group peak observed at 3319 cm^{-1} in the Schiff base ligand and it is disappeared in all the complexes, thereby indicating deprotonation and formation of metal-oxygen bond. The stretching frequencies of O-CH_3 bonds for ligand and its metal complexes are almost the same, indicating the nonparticipation of methoxy oxygen in coordination. In the IR spectra of complexes appearance of a new broad band in the region 3360 – 3450 cm^{-1} corresponding to the stretching frequency of ν(O-H) of H_2O indicated the presence of coordinated (or) lattice water. It is further confirmed by the appearance of non-ligand band in complexes in the region 825- 820 cm^{-1} assignable to rocking mode of water. The new bands in IR spectra complexes in the region 545 – 520 cm^{-1} and 435 – 415 cm^{-1} are attributed to ν(M-O) and ν(M-N) vibrations, respectively. The IR spectra of Schiff base ligand (LH) and its metal(II) complexes are shown in Table 2 and Fig. 1.

Table 2 — IR spectral data analysis of the Schiff base ligand and its mononuclear metal complexes

Compounds	υ(O-H) cm^{-1}	υ(C=N) cm^{-1}	(O-CH_3) cm^{-1}	M-O cm^{-1}	M-N cm^{-1}
Ligand(L)	3319	1620	2838	---	----
[Cu(L)]	3340	1613	2838	476	425
[Co(L)]	3434	1618	2839	477	418
[Ni(L)]	3369	1617	2839	478	430
[Zn(L)]	3368	1615	2838	479	413

Electronic spectra

The UV spectrum of Schiff base ligand is exhibiting two intense bands at 242 nm and 355 nm which can be assigned respectively, to π→π* transition within aromatic moiety and n→π* transition of azomethine group of the ligand. In the spectra of complexes, the bands due to azomethine group are shifted to higher and lower frequencies indicating that azomethine nitrogen atom is involved in coordination with the metal ion. The electronic spectra of Co(II) complex show band at 546 nm is due to charge transfer and two bands at 585 nm and 594 nm due to $^4T_{1g}$ (F)→$^4A_{2g}$ (F) and $^4T_{1g}$ (F) →$^4T_{2g}$ (P) transitions and magnetic moment value is 4.22 B.M which corresponds to an octahedral geometry Co(II) complex. The electronic spectra of the Ni(II) complex observed three bands at 602 nm, 648 nm and 691 nm which corresponds to $^3A_{2g}$ (F)→$^3T_{1g}$ (P), $^3A_{2g}$ (F)→$^3T_{1g}$ (F) and $^3A_{2g}$ (F)→$^3T_{2g}$ (F), respectively, and also charge transfer band exhibits at 583 nm. The Ni(II) complex showed a magnetic moment value at 3.31 B.M. which indicates the presence of Ni(II) complex in an octahedral geometry. The electronic absorption of the Cu(II) complex showed two bands at 545 nm, 584 nm, which are assigned to $^2B_{1g}$→$^2A_{1g}$ and $^2B_{1g}$ → ^2E_g transitions, respectively, and the

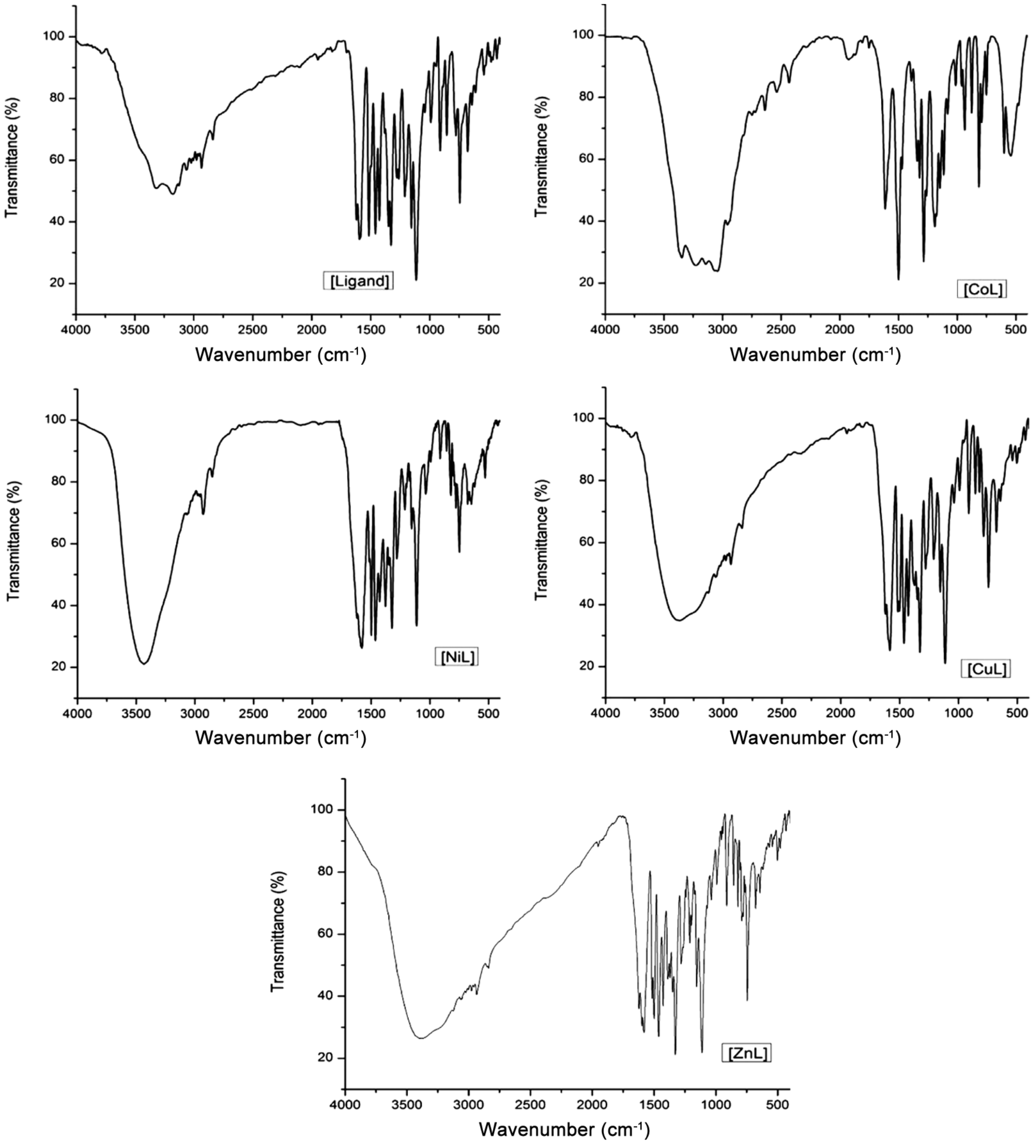


Fig. 1 — FT-IR spectra of Schiff base ligand and their metal(II) complexes

magnetic moment of the Cu(II) complex was 1.91 B.M. From both the electronic and the magnetic values proposed the presence of the square planar geometry for Cu(II) complex[12]. The spectrum of the Zn(II) complex showed a band at 548 nm which is due to charge transfer. The absence of absorption peaks at the visible region indicates an octahedral geometry around Zn(II) ion in the complex. The UV spectra of Schiff base (HL) and its metal(II) complexes are shown in Fig. 2 and Table 3.

NMR spectra

The ^{1}H NMR spectrum of HL was characterized by singlet proton of azomethine group (CH═N) appearing at 8.96 ppm (s, 1H). Multiple signals at 6.38–8.13 ppm (m, 10H) corresponding to the aromatic ring. A characteristic singlet signal of OH proton at 8.73 ppm (s, 1H) appeared. The sharp peak was assigned at 3.83 ppm due to the protons of the (-O-CH_3) group. The ^{1}H NMR spectra of Schiff base ligand (L) are shown in Fig. 3.

The ^{13}C NMR of the Schiff base ligand shows the peak at 161.91 ppm downfield of azomethine (CH=N) group. The methoxy carbon atoms are indicated the sharp peaks at δ 56.49 ppm. The remaining aromatic carbons are shows the peaks at (147.42 – 123.88 ppm). The peak appeared in region 77.24 ppm was attributed to the chemical shift of chloroform solvent. The ^{13}C NMR spectrum of HL is shown in Fig. 4.

Mass spectra

The electron impact mass spectra of HL and its metal(II) complexes were recorded and investigated at an electron energy of 70 eV. The mass spectra of HL and its metal(II) complexes were characterized by moderate to high relative intensity molecular ion peaks. The abundance of the molecular ion depends mainly on the structure. The molecular ion peak of the ligand was found at m/z = 308.12 amu and at m/z = 814, 863, 863 & 834 amu for the Cu(II), Ni(II), Co(II) and Zn(II) complexes, respectively. The Mass spectra of ligand and its metal(II) complexes are shown in Fig. 5.

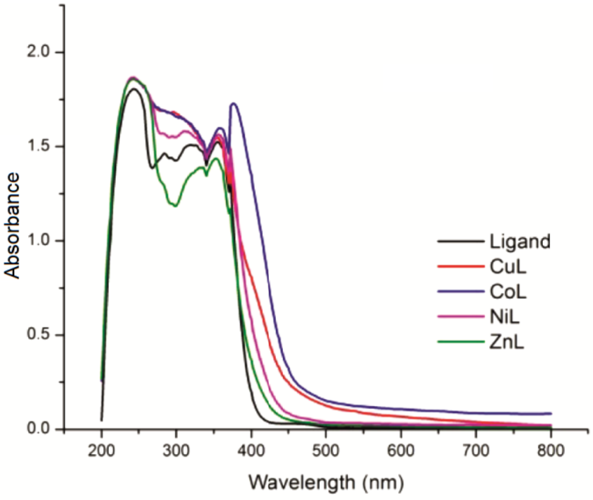


Fig. 2 — UV Spectra of ligand and their metal(II) complexes

ESR spectra

The X-band ESR spectrum of the Cu(II) complex was recorded in the solid-state at room temperature as shown in Fig. 6. The spectrum shows well-defined $g_{\parallel}$ and $g_{\perp}$ values and are as $g_{\parallel}= 2.1560$ and $g_{\perp} = 2.0469$. The $g_{\parallel}$ value of these complex lies below 2.3 ($g_{\parallel}< 2.3$) which indicates the covalent environment around the Cu(II) ion[13]. The calculated G ($G = g_{\parallel} - 2.0023/ g_{\perp} - 2.0023$) value is 3.32 for CuL complex which indicates square planar geometry[14].

SEM analysis

The surface morphology of the synthesized ligand and its mononuclear metal complexes was checked by scanning electron microscopy. The synthesized ligand and their metal complexes were carried out and the obtained images are shown in Fig. 7. The SEM images indicate that the ligand and each metal complex have different distinctive surface morphology[15].

Antimicrobial activity

In the present study, the synthesized ligand complexes showed maximum efficacy against the bacterial pathogens than the parent ligand. Among the four synthesized metal(II) complexes, Cu complex showed maximum inhibition against Gram-positive bacteria (*Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli*) and one fungi (*Candida albicans).* Furthermore, the increase in the

Table 3 — The electronic spectra and magnetic moment data analysis of the Schiff base ligand and its mononuclear metal complexes

Compounds	Absorption(nm)	Band assignment	Geometry	Magnetic moment (BM)
Ligand(L)	243	$\pi\rightarrow\pi^*$	-------	------
	355	$n\rightarrow\pi^*$		
[Co(L)]	242	$\pi\rightarrow\pi^*$	Octahedral	4.22
	358	$n\rightarrow\pi^*$		
	546	LMCT		
	584	$^4T_{1g}$ (F)$\rightarrow^4A_{2g}$ (F) $^4T_{1g}$ (F) $\rightarrow^4T_{2g}$ (P)		
	594			
[Ni(L)]	242	$\pi\rightarrow\pi^*$	Octahedral	3.31
	356	$n\rightarrow\pi^*$		
	583	LMCT		
	602	$^3A_{2g}$ (F)$\rightarrow^3T_{1g}$ (P), $^3A_{2g}$ (F)$\rightarrow^3T_{1g}$ (F) $^3A_{2g}$ (F)$\rightarrow^3T_{2g}$ (F)		
	648			
	691			
[Cu(L)]	242	$\pi\rightarrow\pi^*$	Square- planar	1.91
	354	$n\rightarrow\pi^*$		
	583	$^2B_{1g}\rightarrow^2A_{1g}$		
	584	$^2B_{1g} \rightarrow {}^2E_g$		
[Zn(L)]	244	$\pi\rightarrow\pi^*$	Octahedral	Diamagnetic
	351	$n\rightarrow\pi^*$		
	548	LMCT		

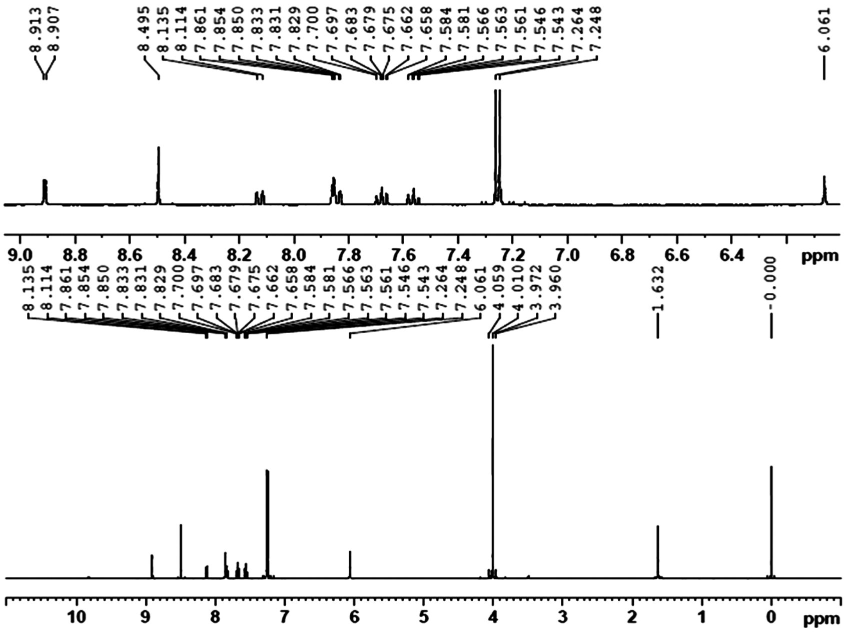


Fig. 3 — ^{1}H NMR spectra of Schiff base ligand (L)

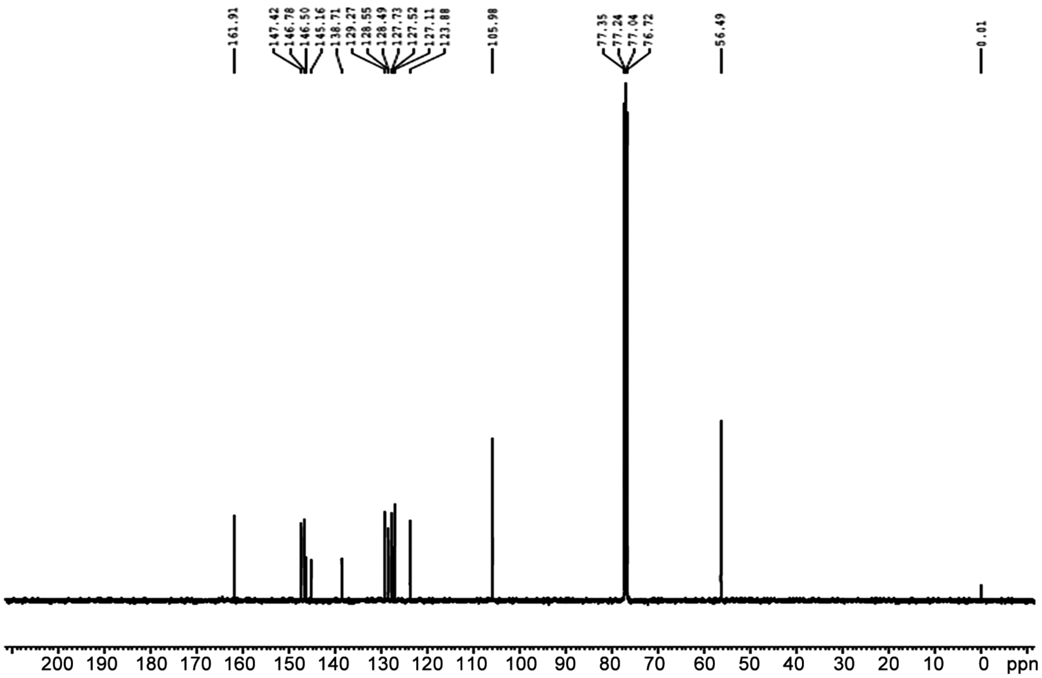


Fig. 4 — ^{13}C NMR spectra for Schiff base ligand(L)

concentration of metal complexes increases the bacterial inhibition activity. The results of antimicrobial activity of the Schiff base ligand and its metal(II)complexes are listed in Table 4 and Fig. 8. This enhanced activity of the complexes is due to their affinity and permeability nature and it could be elucidated based on ligand field theory, Overtone's concept and Tweedy's chelation theory[16-18]. According to Overtone's concept, the lipophilic nature of the complexes is a major factor that determines the degree of antibacterial activity. The coordination metals with ligand decrease the polarity of the complex and increase the lipophilicity by delocalization of electrons

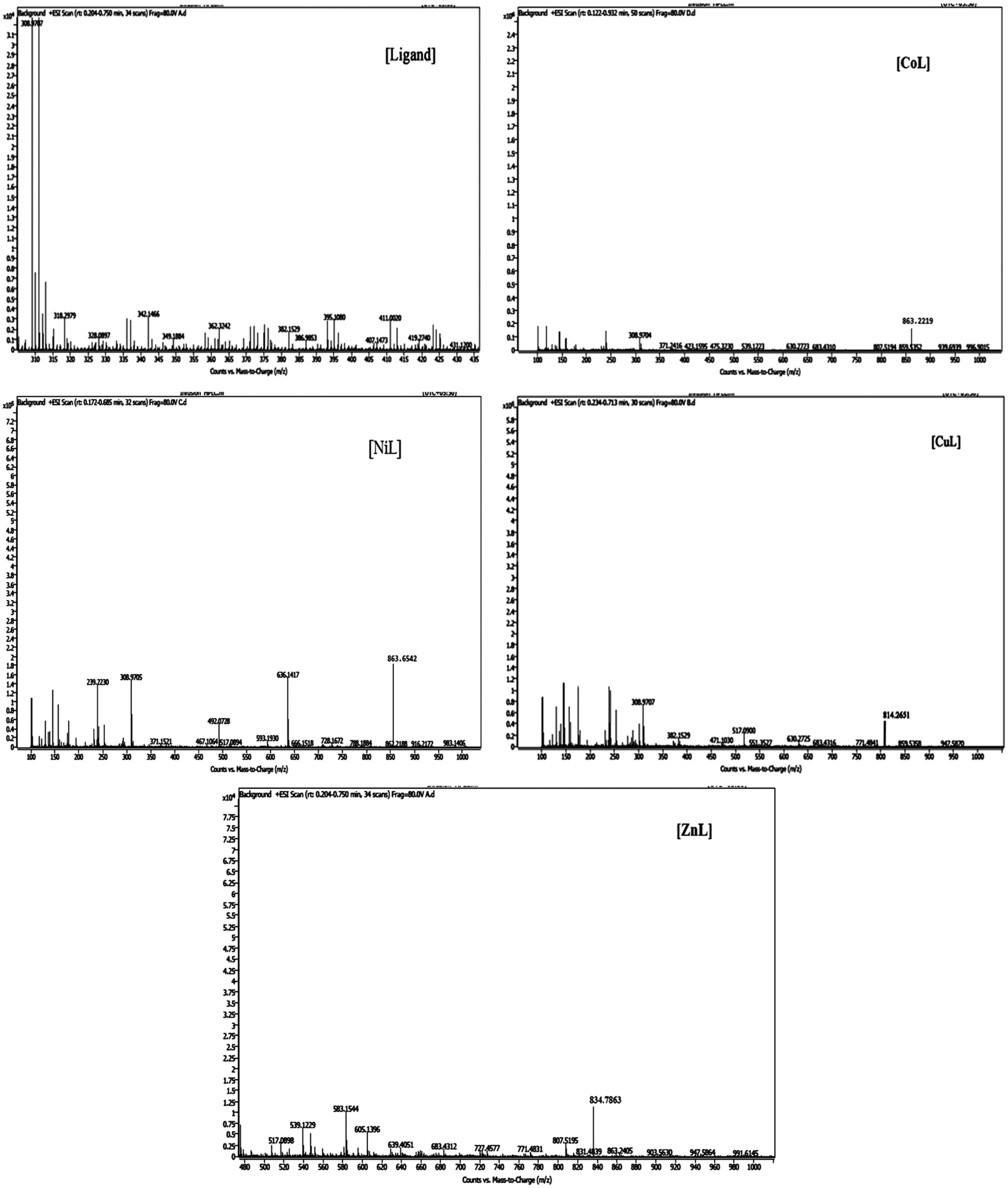


Fig. 5 — Mass spectra of Schiff base ligand and their metal(II) complexes

from ligand to metal. Therefore it will increase the permeability of the metal complexes across the selectively permeable lipid layer and inhibit the growth of the microorganism[16]. Furthermore, the chelation between the complexes and the microbial cell wall might disintegrate the cell wall structure and result in the loss of cellular ingredients, which eventually kill the bacteria.

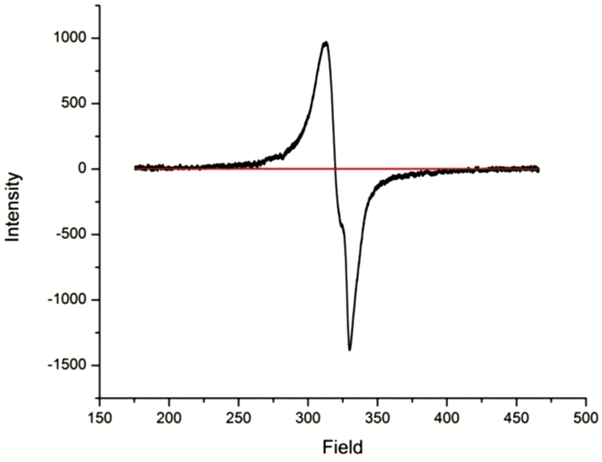


Fig. 7 — ESR spectrum for CuL complex

Anti-inflammatory activity

Anti-inflammatory activity of the ligand and metal complexes has been done by using the HRBC stabilization method. Diclofenac sodium was used as standard and distilled water was used as control. The percentage of membrane stabilization for synthesized ligand, complexes and standard were done at 20, 40, 60, 80 and 100 μg/mL shown in Table 5. The percentage of hemolysis by diclofenac sodium, ligand and its metal complexes by HRBC membrane stabilization method increases with increase in concentration[19]. The percentage inhibition hemolysis by ligand and complexes are found to be concentration-dependent. The copper complex shows higher inhibition of hemolysis (78.31%) at 100 μg/mL compared to the ligand.

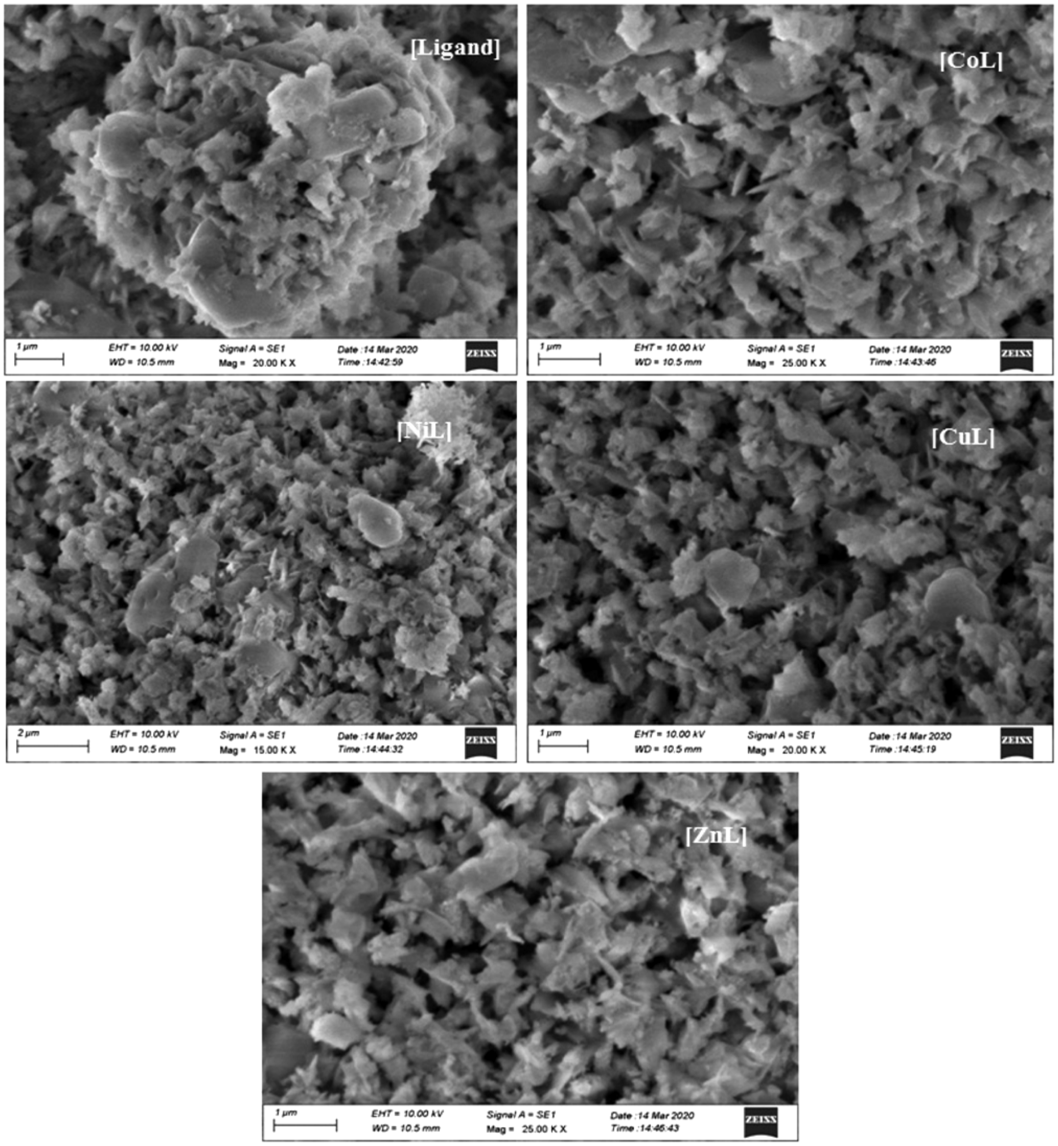


Fig. 6 — SEM micrographs of Schiff base ligand and their metal complexes

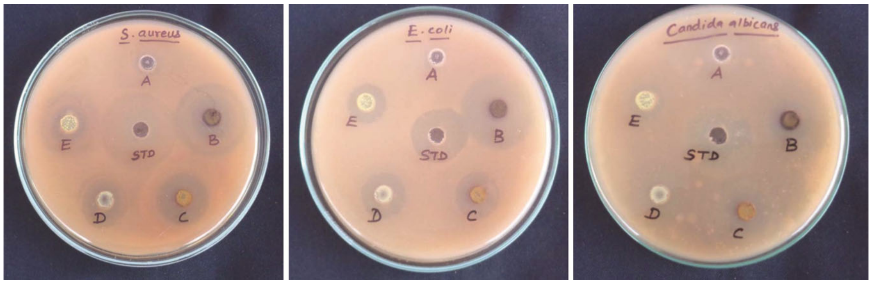


Fig. 8 — Anti-microbial activity of the ligand and MLcomplexes

Table 4 — Antimicrobial activity of Schiff base ligand and its metal(II) complexes

S. no	Sample	Sample concentration (µg/ml)	Zone of inhibition (mm)			
			Gram positive	Gram negative	Sample concentration (µg/ml)	Fungi
			Staphylococcus aureus	*Escherichia coli*		*Candida albicans*
1	Ligand(L) (A)	100	3	4	100	3
2	[Cu(L)](B)		14	8		15
3	[Co(L)] (C)		10	7		10
4	[Ni(L)] (D)		9	6		9
5	[Zn(L)] (E)		8	7		8
6	Standard	Tetracylin	12	12	Fluconazole	14

L=Schiff base ligand

Table 5 — Anti-inflammatory activity of Schiff base ligand and its Copper(II) complex

Concentration (µg/ml)	% Inhibition of hemolysis					
	Standard		Ligand		Cu(II) complex	
20	56.28		36.16	54.88	43.55	
40	60.14	0.592	42.44		55.42	30.76
60	67.49		51.34		64.24	
80	72.78		63.21		70.21	
100	78.69		67.85		78.31	

Table 6 — Anti-diabetic effects of Schiff base and Copper(II) complex

Compounds	Concentration (µg/ml)					IC$_{50}$ (µM)
	10	20	30	40	50	
	% of inhibition at 540 nm					
Ligand	38.25	41.64	45.16	47.31	48.91	51.48
Copper(II)Complex	54.21	60.54	62.21	63.60	65.82	12.85

Anti-diabetic Activity

The anti-diabetic activity was examined by the standard amylase inhibition assay. The inhibition activity of the synthesized compounds against α-amylase is given in Table 6. Cu(II) complexes exhibit more inhibition activity than the free Schiff base ligand. The IC$_{50}$ value of the free Schiff base and CuL complex are 51.48 and 12.85 µg/mL, respectively.

Table 7 — Anticancer effects of Schiff base and its Copper(II) complex

Ligand (A) Conc. (µg/ml)	Cell Viability %	IC$_{50}$ (µM)	CuL (B) Conc. (µg/ml)	Cell Viability %	IC$_{50}$ (µM)
3.125	98.85345658	35.40	3.125	88.32827252	23.85
6.25	91.67436523		6.25	73.93874364	
12.5	74.23906344		12.5	57.83743684	
25	50.93534263		25	35.23673853	
50	37.78435389		50	23.64875653	

Anticancer activity

The ligand and Cu(II) complex has been tested for the anticancerous effect of the human breast cancer cell line (MCF-7) by MTT assay method. The absorbance of the samples at 570 nm at the various concentrations (3.125, 6.25, 12.5, 25 and 50 µg/mL) was observed as IC$_{50}$ values. The IC$_{50}$ values of ligand and its complex were found to be 35.40 and 23.85 µg/mL, respectively. The % cell viability for the ligand and its complex at 50 µg/mL concentration is found 37.78 and 23.64 %. The anticancer activities of ligand and its [CuL] complex against (MCF-7) growth breast cancer cell line were summarized in the Table 7 and Fig. 9. The IC$_{50}$ values indicate that the copper complex has a higher sensitivity towards breast cancer cell lines than the free ligand.

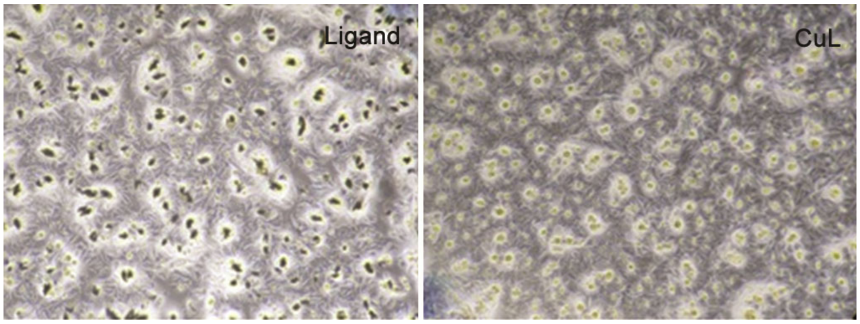


Fig. 9 — Anti-cancer activity of the Ligand and Cu(II)complex

Conclusions

Schiff base transition metal complexes Co(II), Ni(II), Cu(II), and Zn(II) were synthesized from (E)-2,6-dimethoxy-4-((quinolin-3-ylimino)methyl)phenol was clearly described and characterized on the basis of analytical and spectral data. Elemental analysis shows the metal and ligand ratio is 1:2. The physico-chemical methods suggest octahedral geometry for Co(II), Ni(II), and Zn(II) complexes and square planar geometry for Cu(II) complex. The anti-microbial study revealed that Cu(II) complexes have higher potential and all other complexes were more active than the free ligand. In anti-inflammatory activity, the percentage inhibition hemolysis by ligand and complexes increases with increasing concentration. Anti-diabetic activity of the Cu(II) complex has shown 65.82% inhibition of amylase at 50 μg, while ligand has induced alpha amylase activity. The cytotoxic studies showed that the Cu(II) complex exhibits good cytotoxic activity against (MCF-7) cell line with compared to the free ligand.

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