

Research Article

Synthesis, Characterization, and Biological and Cytotoxic Studies of Copper(II), Nickel(II), and Zinc(II) Binary Complexes of 3-Amino-5-methyl Isoxazole Schiff Base

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Binary complexes of Cu(II), Ni(II), and Zn(II) ions have been synthesized by reacting metal salts with a Schiff base, 2-((E)-(5-methylisoxazol-3-ylimino)methyl)-4-methoxyphenol (MIIMMP) in an alcoholic medium. All the metal complexes and schiff base have been characterized by using elemental analysis, IR, UV-VIS, ¹H-NMR, ¹³C-NMR, Mass, ESR spectral data, magnetic moments, TG, and DTA studies. Based on the analytical, spectral data and molecular modeling studies, Ni(II) and Zn(II) metal complexes have octahedral geometry, whereas Cu(II) complex has tetragonal geometry. The antimicrobial and cytotoxic activities of the Schiff base and its metal complexes were studied on bacteria, fungi, and human cervical carcinoma cells (HeLa).

1. Introduction

Heterocyclic Schiff bases are basically important because of their raised biological activity, and also they make possible development of novel materials with unique properties. One very interesting and promising class of heterocyclic Schiff base is the series of 3-amino-5-methyl isoxazole with various aldehydes. This type of heterocyclic isoxazole Schiff base has significant pharmacological and biological activity such as antibacterial, antifungal, anticancer, and anti HIV activity and also has applications as pesticides and insecticides [1–12]. Metal complexes of isoxazole derivatives have been extensively investigated and reported from our laboratory [13, 14]. In the present investigation we report herewith the synthesis and characterization of Schiff base MIIMMP and its Cu(II), Ni(II), and Zn(II) complexes. This Schiff base has N,O donor site and good coordination ability for the metal ions. The novel Schiff base and its metal complexes were evaluated for their antimicrobial properties against bacteria and fungi. Cytotoxic effect of the copper, nickel, and zinc complexes on

human cervical carcinoma cells (HeLa) was measured using the MTT assay.

2. Experimental

2.1. Materials and Methods. All the chemicals used were analytical reagent grade. Solvents such as water, methanol, acetone, petroleum ether, and chloroform were purified by standard procedures [15].

2.2. Physical Measurements. ¹H-NMR and ¹³C NMR spectrum of the ligand was recorded on Bruker 400 MHz NMR instrument and using TMS as internal standard. The EI mass spectrum was recorded on a VG micromass 7070-H instrument. Electronic spectra of metal complexes in DMSO were recorded on Shimadzu UV-VIS 1601 spectrophotometer. Magnetic susceptibilities of the complexes were determined on Gouy balance model 7550 using Hg[Co(NCS)₄] as standard. The diamagnetic corrections of the complexes

were computed using Pascal's constants. TG of complexes was carried on Mettler Toledo Star system in the temperature range of 0–1000°C. Melting point of the ligand and decomposition temperature of complexes were determined on Polmon instrument (model number MP-96). IR spectra of the compounds were recorded using KBr pellets in the range (4000–400 cm⁻¹) on Perkin-Elmer Infrared model 337. The percentage composition of C, H, and N of the ligand and complexes was determined by using microanalytical techniques on Perkin Elmer 240C (USA) elemental analyzer. The EPR spectrum of the copper complex was recorded on EPR Varian-E-112 at low temperature. The percentage composition of metal ions in solid metal complexes was determined by atomic absorption spectrophotometer.

2.3. Antimicrobial Screening. The ligand and its metal complexes were screened against bacteria and fungi. Antibacterial screening was done by the paper disc method (Kirby-Bauer method) [16]. The bacterial organisms used are *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram -ve). Cultures of test organisms were maintained in nutrient agar media and subcultured in Petri dishes prior to testing. The fungal organisms used are *Aspergillus niger* and *Candida albicans*. Cultures were maintained on potato dextrose agar slants and subcultured in Petri dishes prior to testing.

2.4. Cell Culture. The human cervical carcinoma cell lines (HeLa) were cultured as a monolayer with Roswell Park Memorial Institute medium (RPMI-1640), supplemented with 10% (v/v) fetal bovine serum (FBS), 2 mM L-glutamine, 4.5 g/L glucose, 1 × nonessential amino acids, and 1 × antibiotics consisting of penicillin/streptomycin, gentamicin, amphotericin B, and nystatin at 37°C, in a humidified atmosphere of 5% CO₂, in a CO₂ incubator.

2.4.1. Cytotoxicity Assay (MTT Assay). The MTT assay was used to assess cytotoxicity [17]. The human cervical carcinoma cell lines (HeLa) were obtained from national center for cell science (NCCS), Pune, India. Briefly, the metal complexes (from 1 to 6) were dissolved in DMSO, diluted in culture medium, and used to treat the cancer cell, with the complex in the concentration range of 2 to 10 µg/mL, for a period of 72 h. DMSO, diluted in the culture medium, was used as the solvent control. A miniaturized viability assay using 3-[4,5-dimethyl thiazole-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) was carried out according to the method described by Mosmann [18]. HeLa cells growing exponentially were added across the plates cell number to 96-well plates. HeLa cells growing exponentially were added across the plates cell number to 96-well plates (Orange Scientific) at a density of 3 × 10³ per well after counting on Bright line Haemocytometer (Sigma Ltd). Compounds (1–100 µM) were then added to the wells, ensuring an equal volume of 200 µL across the plates. Cell number/proliferation was measured at 72 h using a standard methyl thiazole tetrazolium (MTT) based assay without modifications. Briefly, MTT (Hi Media Ltd.) was added to each well, to yield a working concentration of

0.4 mg mL⁻¹, and the plates were returned to the incubator for a further 2 h. After this time, the medium was aspirated, 200 µL of DMSO (Sigma Ltd.) was then added to each well, and the plates were agitated gently for 5 min before measuring the optical density at 600 nm each well using Thermo Scientific Multiskan EX Elisa reader. The IC₅₀ value was determined as concentration of the complex that is required to reduce the absorbance to half that of the control.

2.5. Synthesis of MIIMMP Ligand. 3-amino-5-methyl isoxazole (5 mmol, 0.49 g) was dissolved in hot methanol to which 5-methoxy salicylaldehyde (5 mmol, 0.76 g) was added, and the mixture was refluxed for 3 hours under nitrogen atmosphere. The dark yellow product formed was filtered and washed with petroleum ether and recrystallized from methanol. Purity of the compound was checked by TLC. Yield: 85%.

2.6. General Procedure for the Synthesis of Metal Complexes. In the preparation of the metal complexes, metal and the ligand were mixed in 1:2 molar ratio using required quantities of methanol. Hot methanol solution of ligand (1 mmol, 0.232 g) and hot methanol solution of CuCl₂·H₂O (0.5 mmol, 0.076 g)/NiCl₂·6H₂O (0.5 mmol, 0.118 g)/Zn(CH₃COO)₂·2H₂O (0.5 mmol, 0.11 g) were mixed together with constant stirring. The mixture was refluxed for 2–3 hours at 70–80°C on water bath. On cooling, colored solid metal complexes were precipitated out. The products were filtered, washed with cold methanol, and dried under vacuum over P₄O₁₀.

3. Results and Discussion

3.1. Characterization of MIIMMP Ligand. This ligand was reported earlier. The following physical and spectral data obtained are in good agreement with the literature data. MIIMMP Schiff base was yellow in colour and is stable to air and moisture. The percentage composition of C, H, N, and O of the compound is presented in the Table 1.

Spectral Data of 2-((E)-(5-methylisoxazol-3-ylimino)methyl)-4-methoxyphenol (MIIMMP)

¹H NMR (CDCl₃, ppm): δ 12.06 (s, -OH), 8.87 (s, CH=N), 6.98–7.47 (m, H-2, 3, 5), 6.13 (s, H-4'), 3.82 (s, -OCH₃), 2.482 (s, 5'-CH₃).

¹³C NMR (DMSO, ppm): 171.0 (C-3'); 167.5 (CH=N); 169.1 (C-5'); 156.0 (C-1); 152.5 (C-2); 122.3 (C-3); 118.4 (C-5); 118.0 (C-6); 115.9 (C-4); 96.6 (C-4'); 55.9 (-OCH₃); 12.5 (C-5'-CH₃).

UV (DMSO): 363 (λ max).

Mass: m/z 233(M⁺).

3.2. Characterization of Metal Complexes. All the complexes are stable at room temperature and are nonhygroscopic.

TABLE 1: Analytical data of Schiff base and metal complexes.

Complex	Formula	M. wt.	C	H	N	O	M
MIIMMP	$C_{12}H_{12}N_2O_3$	232	62.06 (66.65)	5.21 (5.59)	12.06 (12.96)	20.67 (20.85)	—
$[Cu(MIIMMP)_2(H_2O)_2]$	$[CuC_{24}H_{26}N_4O_8]$	561	51.29 (47.13)	4.66 (3.08)	9.97 (9.65)	22.77 (17.03)	11.31 (11.02)
$[Ni(MIIMMP)_2(H_2O)_2]$	$[NiC_{24}H_{26}N_4O_8]$	557	51.74 (50.38)	4.70 (4.12)	10.06 (9.81)	22.97 (19.13)	10.53 (9.99)
$[Zn(MIIMMP)_2(H_2O)_2]$	$[ZnC_{24}H_{26}N_4O_8]$	563	51.12 (51.02)	4.65 (4.32)	9.94 (9.90)	22.70 (22.65)	11.60 (10.97)

*The values mentioned within the bracket are obtained.

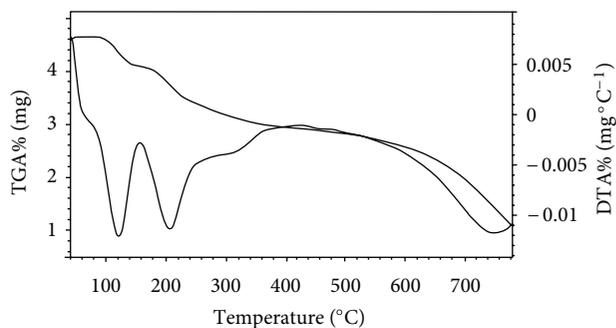
TABLE 2: IR absorption frequencies of metal complexes.

Compound	ν (OH)	ν (CH=N)	ν (C-O)	Coordinated water	ν (M-O)	ν (M-N)
MIIMMP	3418	1608	1248	—	—	—
$[Cu(MIIMMP)_2(H_2O)_2]$	3361	1634	1271	773	585	457
$[Ni(MIIMMP)_2(H_2O)_2]$	3308	1632	1305	794	570	461
$[Zn(MIIMMP)_2(H_2O)_2]$	3273	1631	1284	785	587	457

On heating, they decompose at high temperatures. The complexes are insoluble in water but are soluble in DMSO.

3.2.1. Elemental Analysis. The analytical data of the complexes are presented in Table 1. From the data it is clear that the experimental values shown for each of the complexes are in good agreement with the theoretical values calculated for 1:2 ratio. The composition assigned to the complexes may, therefore, be formulated as presented in the Table 1.

3.2.2. IR Spectra. The important absorption frequencies of all complexes with its ligand and their assignments are given in Table 2. In MIIMMP Schiff base azomethine stretching vibrations appear as split bands with two maxima in the 1608 and 1581 cm^{-1} range. These bands are shifted to higher frequency region to the extent 23–26 cm^{-1} in complexes, indicating the nitrogen of azomethine is coordinated to the metal ion [19, 20]. A broadband around 3418 cm^{-1} in MIIMMP due to the phenolic OH group is disappeared in their complexes indicating coordination through phenolic hydroxyl group [21]. A medium intensity band around 1248 cm^{-1} due to phenolic ν C-O group of the ligand shifted to positive side by 23–40 cm^{-1} in its complexes suggesting the participation of the oxygen of the hydroxyl group in bonding with the metal ion [22]. These facts suggest that the shifts are due to coordination of ligand to the metal atom by the azomethine nitrogen and phenolic oxygen. The presence of coordinated water molecules in all the complexes is indicated by a broadband in the 3273–3361 cm^{-1} range and weaker bands around 773–794 cm^{-1} range, which could be assigned to OH stretching, rocking, and wagging vibrations, respectively [23]. This fact is also supported by the results of elemental analysis, TG of complexes, and also by the appearance of nonligand bands at appropriate positions in the far infrared region (570–585 cm^{-1} and 457–461 cm^{-1}) due to ν M-O and ν M-N vibrations, respectively [24].

FIGURE 1: TGA spectrum of $[Cu(MIIMMP)_2(H_2O)_2]$.

3.2.3. Thermal Analysis. In the present investigation, the following thermo analytical methods have been used: (1) thermogravimetric analysis (TG) and (2) differential thermal analysis (DTA). From the thermograms of these complexes, it is concluded that the coordinated water molecules are eliminated in the temperature range of 60–160°C, and the ligands gradually decompose to their corresponding metal oxides at higher temperatures. Presence of water molecules is further confirmed by the endothermic bands observed in the respective DTA curve in the temperature region where the TG curves loss in weight. In addition to the endothermic bands, the DTA curves of complexes also show exothermic bands. These bands appeared at higher temperatures which represent phase transition, oxidation, and/or decomposition of the compound.

Representative thermogram of $[Cu(MIIMMP)_2(H_2O)_2]$ is given in Figure 1. From the figure it is found that the heating rates were suitably controlled at 10°C min^{-1} under nitrogen atmosphere, and the weight loss was measured from the ambient temperature up to 1000°C. The thermal decomposition process of $[Cu(MIIMMP)_2(H_2O)_2]$ complex can be divided into three stages. The first stage occurs in the range of 100–130°C which corresponds to the loss of two molecules of coordinated water. In continuation to the first

TABLE 3: Electronic spectral data and magnetic susceptibility of metal complexes.

Complex	Frequency in cm^{-1} (nm)	$\epsilon = 10^2 \text{ M}^{-1} \text{ cm}^{-1}$	μ_{eff}
$[\text{Cu}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$	16,920 (591)	0.045	1.87
$[\text{Ni}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$	16,534 (604); 18,963 (527); 24,096 (415)	0.89, 0.64, 0.48	3.21

stage, the degradation stages occur in the range of 180–260°C which corresponds to partial decomposition of the ligand [25]. The degradation stage in the range of 260 to 780°C range corresponds to the pyrolysis of ligand molecules leaving copper oxide as a residue.

3.2.4. Magnetic Susceptibility and Electronic Spectra. The electronic spectra and magnetic moment of the metal complexes are listed in Table 3. The magnetic moment value of Cu(II) complex is 1.87 B.M. falls within the normal range observed for distorted octahedral complexes. The significant electronic absorption bands in the spectrum of the complex recorded in DMSO solution. In the present study, the electronic spectrum of $[\text{Cu}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$ shows a broadband at $16,920 \text{ cm}^{-1}$ that can be assigned to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ transition indicating the copper(II) ion has tetragonal geometry [26].

The magnetic moment of the Ni(II) complex (3.21 B.M.) probably indicates an octahedral structure. The ground state of a regular octahedral complex is ${}^3\text{A}_{2g}$ which is orbitally nondegenerate. Hence, it does not contribute to the magnetic moment in terms of orbital angular momentum, and the value must, therefore, be equivalent to the spin-only value of 2.80 B.M. But the values usually observed for octahedral complexes are slightly more than 2.80 B.M. which could be due to spin-orbit coupling between the ground state ${}^3\text{A}_{2g}$ and the first excited state ${}^3\text{T}_{2g}$. This makes Ni(II) complex has the experimental values in the range 2.9–3.8 B.M. The electronic spectrum of $[\text{Ni}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$ complex shows three bands around 16,534, 18,963, and 24,096 cm^{-1} . These have been assigned, respectively, to the transitions ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{2g}(\text{F})$ (ν_1); ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{F})$ (ν_2); ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$ (ν_3) of octahedral geometry [27].

The Zn(II) complex has been found to be diamagnetic in nature. The electronic spectrum of $[\text{Zn}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$ complex shows no d-d bands as expected for a d^{10} system. On the basis of analytical and spectral data $[\text{Zn}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$ is assigned to an octahedral geometry.

3.2.5. ESR Spectra. The ESR spectrum of Cu(II) complex has been recorded on X-band at frequency 9.1 GHz at low temperature. The spectrum of $[\text{Cu}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$ given in Figure 2 is characteristic of axial symmetry with g_{\parallel} , g_{\perp} , and Δg values of 2.45, 2.09, and 0.36. Anisotropy of the g -tensor is due to the Jahn-Teller effect, which reduces the symmetry from octahedral to distorted octahedral [28]. The fact that $g_{\parallel} > g_{\perp} > 2.0023$ (g_e) and $G = 5.05, >4$ indicates octahedral geometry of the Cu(II) ion of $d_{x^2-y^2}$ ground state with negligible exchange interaction in the complex

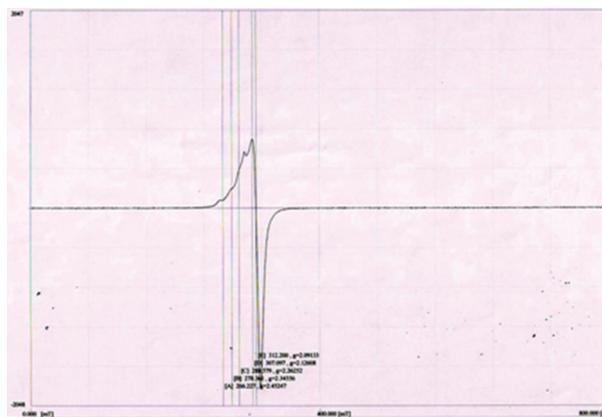
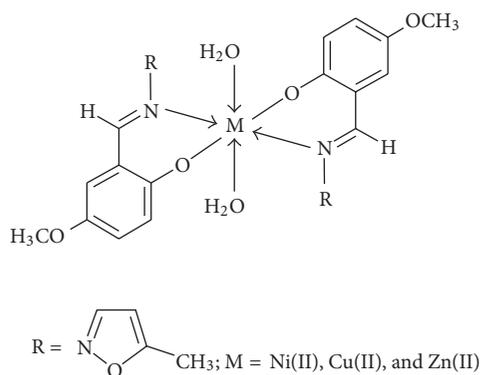
FIGURE 2: ESR spectrum of $[\text{Cu}(\text{MIIMMP})_2(\text{H}_2\text{O})_2]$.

FIGURE 3: Tentative structure of M(II) complexes.

[29, 30]. The tentative structure of metal complexes is shown in Figure 3.

4. Molecular Modeling Studies

In the absence of crystal data, it was thought worthwhile to obtain structural information through molecular modeling. Molecular mechanics, which provides the energy minimized conformation, is a tool of increasing importance for structural investigation of coordination and organometallic compounds. These were carried out with semiempirical PM3 Hamiltonian as implemented in HyperChem 7.0 software programme package. The ball and stick representation of the complexes were shown in Figure 4. The relative minimum energies and HOMO energy values for all the complexes are presented in Table 4.

TABLE 4: Relative energies and HOMO energy values of proposed energy-minimized molecular structures of metal complexes.

Complex	PM3 (total energy) in K.Cal/mole	PM3 (Homo values in eV)
[Cu(MIIMMP) ₂ (H ₂ O) ₂]	-6398.8971	-4.4390
[Ni(MIIMMP) ₂ (H ₂ O) ₂]	-6711.9254	-6.7615
[Zn(MIIMMP) ₂ (H ₂ O) ₂]	-6141.5301	-7.5137

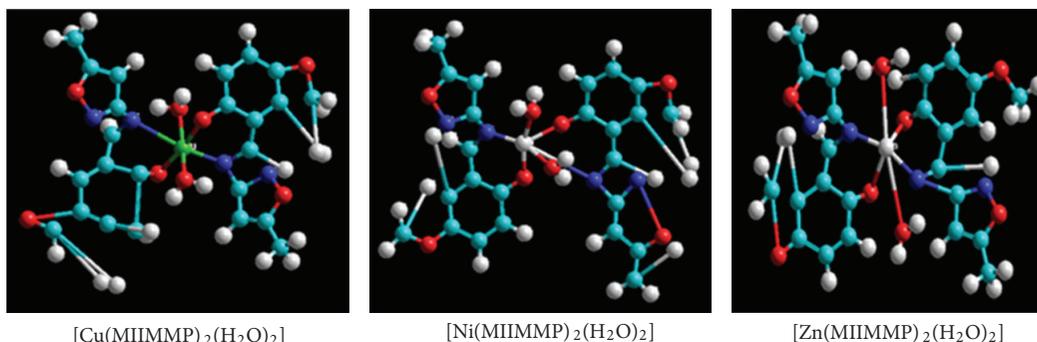


FIGURE 4: Proposed energy minimized structure of M(II) complexes.

5. Antimicrobial Activity

In the present investigation, biological activity of the MIIMMP ligand and its binary complexes with Cu(II), Ni(II), and Zn(II) have been screened for antimicrobial activity against bacteria (*E. coli* and *S. aureus*) and fungi (*A. niger* and *C. albicans*) by paper disc method. The results thus obtained are explained on the basis of Overton's concept and Chelation theory [31, 32]. The mode of action of the compounds may involve formation of a hydrogen bond through the azomethine group with the active centers of cell constituents, resulting in an interference with the normal cell process [33].

The variation in the activity of different complexes against different organisms depend either on the impermeability of the cells of the microbes or difference in ribosome of microbial cells. Comparison of the biological activity of the synthesized compounds with some known antibiotics (Ciprofloxacin and Ketoconazole) presented in Figures 5 and 6 shows generally the free Schiff base ligand and some of its complexes exhibit comparable effect with these antibiotics. Among these [Cu(MIIMMP)₂(H₂O)₂] complex exhibits good antimicrobial activity.

6. Cytotoxic Activity

The cytotoxic activity of copper, nickel, and zinc complexes was examined on cultured human cervical carcinoma cell lines (HeLa) for 72 h to the medium containing the respective complexes from 2 to 10 μg/mL concentration, and adopting MTT assay and results are given in Table 5. The cytotoxic activity that was determined according to the dose values of the exposure of the complex required to reduce survival of the cell is given in Figure 7. The toxicities of 10 μg/mL of [Cu(MIIMMP)₂(H₂O)₂], [Ni(MIIMMP)₂(H₂O)₂], and [Zn(MIIMMP)₂(H₂O)₂] complexes are found to be 64.65%,

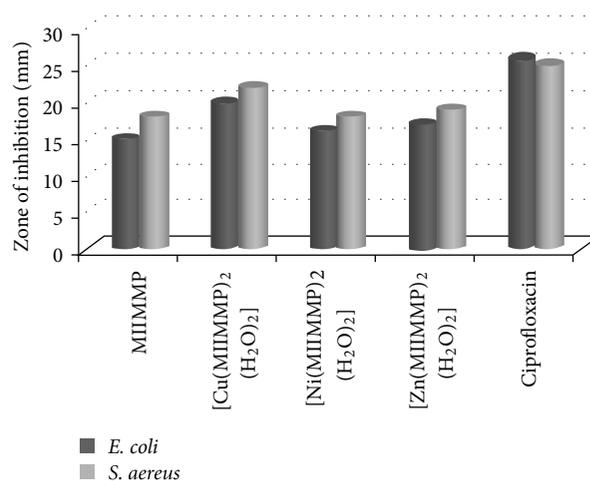


FIGURE 5: Antibacterial activity of the Schiff base and metal complexes.

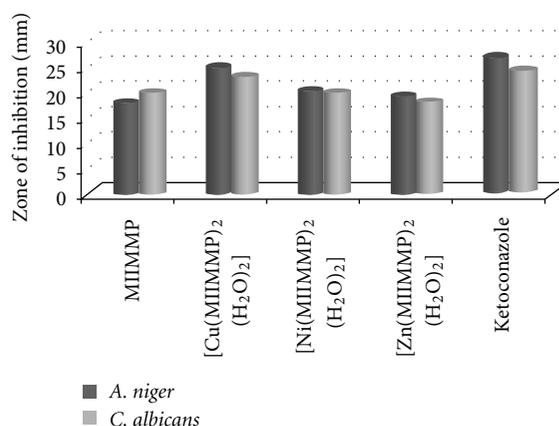


FIGURE 6: Antifungal activity of the Schiff base and metal complexes.

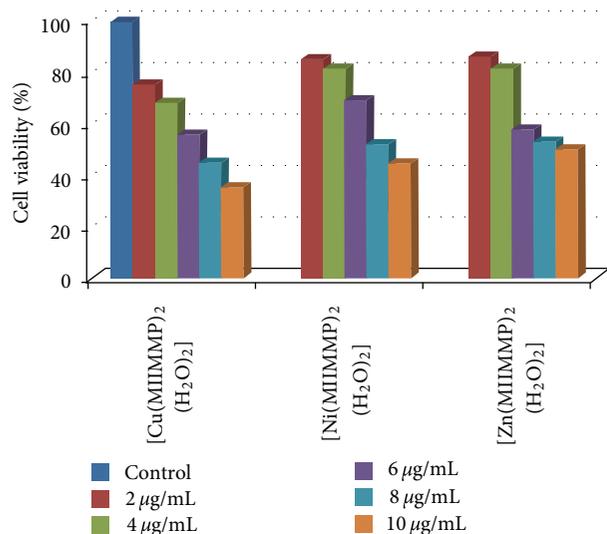


FIGURE 7: Percentage of cell viability versus different concentrations for HeLa cells exposed to the metal complexes after 72 h incubation.

TABLE 5: In vitro cytotoxicity (HeLa cell line) of M(II) complexes.

Conc. ($\mu\text{g/mL}$)	Absorbance	Cell viability (%)	Toxicities (%)
Control	0.1205	100	0
[Cu(MIIMMP) ₂ (H ₂ O) ₂]			
2	0.0910	75.51	24.49
4	0.0821	68.13	31.87
6	0.0670	55.60	44.40
8	0.0545	45.22	54.78
10	0.0426	35.35	64.65
[Ni(MIIMMP) ₂ (H ₂ O) ₂]			
2	0.1025	85.06	14.94
4	0.0980	81.32	18.68
6	0.0835	69.29	30.79
8	0.0630	52.28	47.72
10	0.0540	44.81	55.19
[Zn(MIIMMP) ₂ (H ₂ O) ₂]			
2	0.1040	86.30	13.70
4	0.0815	67.63	32.37
6	0.0701	58.17	41.83
8	0.0640	53.11	46.89
10	0.0610	50.62	49.38

55.19%, and 49.38%, respectively. According to these results, [Cu(MIIMMP)₂(H₂O)₂] complex is found to behave as a good antitumor agent on HeLa cell lines. The IC₅₀ values obtained in this study are given in Table 6. The IC₅₀ value of the [Zn(MIIMMP)₂(H₂O)₂] complex is higher for the 72 h treatment groups that are in the range of 10 ± 0.12 µg/mL, whereas [Cu(MIIMMP)₂(H₂O)₂], [Ni(MIIMMP)₂(H₂O)₂] are in the range of 8 ± 0.84 µg/mL to 8 ± 0.34 µg/mL.

TABLE 6: IC₅₀ range of M(II) complexes for HeLa cells.

Complex	IC ₅₀ ($\mu\text{g/mL}$)
[Cu(MIIMMP) ₂ (H ₂ O) ₂]	8 ± 0.84
[Ni(MIIMMP) ₂ (H ₂ O) ₂]	8 ± 0.34
[Zn(MIIMMP) ₂ (H ₂ O) ₂]	10 ± 0.12

7. Conclusions

The metal chelates of MIIMMP have been structurally characterized. The metal ligand stoichiometry in all these complexes is 1:2 associated with two coordinated water molecules. MIIMMP ligand acts as mononegative bidentate coordinating through nitrogen of azomethine and phenolic oxygen atom of salicylaldehyde, respectively. Based on analytical, magnetic, and electronic spectral data Ni(II) and Zn(II) complexes are assigned to be in octahedral geometry, whereas Cu(II) complex is assigned to be in tetragonal geometry. Energy minimized structures of metal complexes are proposed by the molecular modeling studies. Antimicrobial studies of these complexes reveal that copper complex shows better antibacterial and antifungal activity compared to its respective ligand and other metal complexes. The cytotoxicity of all the metal complexes was studied, and it is found that the cytotoxic activity of the [Cu(MIIMMP)₂(H₂O)₂] complex at 10 µg/mL concentration shows 64.65% toxicity suggesting good antitumor agent on human cervical carcinoma cell lines.

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