



Synthesis, characterization and biological studies on Co(II), Ni(II), Cu(II) and Zn(II) complexes derived from 4-(2-amino ethyl) benzene-1,2-diol and 1,4 benzoquinone

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A novel Schiff base ligand (L) has been synthesized using 4-(2-amino ethyl) benzene-1,2-diol (Dopamine) and 1,4 benzoquinone. Co(II), Ni(II), Cu(II) and Zn(II) complexes with this hexadentate ligand have been synthesized with metal:ligand (1:1) stoichiometry. The Schiff base ligand and its metal complexes have been characterized by elemental analysis, molar conductance, magnetic susceptibility, infrared and electronic spectra, ESR, NMR, Mass spectra, powder X-ray diffraction and SEM studies. Molar conductance showed that all complexes are non-electrolytic in nature. The Co(II), Ni(II), Zn(II) complexes are found to be octahedral and distorted octahedral structure for Cu(II) complex. Powder X-ray diffraction reveals that Schiff base ligand and its metal complexes are nano-crystalline in nature but Co(II) complex is amorphous. Different morphologies of synthesized compounds are identified by SEM images. Schiff base ligand and its metal complexes were screened against gram-positive bacteria, gram-negative bacteria and one fungus strain. The data show that the ligand and its metal complexes have significant activity. Copper(II) complex shows better activity than other complexes. The Schiff base ligand and its copper(II) complex are evaluated for the anti-inflammatory by HRBC membrane stabilization method. The anti-cancer activity of Schiff base ligand and its copper complex was also studied against human breast cancer cell line by MTT assay method. The anti-diabetic activity of Schiff base ligand and its copper(II) complex is also studied by alpha-amylase method.

Keywords: Schiff base, Molar conductance, Co(II), Ni(II), Cu(II) and Zn(II) complexes, Anti-bacterial, Anti-inflammatory, Anti-cancer

A dopamine molecule comprises a catechol structure (a benzene ring with two hydroxyl side groups) with one amine group appended through an ethyl chain. It is most usually utilized as an energizer sedate in the treatment of severe low blood pressure, slow heart rate and cardiac arrest¹. Dopamine is additionally integrated with plants and most animals. In the brain, dopamine work as a neurotransmitter—a chemical discharged by neurons (nerve cells) to send signals to other nerve cells².

Schiff base ligands and their metal complexes have extended massively and include a tremendous area of organometallic complexes and different aspects of bioinorganic science³. Schiff base ligands are considered “privileged ligands” because they are easily prepared by condensation between carbonyl compounds (aldehydes or ketones) and primary amines⁴. Schiff base ligands are able to coordinate many different metals and can stabilize them in different oxidation states⁵. Schiff bases, moreover known as imines or azomethines, have increased

incredible popularity for the most part because of their simplicity of synthesis, air stability and relatively cheap beginning materials⁶. The presence of nitrogen and oxygen donor atoms renders these compounds effective and stereospecific as catalysts for bond formation, oxidation, reduction, hydrolysis and other transformation⁷. Enormous quantities of Schiff bases have additionally been appeared to exhibit a wide scope of biological activities, antitumor, antibacterial, antifungicidal and anticarcinogenic properties⁸.

The present work is to prepare a Schiff base ligand derived from the condensation of dopamine with 1, 4 benzoquinone. The study has been extended to Co(II), Ni(II), Cu(II) and Zn(II) complexes with the prepared ligand. All the prepared complexes have been characterized by IR, ¹H and ¹³C NMR, Mass spectra, ESR, UV-visible, in addition to elemental analysis, molar conductivity and magnetic susceptibility. Morphologies of ligand and its complexes were analyzed by utilizing powder XRD pattern and SEM.

Schiff base ligand and its metal complexes were accessed for their antibacterial activity. Anti-hemolytic, anti-inflammatory, anti-cancer activity and anti-diabetic are also evaluated for Schiff base ligand and its copper(II) complex.

Materials and Methods

Metal acetate salts were purchased from Sigma Aldrich Ltd., and were used without further purification. Dopamine and 1, 4 benzoquinone of AR grade were purchased from TCI chemicals and the solvents used for synthesis and characterization were of high-performance liquid chromatography grade.

Elemental analyses were carried out on EURO EA-3000 RS-32. IR spectra was recorded on 8400 FTIR Shimadzu spectrometer as KBr discs. UV-visible spectra (using DMSO as the solvent) were measured on Shimadzu UV-2100 spectrometer. Melting points were determined on a Buchi 530 apparatus in open capillary tubes. Molar conductance of 10^{-3} M solution of the complexes in DMSO was recorded on Hanna EC 215 conductivity meter by using 0.01 M KCl solution as calibrant. ^1H & ^{13}C NMR spectra of the ligand and its complexes in DMSO- d_6 were recorded on a Bruker Advance II 400 spectrometer at room temperature using TMS as an internal standard. The ESI mass spectra of ligand and its metal complexes were recorded on Q-ToF Mass spectrometer. Magnetic susceptibility measurements were done in a Sherwood scientific magnetic susceptibility balance at room

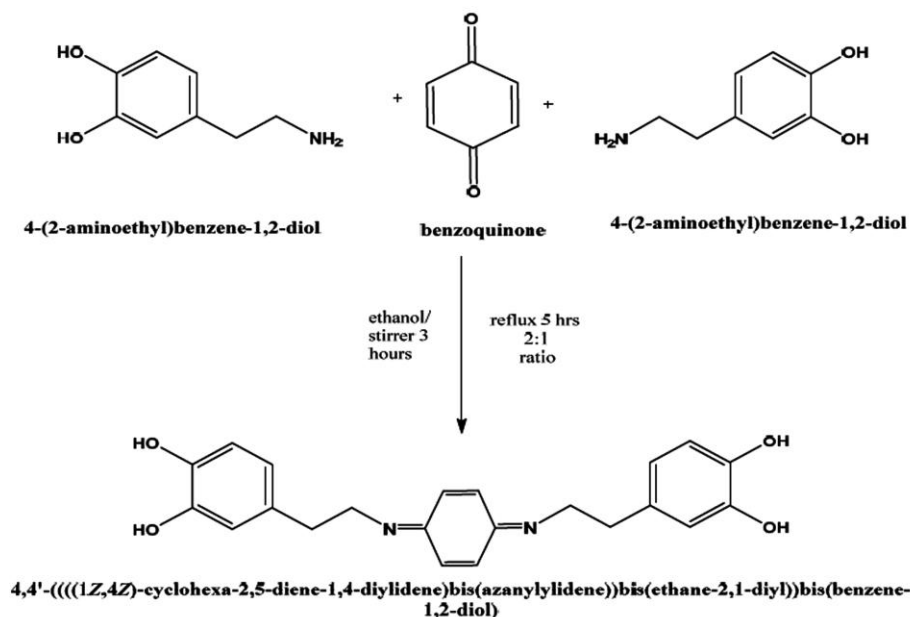
temperature. TG-DTA analysis was carried out under nitrogen atmosphere using Perkin Elmer Pyres Diamond TG/DTA Analyzer. The crystalline size of the ligand and its complexes were evaluated with X-ray diffraction. The powder X-ray diffraction pattern of HQCAAP was recorded on Bruker model D8 X-ray diffractometer. Scanning electron surface morphological studies were obtained using the JSM-5610 scanning electron microscope (SEM). X-Band EPR spectra of the copper(II) complex in DMSO was recorded on Varian E-4X band spectrometer using DPPH as the g-marker at room temperature.

Preparation of Schiff base ligand (L)

Schiff base ligand was prepared by the addition of methanolic solution of 1, 4 benzoquinone (1 mmol) drop wise into the methanolic solution of 4-(2-amino ethyl) benzene-1, 2-diol (2 mmol) taken in a round bottom flask at room temperature. The mixture was thoroughly mixed on a magnetic stirrer for 3 h which was followed by refluxing for 6 h resulting in the dark brown colored solid product (Scheme 1). The product was filtered, washed several times with methanol and finally dried in vacuum over anhydrous calcium chloride.

Preparation of Schiff base complexes (ML)

A solution of metal acetate salts of methanol taken in a round bottom flask was slowly added to the solution of Schiff base ligand (L) (1 mmol) in DMSO. The solution was then thoroughly mixed and was



Scheme 1 — Synthesis of Schiff base ligand (L)

stirred under reflux for 7 h resulting in the isolation of the product. The obtained product was filtered, washed several times with methanol finally dried in vacuum over anhydrous calcium chloride. The Co(II), Ni(II), Cu(II) and Zn(II) metal complexes of Schiff base were prepared by above general method. The preparation of metal complexes is shown in Scheme 2.

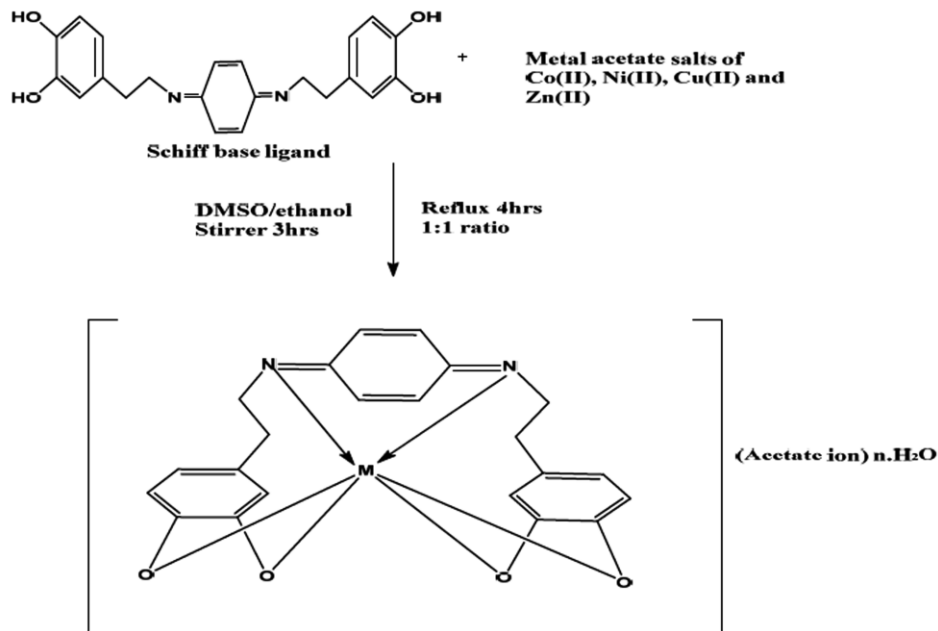
Results and Discussion

The physical properties and elemental analysis data for the Schiff base ligand (L) and its metal complexes (ML) are tabulated in Table 1. The melting point of the metal complexes are higher than the ligand because of the increased molecular sizes and the presence of strong ionic and covalent bonds⁹. The

experimental percentages of C, H and N are in close agreement with the theoretical values, indicating the formation of the proposed compounds. The complexes are slightly soluble in ethanol, methanol, acetone and chloroform, completely soluble in DMSO and DMF. The molar conductivity of the metal complexes in DMSO solution (10^{-3} M) at room temperature was measured. The low molar conductance values (Table 1) portentous that all the metal complexes belong to 1:1 electrolyte¹⁰.

FTIR spectral studies

The significant infra-red (IR) spectral details of Schiff base ligand and its complexes are tabulated in Table 2. The spectra, as shown in Fig. 1 provide



Scheme 2 — Synthesis of Schiff base Metal complexes (ML) M= Co(II), Ni(II) and Zn(II) (n=2, 4) and Cu(II) complex (n=1)

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

Compounds	Mol.Wt.	Colour	M.P. (°C)	Molar conductance ($\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$)	Elemental analysis			
					C	H	N	M
Ligand	450.11	Dark Brown	165	---	69.83 (68.15)	5.86 (5.12)	7.40 (6.99)	---
Cobalt(II) complex	698.13	Dark red	210	12.11	51.03 (51.65)	5.08 (4.86)	4.41 (4.01)	9.27 (9.07)
Nickel(II) complex	699.13	Brown	205	11.01	51.05 (51.74)	5.08 (5.04)	4.41 (4.15)	9.24 (9.01)
Copper(II) complex	649.09	Black	180	9.81	55.34 (55.12)	4.47 (4.12)	4.78 (4.32)	10.84 (10.56)
Zinc(II) complex	669.91	Light brown	182	8.76	53.52 (52.95)	4.66 (4.03)	4.62 (4.14)	10.79 (10.11)

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

Compound	Wavenumber (cm ⁻¹)				
	Hydroxyl group	H ₂ O(OH) lattice water	Imine	M-O	M-N
Ligand	3345	---	1610	---	---
Cobalt(II) complex	----	3408	1627	558	436
Nickel(II) complex	----	3393	1613	560	451
Copper(II) complex	----	3413	1621	558	498
Zinc(II) complex	----	3222	1605	520	463

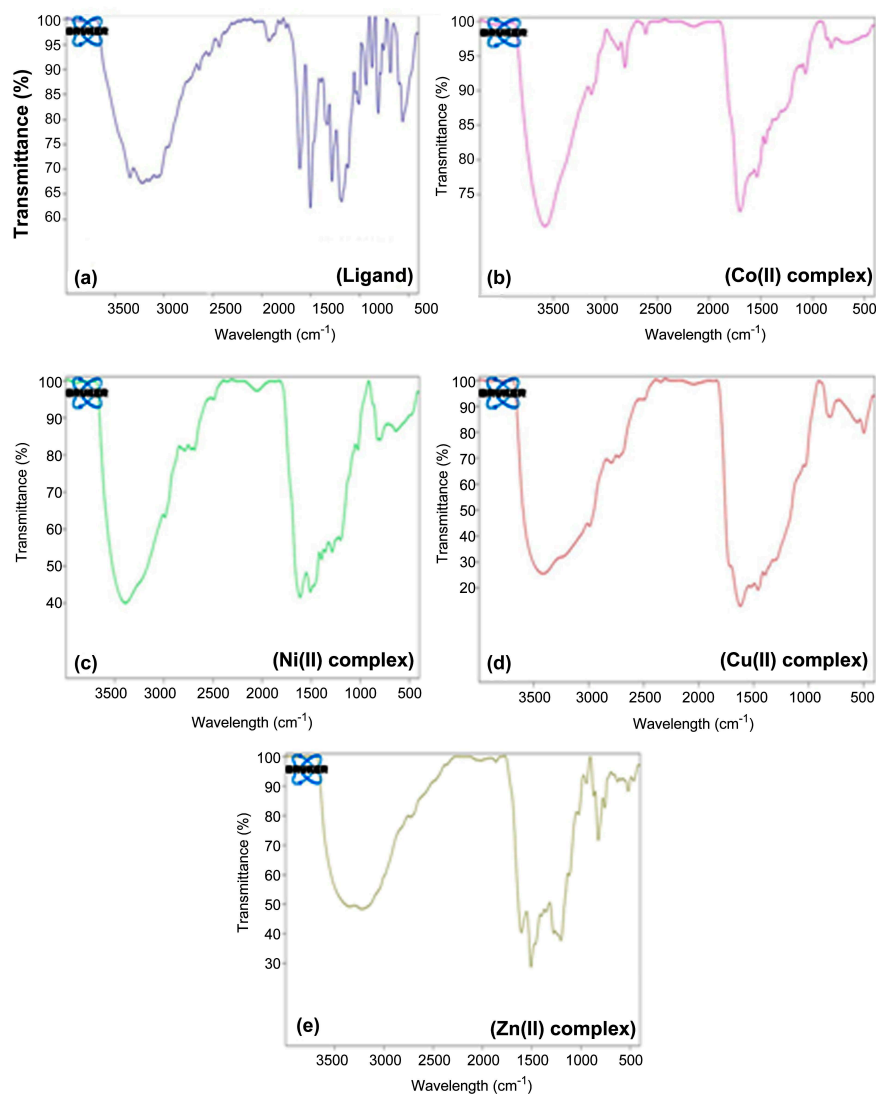


Fig. 1 — FT-IR spectra of (a) Schiff base ligand and (b-e) its metal complexes

valuable information about the functional group present in the compounds¹¹. The IR spectra of the prepared ligand showed a strong band at 1620 cm⁻¹ assigned to the formation of the azomethine (C=N) group and it is shifted to a lower frequency in the region 1605-1615 cm⁻¹ in the complexes¹².

Furthermore, the hydroxyl group in ligand is observed in 3345 cm⁻¹ and its absence in the complexes is due to the involvement of the phenol O in bonding to the metal ion¹³. The absorption bands in the range between 2054-2016 cm⁻¹ are assigned to $\nu(\text{C-H})$ stretching frequencies¹⁴. The appearances of bands at

3408-3413 cm^{-1} are due to lattice water molecules which are further confirmed by the appearance of a new band at 823-795 cm^{-1} which is due to $\nu(\text{OH})$ (rocking)¹⁵. The spectra of the prepared complexes show some new band in between (520-560 cm^{-1}) and (436-498 cm^{-1}) which might be because of the formation of the (M-O) and (M-N), respectively¹⁶.

NMR Spectral studies (¹H and ¹³C NMR)

¹H NMR data and assignments of Schiff base ligand obtained in d_6 -DMSO at room temperature with tetramethylsilane (TMS) as an internal standard¹⁷. In the spectrum, the peak at 3.48 ppm is (s, -HC=N-CH₂-) due to the methyl proton of the azomethine group in the Schiff base ligand¹⁸. The aliphatic protons (s, 4H aliphatic -CH₂-) in the dopamine chain show a single peak at 2.86 ppm and the aromatic protons (m, 8H aromatic -CH=CH-) appear as a multiplet at (6.62-7.46 ppm)¹⁹. The -OH proton of the phenolic group is observed as a singlet at 9.51 and 9.41 ppm (m, 4H,-OH)²⁰ as given below in Fig. 2.

¹³C NMR spectrum of the free ligand L shows a sharp signal at 154 ppm which may be assigned to azomethine carbon²¹. The resonance signals observed in the region 115.43-128.44 ppm are assigned to carbon atoms of aromatic moieties in the ligand framework²². The signals assigned to the chemical shift of the methylene group are observed at 50.49 ppm (-CH₂) and 40.15 (-CH₂) ppm²³. The carbon

atom of the -OH phenyl group exhibited a peak at 145.73 ppm²⁴ as shown in Fig. 3.

Electronic spectra and magnetic moment

The electronic spectra and magnetic moment of the Schiff base ligand and its metal complexes are presented in Table 3 and Fig. 4. The electronic spectra of the Schiff base ligand (L) revealed two intense bands in the region 263 nm (38022 cm^{-1}) and 290 nm (34482 cm^{-1}) which are attributed to π - π^* and n- π^* , respectively²⁵. In the electronic spectra of complexes, these bands are shifted to the higher frequencies indicating that azomethine nitrogen atom is involved in coordination to the metal ion²⁶.

Cobalt (II) complex (CoL)

The electronic spectrum of Co(II) complexes exhibits two bands in the region of 570 nm (17543 cm^{-1}) and 608 nm (16447 cm^{-1}) which are assignable to ${}^4T_{1g}(\text{F}) \rightarrow {}^4A_{2g}(\text{F})$ and ${}^4T_{1g}(\text{F}) \rightarrow {}^4T_{2g}(\text{P})$ transitions, respectively²⁷, corresponding to an octahedral geometry and band at 428 nm (23364 cm^{-1}) is due to charge transfer (L-M) and the geometry is further confirmed by its magnetic moment value of 4.31 B.M²⁸.

Nickel(II) complex (NiL)

Based on the spectrum of Ni(II) complex, d-d transition showed two bands in the region 529 nm (18903 cm^{-1}) and 616 nm (16233 cm^{-1}), which

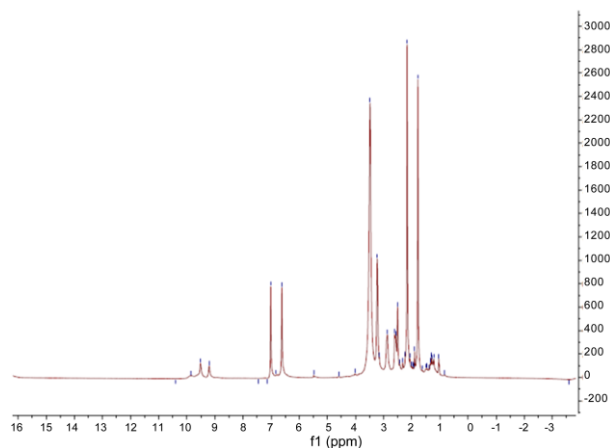


Fig. 2 — ¹H NMR of Schiff base ligand (L)

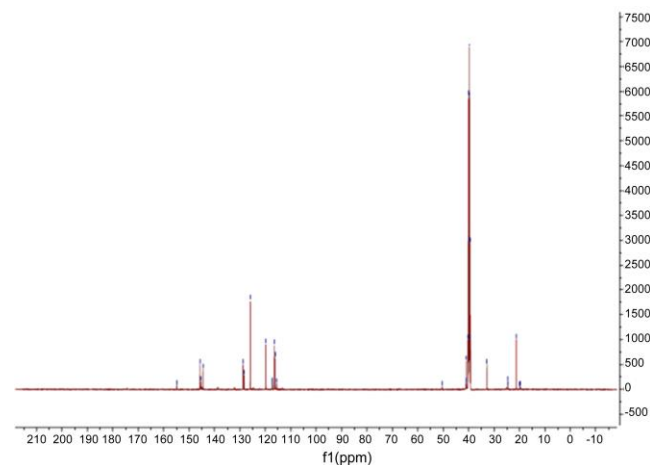


Fig. 3 — ¹³C NMR for Schiff base ligand (L)

Table 3 — UV spectral data analysis of the Schiff base ligand and its metal complexes

Compound	Absorption bands (nm) in DMSO	μ_{eff} (BM)
Ligand	263, 290	---
[CoL]	268, 294, 428, 570, 608	4.31
[NiL]	268, 303, 498, 529, 616	3.12
[CuL]	266, 302, 402, 545	1.92
[ZnL]	268,302,416	Diamagnetic

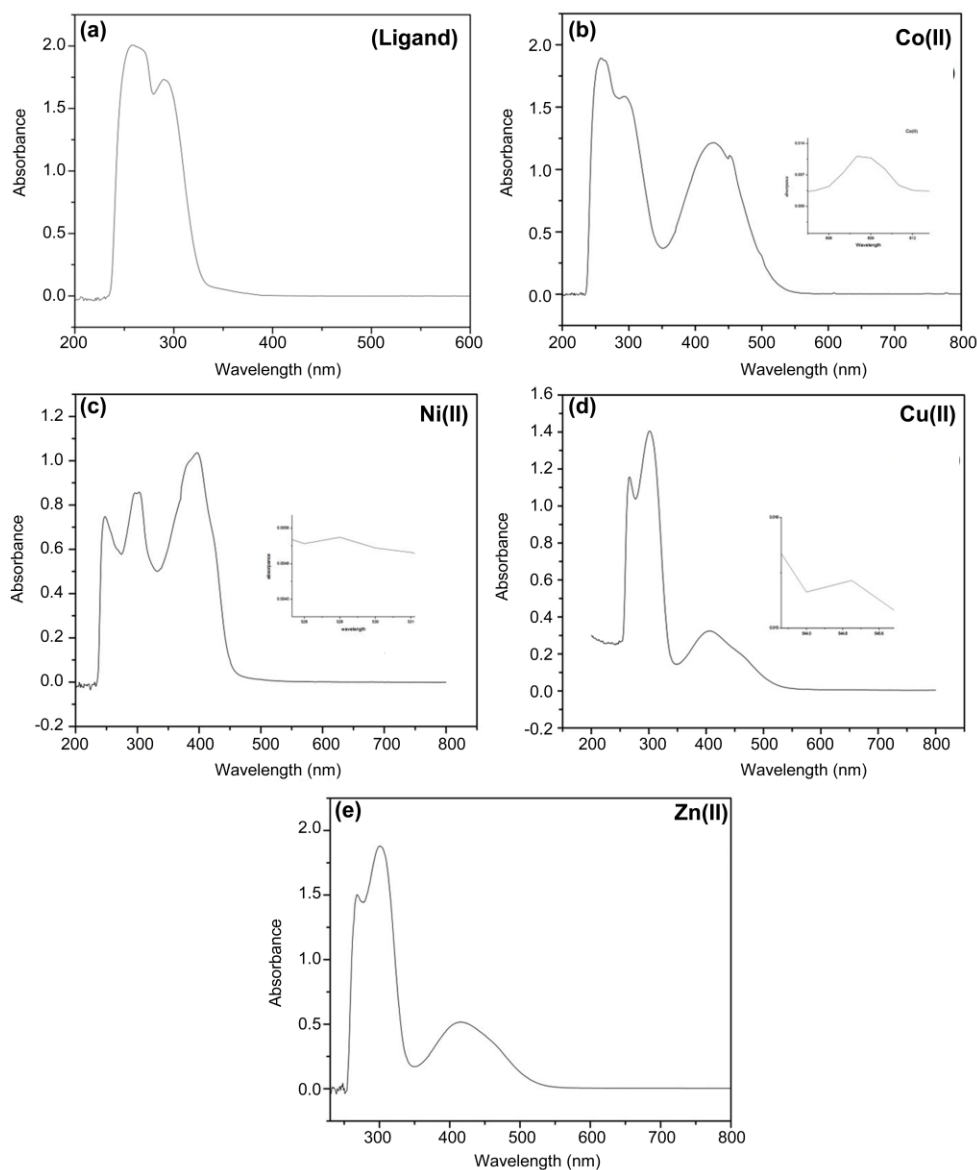


Fig. 4 — ESR spectra for (a) Schiff base ligand and (b-e) its metal complexes

corresponding to ${}^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$, respectively. The two bands are consistent with an octahedral geometry of the complex and a band at 498 nm (20080 cm^{-1}) is due to charge transfer²⁹. The octahedral geometry of Ni(II) complex is further supported by the magnetic moment value of 3.12 B.M^{30} .

Copper(II) complex (CuL)

The electronic spectrum of the Cu(II) complex exhibits a charge transfer band at 402 nm (24875 cm^{-1}) and a d-d transition band at 545 nm (18348 cm^{-1}) which is assigned to ${}^2E_g \rightarrow {}^2T_{2g}$ transition indicating a distorted octahedral geometry. The observed magnetic value for Cu(II) complex is 1.92 B.M^{31} .

Zinc(II) complex (ZnL)

The spectrum of the Zn(II) complex showed a high-intensity band at 416 nm (24038 cm^{-1}) which is due to charge transfer. The absence of absorption peaks at the visible region indicates an octahedral geometry around Zn(II) ion complex³².

ESR Spectral studies

The ESR spectrum of the Cu(II) complex affords information about the geometry and the nature of the coordination sites at the Schiff base and the metal. The X-band ESR spectrum of the Schiff base copper(II) complex at 77 K shows two different g-values indicating the magnetic anisotropy in the complex as shown in Fig. 5.

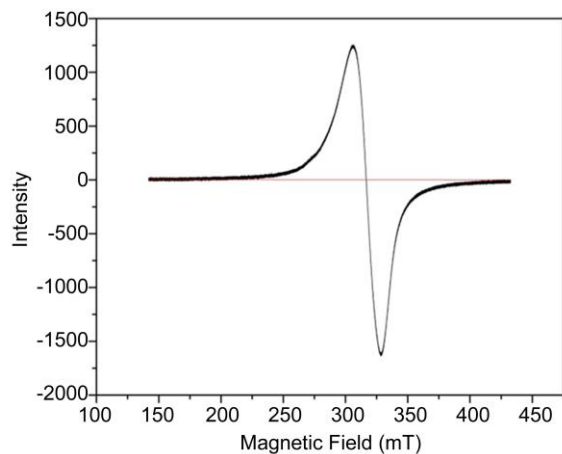


Fig. 5 — Mass spectra of Schiff base ligand and its metal complexes

In the octahedral complex, the unpaired electron is in the $d_{x^2-y^2}$ orbital. In the present complex, the observed g values are $g_{\parallel} > g_{\perp} > g_{av}$ (2.002), which endorse that this complex has a distorted octahedral geometry³³.

Mass spectra

Mass spectra of ligand and its mononuclear complexes are shown in Fig. 6. Schiff base ligand $C_{22}H_{22}H_{16}N_4$ shows a molecular ion peak at m/z 452[M+1] for its monomeric formulation. The m/z value observed at 699 [M+1], 698 [M+1]⁺, 649 [M] and 669[M+1] are the molecular ion peak of Co $C_{27}H_{32}N_2O_{12}$, Ni $C_{27}H_{32}N_2O_{12}$, Cu $C_{27}H_{26}N_2O_9$, Zn $C_{27}H_{28}N_2O_{10}$ complexes, respectively, which indicate the stoichiometry composition of complexes³⁴.

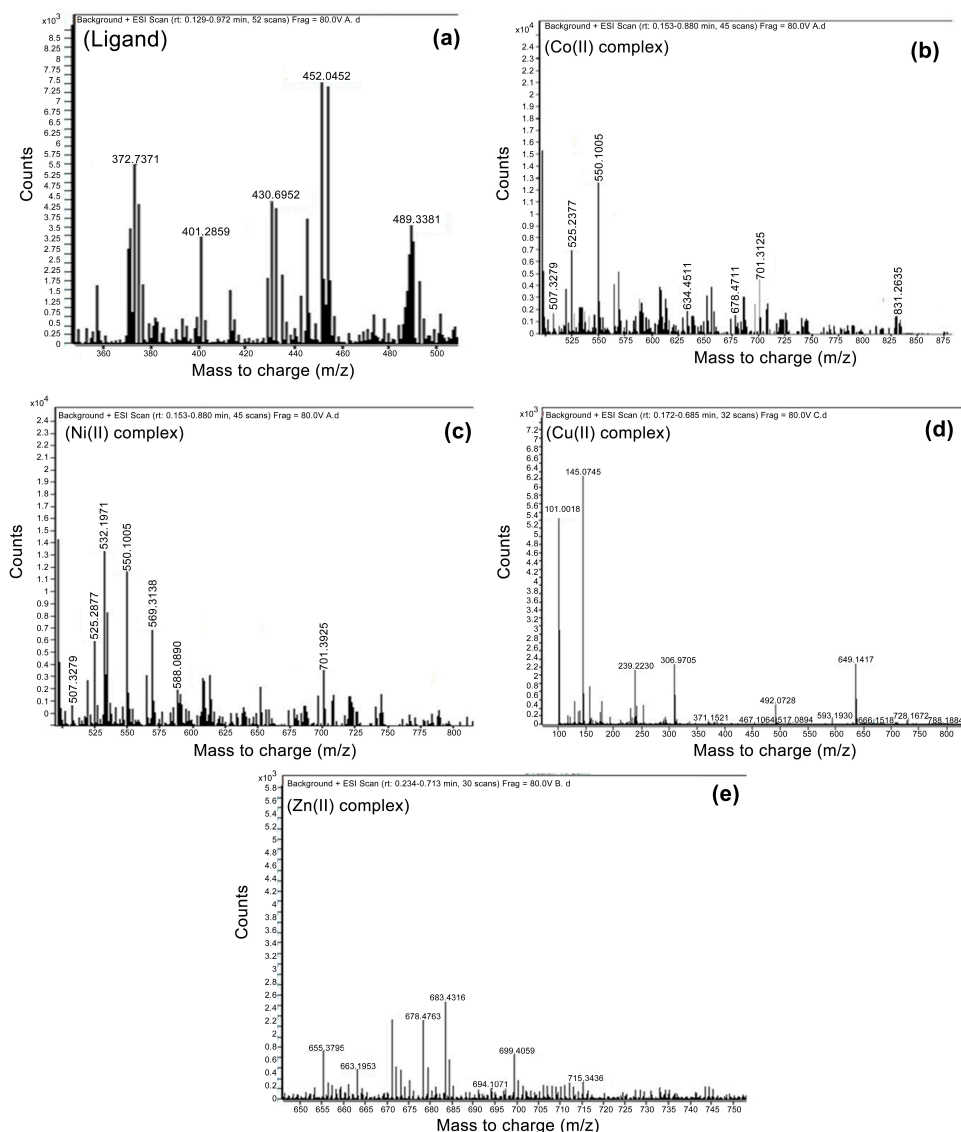


Fig. 6 — X-ray diffraction pattern of the (a) Schiff base ligand and (b-e) its metal complexes

Powder XRD pattern

The Powder x-ray diffraction pattern of Schiff base ligand and its metal complexes are shown in Fig. 7(a-e). The X-ray powder pattern learns about the compounds that have been carried out in order to decide whether the nature of the sample is crystalline or amorphous³⁵. From the observed d_{xrd} patterns, the crystalline size of the complexes was calculated from Scherer's formula:

$$D_{xrd} = 0.9\lambda / \beta \cos\theta$$

Where, λ is the wavelength (1.5406 Å), β is the full-width half maximum of the characteristic peak and θ is the diffraction angle for the hkl plane³⁶. The calculated average grain size value is found to be 1.30 nm (L), Ni(II) [2.77 nm], Cu(II) [3.20 nm] and Zn(II) [7.95 nm] and Co(II) complex is amorphous.

SEM analysis

The SEM micrographs of the Schiff base ligand and Co(II), Ni(II), Cu(II) and Zn(II) mixed ligand complexes are shown in Fig. 8. The SEM micrograph of ligand

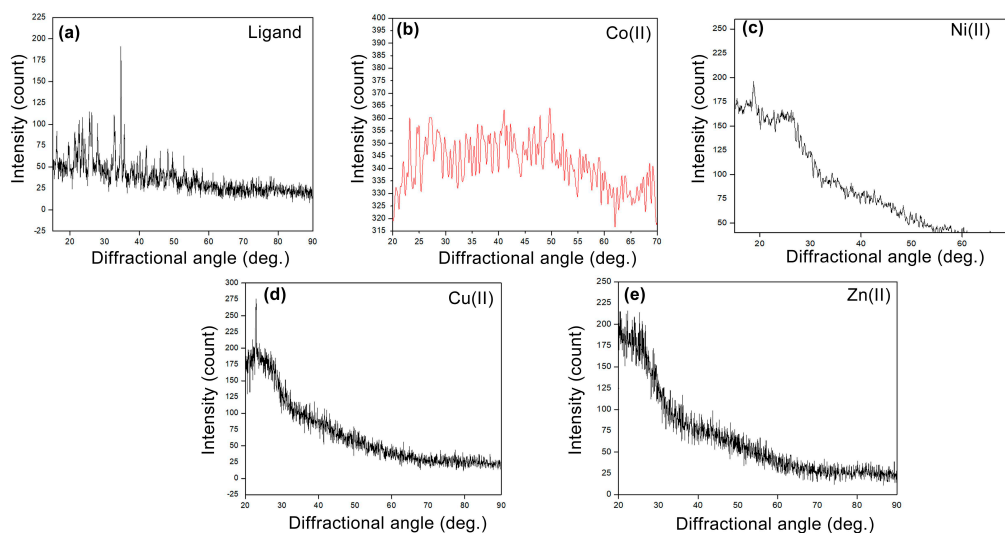


Fig. 7 — X-ray diffraction pattern of the (a) Schiff base ligand and (b-e) its metal complexes

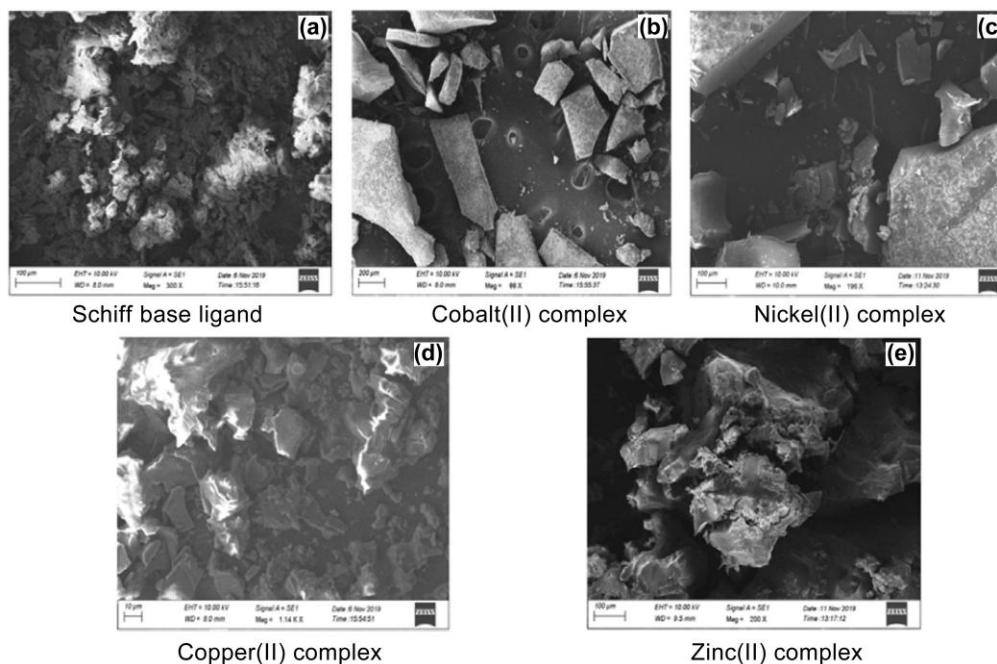


Fig. 8 — SEM analysis of (a) Schiff base ligand and (b-e) its mononuclear complex

exhibits spherical structured particles with small grains. The micrograph of Co(II), Ni(II) and Cu(II) complexes exhibit irregular small grains. The Zn(II) complexes showed fringing reef like morphology.

Antimicrobial activity

Schiff base ligand and its metal complexes were tested for *in vitro* antibacterial activity against Gram-positive bacteria viz. *Staphylococcus aureus* and Gram-negative bacteria viz. *Escherichia coli*. The antifungal activity was studied against *Candida albicans*. The MIC values of the synthesized compounds were evaluated by agar plate disc method. Tetracycline and Fluconazole were used as standards. The results of antimicrobial evaluation and their MIC are given in Table 4. The antimicrobial activity suggested that Schiff base ligand and metal complexes show significant efficacy against all the bacteria and fungi strains. *In vitro* activity of the ligand is better on complexation with metal ions. The enhancement in the effectiveness of complexes is clarified based on Overtone's concept of cell permeability and chelation theory³⁷. According to these theories, in a metal complex, the coordination diminishes the polarity of metal ion because of the partially sharing of the positive charge of the metal with donor atoms of the ligand within the chelating system. This could increase the lipophilic nature of the central metal chelates and favours its permeation through the lipid layer of the microbial

membranes more effectively thus destroying them more fierce³⁸. The microbial activity of the complexes may not be due to chelation alone but it blends with various contributions such as dipole moment, solubility, size, redox potential of metal ions, coordinating sites, solubility, bond length between metal and ligand, geometry of the complexes³⁹. The order of activity for bacterial species is found to be Tetracycline > Cu(II) > Zn(II) = Ni(II) > Co(II). The order of activity for fungicide is found to be Fluconazole > Cu(II) > Ni(II) > Zn(II) > Co(II).

In vitro anti-inflammatory activity

The anti-inflammatory activities of the Schiff base ligand and its copper(II) complex were examined by the HRBCs membrane stabilization method. The percentage of inhibition of synthesized compounds presented Table 5. Schiff base ligand and its copper(II) compounds exhibit minimum efficiency compared to standard diclofenac sodium. The percentage inhibition of hemolysis increases with the increase in concentration⁴⁰. Copper(II) complex showed maximum inhibition of 69% and the complex stabilized human blood cell membrane in a dose-dependent manner⁴¹.

In-vitro Cytotoxic activity

The anticancer activities of Schiff base ligand and its copper(II) complex were determined by MTT assay on human breast cancer cell line MCF7. The absorbance of the samples at 570 nm, at various

Table 4 — Antibacterial and Antifungal activities of the Schiff base ligand and its metal complexes

S. No.	Sample	Sample concentration (mg/mL)	Zone of inhibition (mm)		Sample concentration (mg/mL)	Fungus
			Gram-positive <i>Staphylococcus aureus</i>	Gram-negative <i>Escherichia coli</i>		
1	A		4	4		6
2	B	100	4	5	100	6
3	C		6	6		8
4	D		10	8		9
5	E		6	6		7
6	Standard	Tetracycline	12	12	Fluconazole	14

A=Schiff base ligand B= Co(II) complex

C=Ni(II) complex D=Cu(II) complex

E=Zn(II) complex

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

Concentration (µg/mL)	% Inhibition of hemolysis					
	Standard	IC ₅₀ values	Ligand	IC ₅₀ values	Cu(II) complex	IC ₅₀ values
20	56.28	0.592	30.07	60.20	35.33	52.80
40	60.14		46.61		45.86	
60	67.49		51.12		54.13	
80	72.78		58.64		60.90	
100	78.69		63.15		68.42	

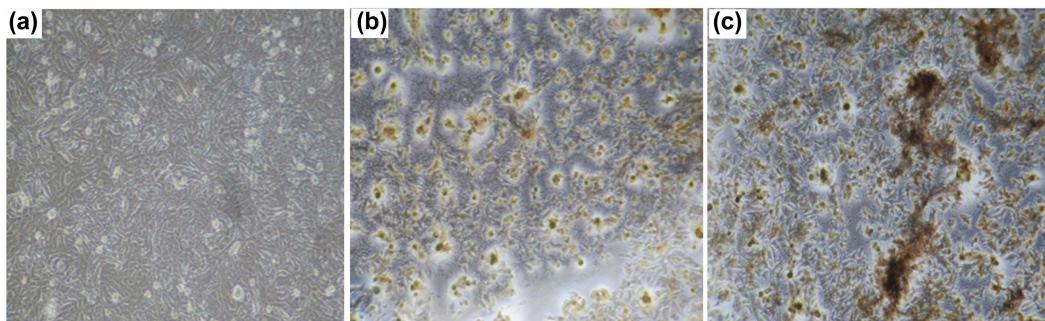


Fig. 9 — Anti-cancer activities of (a) Control, (b) Schiff base ligand and (c) its Copper(II) complex

Table 6 — Anticancer effects of Schiff base and its Copper(II) complex in term of % cell inhibition at various concentrations

Ligand (A) Concentration ($\mu\text{g/mL}$)	Cell viability %	IC ₅₀ ($\mu\text{g/mL}$)	CuL (B) Concentration ($\mu\text{g/mL}$)	Cell viability %	IC ₅₀ ($\mu\text{g/mL}$)
3.125	97.53	32.18	3.125	95.65	
6.25	93.72		6.25	87.85	24.05
12.5	79.48		12.5	76.52	
25	57.62		25	48.00	
50	43.61		50	28.93	

Table 7 — Anti-diabetic effects of Schiff base ligand and its Copper(II) complex

Compounds	Concentration ($\mu\text{g/mL}$)					IC ₅₀ ($\mu\text{g/mL}$)
	10	20	30	40	50	
	% of inhibition at 540 nm					
Ligand	23.85	30.05	34.01	45.07	51.16	48.95
Copper(II) Complex	31.57	38.88	43.17	47.91	56.75	40.75

concentrations (3.125-50 ($\mu\text{g/ml}$)), the percentage of cell inhibition and IC₅₀ values are found and reported in Table 6 and Fig. 9. The % cell inhibition and IC₅₀ values indicated that the copper complex has valuable features for potential anticancer agents^{42,43}.

In-vitro antidiabetic activity

The anti-diabetic activity was examined by the Alpha-amylase inhibition assay. Inhibition activity of standard drug (Maltose), Schiff base ligand and its copper(II) complex against Alpha-amylase is shown in Table 7. Copper(II) complex shows more inhibition efficiency than Schiff base ligand.

Conclusions

A new Schiff base ligand derived from 4-(2-amino ethyl) benzene-1,2-diol and 1,4 benzoquinone and its Co(II), Ni(II), Cu(II) and Zn(II) metal complexes were synthesized and characterized by using elemental and spectroscopic analysis. The molar conductance values showed non-ionic nature for all the metal complexes. Electronic, magnetic, ESR and mass data reveal octahedral geometry for Co(II), Ni(II) and Zn(II) complexes and distorted octahedral geometry for Cu(II)

complex. Schiff base ligand acts as hexadentate coordinating through two nitrogens of the azomethine group and four hydroxyl groups in an N₂O₄ manner. The powder XRD pattern and SEM analysis revealed nanocrystalline nature for Schiff base ligand and its metal complexes except Co(II) complex which exhibit amorphous nature. The Schiff base ligand and its metal complexes (a-e) were screened against gram-positive (*Staphylococcus aureus*), gram-negative (*Escherichia coli*) bacteria and one fungus (*Candida albicans*). From the antimicrobial data, it reveals that Cu(II) complex exhibits more inhibition compared to Schiff base ligand, Co(II), Ni(II) and Zn(II) complexes. The anti-inflammatory activity of Schiff base ligand and copper(II) complex was done by HRBCs stabilization method. The concentration plays a vital role in increasing the degree of inhibition, the activity increased with increasing concentration of the synthesized compounds. Copper(II) complex has good inhibition activity than Schiff base ligand. *In vitro* anti-cancer studies of copper(II) complex showed safer anticancer agent against human breast cancer cell lines. The anti-diabetic activity of the Schiff base ligand and its copper(II) complex was examined by Alpha-amylase

inhibition assay method. Copper(II) complex showed good anti-diabetic activity. In view of such a result, the anti-diabetic therapeutic approach may reduce the postprandial glucose level in blood by the inhibition of alpha-amylase enzymes, which can be an important strategy in the management of blood glucose which can be useful for drug designing.

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