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Synthesis, Characterization, Biocidal, Anti-diabetic, Anti-inflammatory and Anti-Cancer(MCF-7) Studies of Schiff base Ligand and its Metal(II) Complexes

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ABSTRACT

A new Schiff base ligand (L^1) was prepared from 3-aminoquinoline with 2,5 dimethoxybenzaldehyde in 1:1 molar ratio. Two different co-ordination of mononuclear metal(II) complexes [(ML^1) & (ML^1L^2)] [M = Co(II), Ni(II), Cu(II) and Zn(II)] were synthesized & characterized. ML^1 were prepared from L^1 and metal acetate salts molar proportion One:Two. ML^1L^2 synthesized from L^1, metal salts and 8-hydroxy quinoline (L^2) molar ratio is 1:1:1. Elemental analyses, IR, NMR, Electronic spectra, Mass spectra, EPR, SEM and Powder XRD & molar conductivity are need to clarify the structure of synthesized metal(II) complexes. The square planar geometry is proposed for CuL^1, NiL^1, ZnL^1, NiL^1L^2 and ZnL^1L^2, tetrahedral geometry for CoL^1 & CoL^1L^2 and distorted square planar geometry for CuL^1L^2 complex. Powder XRD reveals that L^1, ML^1 & ML^1L^2 have crystalline nature. Antibacterial activity of Ligand, ML^1 & ML^1L^2 were screened against bacterium *Gram(+)*, *Gram(-)* & antifungal activity was determined against fungus. The anti-inflammatory and anti-diabetic actions of the L^1, CuL^1 & CuL^1L^2 complexes were studied. The anticancer activity of L^1, CuL^1 and CuL^1L^2 were studied opposed to MCF-7 using MTT assay method.

Keywords: Schiff base, Schiffbase complexes, Co-ligand complexes, Anti-diabetic, Anti-cancer.

INTRODUCTION

Schiff bases obtain by the condensation of amino and carbonyl compounds are intrinsic class of ligand that coordinate to metal ions via azomethine nitrogen and have been extensively for its wide range of medicinal applications[1].

In the past years, many new antibiotics failed to meet the challenges posed by multidrug-resistant bugs, such drugs are needed which are enough to work against & control antibiotic resistance[2]. Over the years, Schiff base and their metal complexes have amazing properties like catalysts in different biological systems, polymers, dyes, antimicrobial activities, antitumor, cytotoxic and drug fields[3, 4,5].

Quinolines are a class of nitrogen heterocycles, present in a large number of natural and synthetic

compounds that exhibit antimicrobial, antibiotic, anti malarial, antitumor, immunosuppressive, analgesic, anticonvulsant and antihypertensive activities[6].

Schiff base complexes are play an important role in biological, pharamecutical, agrochemical and organic industries and to design of new mixed ligand complexes greater potential application in this field[7].

In the this work, mononuclear metal(II) complexes with L^1 and with a co-ligand (8-hydroxy quinoline) were prepared. The prepared ML^1 & ML^1L^2 have been characterized by physicochemical properties and *In vitro* antimicrobial activity, anti-inflammatory, anti-diabetic and anti-cancer activities of metal complexes were also studied.

MATERIALS AND METHODS

The 3-aminoquinoline and 2,5-dimethoxy benzaldehyde utilized for the preparation of ligand were purchased from TCI chemicals. The Metal acetate salts were purchased from Sigma Aldrich. All the solvents were purchased from Loba and used without further purification. 8-Hydroxyquinoline used in the present work was acquired from S.D Fine chem. Limited.

The percentage of C, N, O, and metal was determined by a FEI Quanta-250 FEG elemental analysis apparatus. The absorbention spectra of the L^1, ML^1 & ML^1L^2 dissolved in dimethylformamide were recorded on the JASCO V 650 in the range of 200 – 800 nm. Vibrational spectra of the compounds was recorded in Bruker Tensor 27 in the range of 4000-400 cm^{-1}. ^1H & ^{13}C NMR spectra were recorded on the Bruker 300 Hz spectrometer using DMSO-d_6 as a solvent. Mass spectrum was recorded for the L^1, ML^1 & ML^1L^2 using 410 Prostar Binary LC with 500MS IT PDA Detectors. TG/DTA analysis was carried out under nitrogen atmosphere using Shimadzu TG-50 thermo balance. The surface nature of the compounds were determined by CAREL ZEISS EVO 18 Scanning electron microscope.

Synthesis of L^1

The ligand (E)-1-(2,5-dimethoxyphenyl)-N-(quinolin-3-yl)methanimine was prepared using 2,5-dimethoxybenaldehyde and 3-aminoquinoline. 1mmol of 2,5-dimethoxybenaldehyde (0.166 g) dissolved in 20 mL of methanol was mixed dropwise into 1mmol CH_3OH solution of 3-aminoquinoline (0.144 g). The mixture was stirred continuous by and refluxed for 3 h at 50–70°C, product obtained was filtered and dried.

Synthesis of ML^1

Methanolic solution of ligand (E)-1-(2,5-dimethoxyphenyl)-N-(quinolin-3-yl)methanimine (2mmol, 0.584 g) was added to the methanolic solution of Metal(II) acetate salts (1 mmol) of Cu(II), Ni(II), Co(II) and Zn(II) in the molar ratio 2:1. All complexes were stirred and refluxed at 70°C for about 4 hours. The hot solution was cooled and dried at room temperature.

Synthesis of mixed ML^1L^2

The methanolic solution of (1mmol) (E)-1-(2,5-dimethoxyphenyl)-N-(quinolin-3-yl) methanimine (L^1) was added to the methanolic solution of Metal(II) acetate salts (1mmol) of (Cu(II), Ni(II), Co(II), and Zn(II)) in the RB Flask. 8-Hydroxy quinoline (L^2) (1mmol) dissolved in methanol was mixed dropwise into the above mixture. The ligand, metal salt and 8-hydroxyquinoline were taken in the ratio 1:1: 1. The mixture was stirred and refluxed for 3 h then dried at room temperature.

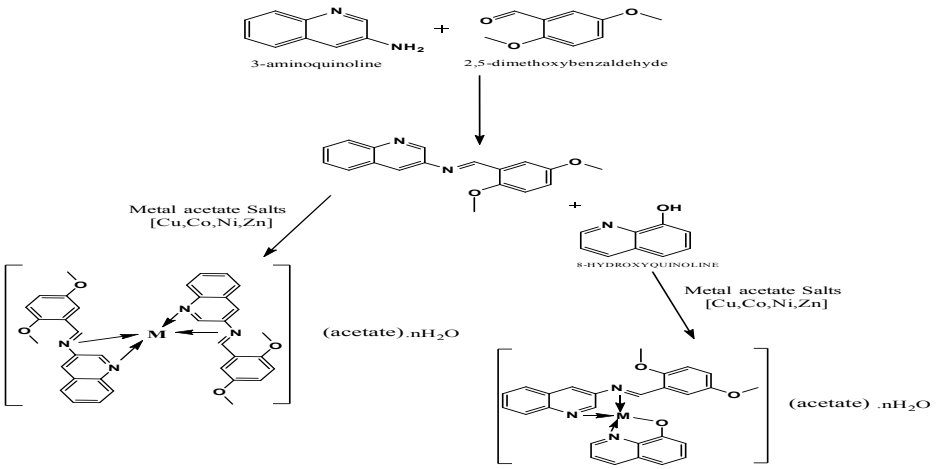


Fig. 1. Synthesis of Schiff base ligand[L^1], [ML^1] & [ML^1L^2] complexes

RESULTS AND DISCUSSION

The analytical data of the L^1, ML^1 & ML^1L^2 are given in Supplementary Table 1. ML^1 & ML^1L^2 are coloured and sparingly soluble in ethanol, methanol, acetone, chloroform and soluble in DMSO and DMF but insoluble in water.

Molar Conductance

Molar conductance was measured at 1×10^{-3} M for ML^1 & ML^1L^2 in DMSO at room temperature. The mononuclear metal complexes exhibit low value in the range of 11-23 ohm^{-1} cm^2 mo l^{-1} [8] indicates that ML^1 & ML^1L^2 are non-electrolytic as given in Supplementary Table 1.

FT - IR spectral studies

The IR spectra of complexes are studied with L^1 to determine the co-ordination sites that may be involved in chelation. The FT-IR data with the assignments of band frequencies of L^1, ML^1 & ML^1L^2 complexes are presented Supplementary Table 2 and the spectrum, are shown in Supplementary Figure 1.

The sharp peak observed at 1581cm^{-1} in the IR spectra of L^1 assigned to υ(CH=N) is shifted to lower frequency for ML^1 & ML^1L^2, indicating the involvement of azomethine nitrogen in chelation with the metal ion[9]. However, stretching frequency of methoxy (-OCH_3) group appeared in the range of 2828-2833 cm^{-1} as observed in L^1, [ML^1] and [ML^1L^2] complexes, indicates the non-participation of methoxy oxygen in co-ordination[9]. The new bands in IR spectra of ML^1 & ML^1L^2 in regions 493-533 cm^{-1} and 472-497 cm^{-1} are ascribed to υ(M-O) and υ(M-N) respectively, which indicates the co-ordination of L^1, co-ligand with the metal ion[10].

Electronic spectral studies and magnetic moment

The Absorption spectrum of the L^1, ML^1 and ML^1L^2 were recorded in DMSO solution over the range of 200-800 nm and the spectral data are listed in Supplementary Table 3 and shown in Fig. 2. The UV-spectra of L^1 reveals high intense absorption peaks at 270 nm (37037 cm^{-1}) and 369 nm (27100 cm^{-1}) which are due to π-π^* and n-π^* transitions respectively. But in metal complexes, azomethine peak was shifted to shorter wavelength, this shift is attributed to the coordination of the nitrogen atom of the imine group with the metal ion.

The Absorption spectra of Cu(II) complexes [CuL^1] and [CuL^1L^2] exhibit two bands, the charge transfer region at 439 nm for CuL^1 complex and another band in the region 594 nm assigned to $^2T_{2g}\rightarrow{}^2E_g$ transition indicating the square planar geometry and the magnetic value is 1.95 B.M. Another Cu(II) complex CuL^1L^2 exhibits intense broad band at 440 nm which maybe reasonably assigned to $^2B_{1g}\rightarrow{}^2A_{1g}$ transition, corresponds to a distorted squareplanar geometry for Cu(II) ion and the observed magnetic moment value is 1.81 B.M.[11].

The visible spectra of Ni(II) complexes, [NiL^1] and [NiL^1L^2] show three bands. One intense peak show 381-392 nm due to charge transfer transition and the d-d transition exhibits in the range of 470-550 nm are assigned to $^3A_{2g(F)}\rightarrow{}^3T_{1g(P)}$ and $^3A_{2g(F)}\rightarrow{}^3T_{1g(F)}$ transitions respectively, consistent with a square planar geometry around Ni(II) ion, which are further supported by the magnetic value range between 3.81-3.05 B.M.[12]

The UV-spectrum of cobalt(II) complex [CoL^1] shows three intense peaks and [CoL^1L^2] complex shows two intense peaks. One peak at 382-393 nm for complexes CoL_1 and CoL^1L^2 is due to charge transfer transition and another two peaks exhibited d-d transition in the visible region at 450-457 nm and 510-511 nm corresponding to tetrahedral geometry for Co(II) ion. The magnetic moment value of Co(II) complexes are in the range of 4.41-4.83 B.M.[13]

The UV-spectrum of Zn(II) complexes [ZnL^1] and [ZnL^1L^2] shows bands in the range 392-482 nm may be due to L$\rightarrow$ M charge transfer which indicates square planar geometry and it is diamagnetic nature[14].

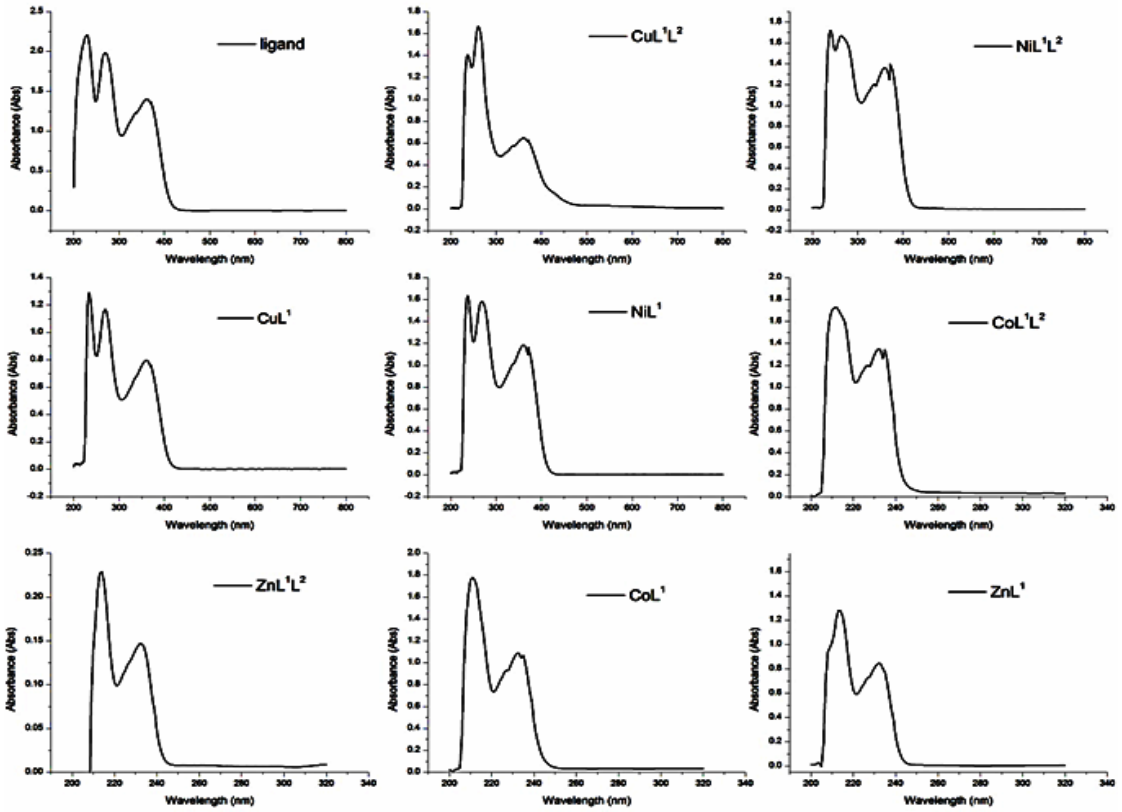


Fig. 2. UV Spectra of L^1, ML^1 and ML^1L^2

^{1}H NMR

The structure of the Schiff base ligand is fairly supported by ^{1}H NMR spectra recorded in $CDCl_3$ as a solvent. On examining the ^{1}H NMR spectrum of the ligand it exhibited a multiplet signal at δ (8.51–6.93) ppm for aromatic protons. The presence of azomethine(CH=N) group is indicated by a singlet at δ (8.92) ppm. Which confirms the formation of imine ligand. A signal at δ (3.81) ppm indicates the presence of methoxy (O-CH_3) protons as shown in Supplementary Figure 2.

^{13}C NMR

In ^{13}C NMR, the number of signals represents the number of carbons of the synthesized compound which are non-equivalent. The signal that appeared at δ (158.34) ppm is attributed to azomethine carbon. Signals observed at δ=110–129 ppm are assigned for aromatic carbons. Phenyl ring of ligand showed the following signals 146.61(CH=N), 147.15, 145.73 (C-N). The methoxy carbons show peaks at 56.25 and 55.94 ppm as shown in Supplementary Figure 3.

Mass Spectra

Mass spectral data gives valuable information on molecular weights, the synthesized ligands and its metal(II) complexes were characterized by ESI–MS spectrometry in positive ion mode[15]. The ESI mass spectra of the L^1, ML^1 & ML^1L^2 were recorded and the obtained molecular peaks confirmed the proposed structures. The ESI mass spectrum of the Schiffbase ligand shows an intense peak at 294.05. The mass spectrum of the CuL^1, NiL^1, CoL^1, ZnL^1, CuL^1L^2, NiL^1L^2, CoL^1L^2 and ZnL^1L^2 complexes gives a molecular ion peak at 781.99, 833.28, 835.03, 802.84, 636.14, 678.48, 683.43 and 647.24 m/z respectively which indicate the stoichiometry composition of complexes as shown in Supplementary Table 4 and Supplementary Figure 4.

EPR Spectra

EPR spectrum of Cu(II) complexes were recorded in the solid-state at room temperature as shown in Supplementary Fig. 5. The CuL^1 & Cu L^1L^2 complexes gives $g_{\parallel} = 2.0610, 2.06145$ and $g^{\perp} = 2.00975, 2.02272$ respectively. The $g_{\parallel}$ values of these complexes lie below 2.3 ($g^{\perp} < 2.3$)which indicates the covalent environment around the Cu(II) ion[16]. The calculated G ($G = g_{\parallel}$-2.0023/$g^{\perp}$ -2.0023) value is 7.88 for CuL^1 complex and 2.86 for Cu L^1L^2 complex which indicates squareplanar geometry for CuL^1 complex and distorted square planar geometry for Cu L^1L^2 complex.

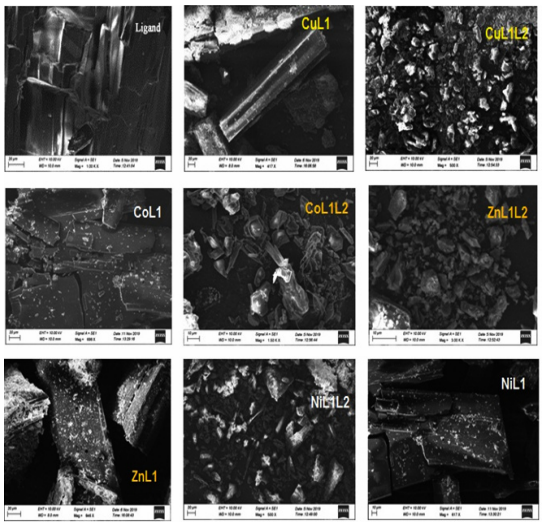


Fig. 3. SEM analysis of Schiff base ligand, ML^1 and ML^1L^2

SEM

The surface morphology of the synthesized L^1, ML^1 & ML^1L^2 was done by scanning electron microscopy. The synthesized L^1, ML^1 & ML^1L^2 were carried out and the obtained images are shown in Fig. 3. The SEM images indicates that the L^1, ML^1 & ML^1L^2 have different distinctive surface morphology[15].

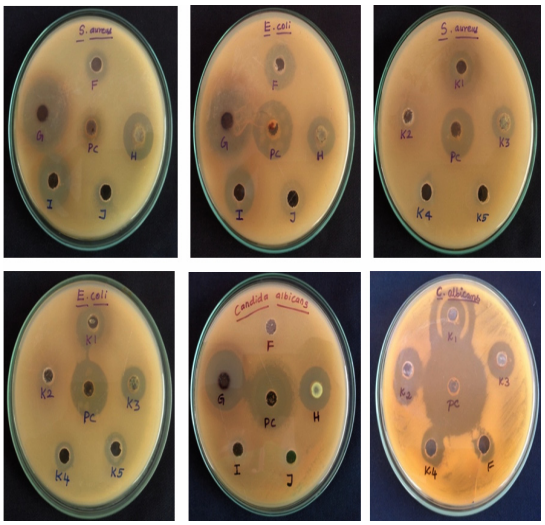
Powder X-Ray diffraction

The powder XRD for the L^1, ML^1 and ML^1L^2 were performed. The synthesized compounds show well explicates crystalline peaks indicating that the samples are crystalline.The ligand and all synthesized complexes have specific'd' values which can be used for its characterization. The crystalline size of the ligand and their complexes dXRD could be estimated from XRD patterns by the Scherrer's formula[17]. The value of crystalline size of the ligand and all complexes are (Ligand =100.74, CuL^1=49.87, NiL^1=74.45, CoL^1=78.02, ZnL^1=64.44, CuL^1L^2 = 64.92, NiL^1L^2 = 47.72, CoL^1L^2 = 29.65, ZnL^1L^2 = 41.03) respectively as shown in Supplementary Table 5 and Supplementary Figure 6.

Antimicrobial activity

The ligand, ML^1 & ML^1L^2 were screened for antimicrobial activity by disc diffusion method and are compared with standards tetracycline and fluconazole as shown in Fig. 4. The results are presented in Supplementary Table 6.

The antibacterial and antifungal actions of the Schiff base ligand, ML^1 & ML^1L^2 were tested against *Gram(+)* bacteria (*Staphylococcus aureus*), *Gram(-)* bacteria (*Escherichia coli*) and one fungus (*Candida albicans*). All metal(II) complexes show maximum inhibition zone than the free ligand. ML^1L^2 complexes show good activity compared to the ML^1 complexes because L^2 (8-Hydroxyquinoline) acted as a co-ligand in ML^1L^2 complexes. From the above results, it is concluded that CuL^1L^2 complex exhibits the highest antimicrobial activity.



F-Ligand , G-CuL^1, H-CoL^1, I-NiL^1, J-ZnL^1, K_1-CuL^1L^2, K_2-CoL^1L^2, K_3-NiL^1L^2, K_4-ZnL^1L^2

Fig. 4. Anti-microbial activity of the ligand, ML^1 & ML^1L^2 complexes

Anti-inflammatory activity

The synthesized Schiff base-ligand and its Copper(II) complexes [CuL^1 & CuL^1L^2] were examined for anti-inflammatory activity by HRBC stabilization method at various concentrations (20, 40, 60, 80, 100 µg/mL). Diclofenac sodium was used as a standard. The percentage inhibition of hemolysis by the ligand, ML^1 & ML^1L^2 are presented in Supplementary Table 7. In all the concentration of CuL^1 and CuL^1L^2 complexes show a maximum% inhibition of hemolysis compared to the free ligand. The CuL^1L^2 complex shows a minimum IC_{50} value of 28.50 µg/mL and the complexes stabilized human blood cell membrane in a dose-dependent manner[18]. Thus CuL^1L^2 complex shows the best anti-inflammatory activity.

Antidiabetic Studies

The antidiabetic activity was examined by the standard amylase inhibition assay. The inhibition activity of the synthesized compounds

against α-amylase is given in supplementary Table 8. Both copper(II) complexes exhibit more inhibition activity than the free Schiff base ligand. CuL^1L^2 complex shows excellent amylase inhibition activity. CuL^1 complex shows fine activity as compared to the schiffbase ligand. The IC_{50} value of the free Schiffbase, CuL^1 and CuL^1L^2 complexes are 54.80, 11.91 and 3.86 µg/ml respectively.

Anticancer activity

Anti-cancer activity of the (E)-1-(2,5-dimethoxyphenyl)-N-(quinolin-3-yl)methanimine, CuL^1 and CuL^1L^2 metal complexes were tested against MCF-7 (breast cancer) at different concentrations (3.125, 6.25, 12.5, 25, 50µg/mL) as shown in Fig. 5. The viability of the cancer cells by ligand and its metal complexes are 100% at zero concentration. (97.85, 90.40, 71.81, 46.72, 33.49%) for ligand, (97.09, 87.39, 70.84, 48.98, 26.93%) for CuL and (89.91, 74.46, 59.78, 37.58, 24.34%) for CuL^1L^2 when the concentration increases the cell viability of cancer cells decreases, that mean the cytotoxicity of the cells decreases and the complex is potential which is due to less number of live cells[19]. The *In vitro* anticancer studies reveal that the CuL^1 and CuL^1L^2 have moderate activity than the ligand. Particularly CuL^1L^2 complex are highly active with IC_{50} value 24.92 µg/mL compared to the free ligand and CuL^1 complex.

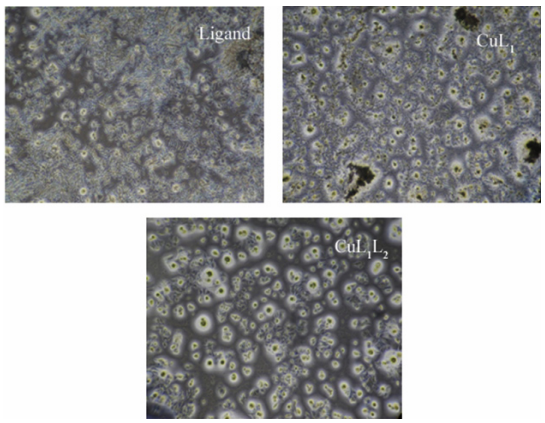


Fig. 5. Anti-Cancer activity of synthesized ligand, CuL^1 and CuL^1L^2 complexes

CONCLUSION

Schiff base complexes of (b-e) obtained from (E)-1-(2,5-dimethoxyphenyl)-N-(quinolin-3-yl) methanimine in a ratio (1:2) and co-ligand complex with 8-hydroxy quinoline at ratio (1:1:1) have been synthesized and characterized. The stoichiometry of all complexes are confirmed by elemental analysis. All the metal complexes are non-electrolyte nature dependent upon molar conductance value. The physicochemical data reveals that CuL^1, NiL^1, ZnL^1, NiL^1L^2, ZnL^1L^2, complexes have square planar geometry, CoL^1 & CoL^1L^2 complexes have tetrahedral geometry, CuL^1L^2 complex have distorted square planar geometry. The powder XRD pattern showed the crystalline nature of the L, ML^1 & ML^1L^2. By using the SEM analysis, morphology of all complexes is have been studied. The synthesized ligand and their ML^1 and ML^1L^2 metal complexes were tested against *Gram(+), Gram(-)* and one fungus strain. The data showed that CuL^1 and CuL^1L^2 exhibits better activity than other compounds. CuL^1L^2 shows high zone of inhibition compared to the CuL^1 complex. The anti-inflammatory, anti-diabetic and anticancer studies of ligand, CuL^1 and CuL^1L^2 were done. From the studies, it is suggested that CuL^1L^2 shows better activity than the free ligand and CuL^1. Finally, it is concluded that CuL^1L^2 may be used as effective biological agents with reduced toxicity and higher efficiency.

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Conflicts of Interest

The authors declare no conflict of interest.

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