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Synthesis, Spectral Characterization and Biological Evaluation of Metal Complexes of 2-Thioxoquinoline Aminophenol

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A series of novel 2-thioxoquinoline aminophenol Schiff base based Co(II), Ni(II), Cu(II) and Zn(II) metal complexes $[M(L)_2]$, (M = Co^{2+}, Ni^{2+}, Cu^{2+} & Zn^{2+}; L = 2-thioxoquinoline aminophenol) were synthesized and characterized by elemental analysis and spectral studies (FT-IR, UV-Vis, ^{1}H NMR, ESR and ESI-Mass). All experimental results showed that in these metal complexes, the central metal atom was coordinated by oxygen, nitrogen and sulfur donor atoms of deprotonated Schiff base. Further, the ligand and its metal(II) complexes were screened against Gram-positive (*Staphylococcus aureus*), Gram-negative (*Escherichia coli*) bacteria and fungus (*Candida albicans*) strains. *in vitro* Anticancer activity of ligand and its metal(II) complexes were also screened against HeLa cells (Human cervical cancer cells).

Keywords: Aminophenol, 2-Thioxoquinoline, Metal(II) complexes, Antimicrobial, Anticancer activity.

INTRODUCTION

In coordination chemistry, Schiff bases belong to a crucial class of ligands and are widely applied in various fields. These bases easily coordinate with various transition metal ions, leading to intensely coloured and stable metal complexes [1-7]. These metal complexes are extensively investigated for years due to their significance in numerous applications and provide crucial contributions to magnetism, catalyst development, molecular architectures and material chemistry. In the medicinal field, metal-based drugs have received considerable importance and are used medicines to treat cancer, diabetes, cardiovascular and anti-inflammatory diseases [8-10]. Some ligands of Schiff bases and their transition metal complexes are used as antitubercular, antimicrobial and antiviral agents [11-13]. In a coordination zone, the electronic and steric effects of substituents cause an increase in the metal activity. Other functional groups present in ligands, which do not participate in coordination, may also influence this activity [14]. In particular, metal complexes having nitrogen, oxygen and sulphur donor sets are significant due to their potential applications in applied and fundamental sciences, principally in coordination chemistry. These applications are attributed to their varied pharmacological and catalytic properties and diverse roles in metalloenzymes [15-17].

Recently, scientists have focused on Schiff bases acquired from aldehydes or amines with heterocyclic rings due to their significance in industrial, biological, medicinal, pharmacological and analytical fields [18-20]. Among various heterocyclic compounds, a crucial class of nitrogen-containing heterocycles comprises quinoline and its derivatives, present in structures of different natural compounds with numerous biological activities [21]. Moreover, quinolines frequently contribute to the synthesis of numerous chemical compounds having different pharmacological properties, including anti-inflammatory [22], fungicidal [23], cytotoxic [24], antimicrobial [25], antibacterial, antidotal [26], antimalarial [27] and antitumor activities [28]. Due to the growing importance of quinolone Schiff bases, in present study, we present the synthesis, characterization and the biological activities of 2-thioxoquinoline aminophenol Schiff base and its metal complexes with Ni(II), Co(II), Zn(II) and Cu(II).

EXPERIMENTAL

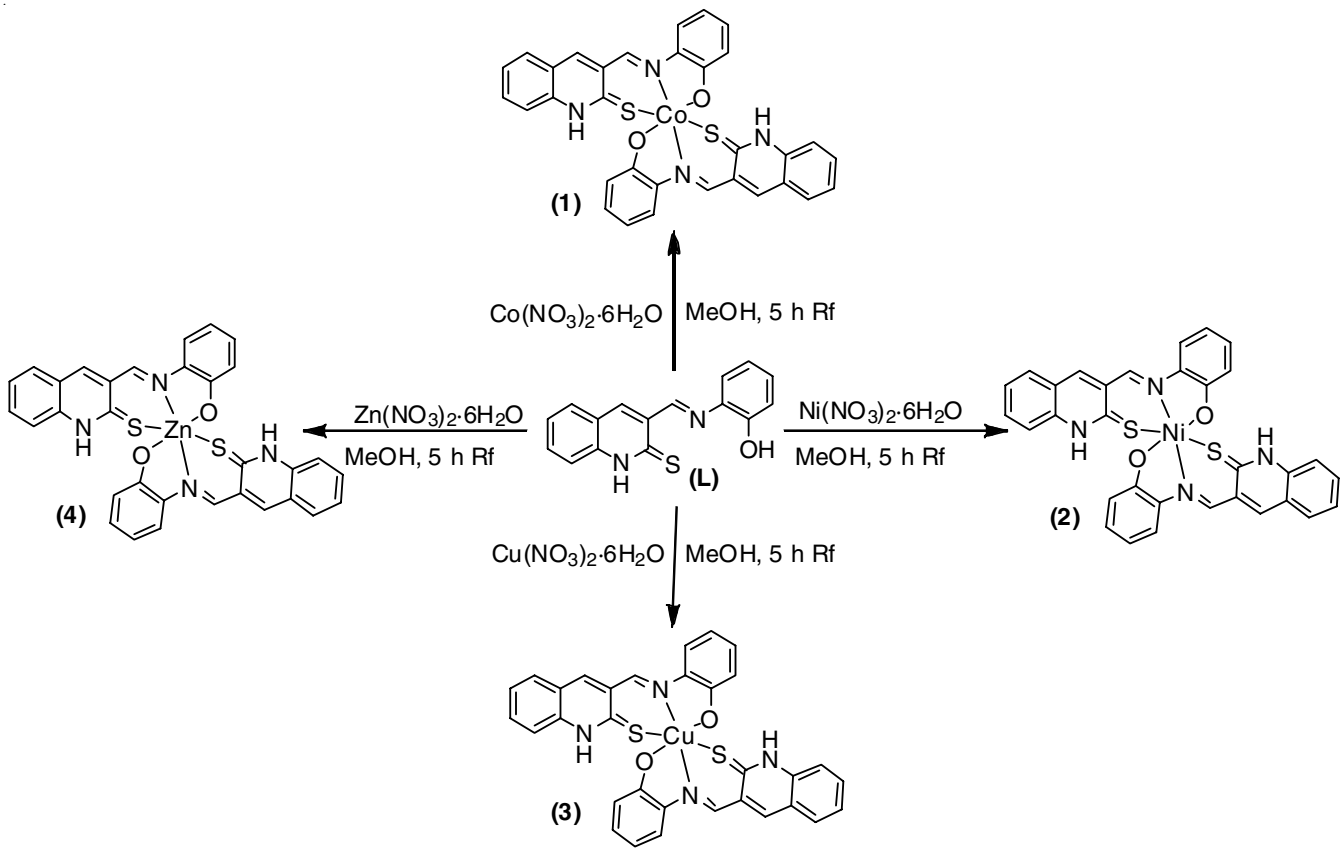
The solvents and chemicals used were of pure and AR grade. The solvents were purified and dried according to standard procedures [29]. All the studied metal(II) nitrates, aminophenol and acetanilide were purchased from Sigma-Aldrich, USA. Elemental analyses of carbon, hydrogen, nitrogen and sulfur were carried out using a Vario EL III elemental analyzer. Infrared spectra were recorded on a Nicolet Avatar model spectrometer from 4000 to 400 cm^{-1} using KBr pellets. Electronic spectra were recorded on Shimadzu UV-1650 PC spectrophotometer in 800-200 nm range using methanol as solvent. Molar conductivity measurements were recorded using Deep Vision digital conductivity meter with DMSO solution. ^{1}H NMR spectra were recorded on a Jeol GSX-400 MHz instrument using DMSO-d_6 as solvent. Electron spin resonance spectra (ESR) of the powder samples are recorded with a JEOL JES-FA200 instrument in X-band frequencies at room temperature using 2,2′-diphenyl-1-picrylhydrazyl radical (DPPH$^•$) as an internal standard at SAIF-IIT Madras, Chennai, India. The ESI-Mass spectra were performed on LC-MS Q-ToF Micro Analyzer (Shimadzu) at SAIF-Panjab University, Chandigarh, India. Melting points were checked on a Technico micro-heating table and are uncorrected. 2-Thioxo-3-formylquinoline was synthesized according to the literature procedure [30].

Synthesis of 2-thioxoquinoline aminophenol ligand (L): 2-Aminophenol (1 mmol) dissolved in warm methanol (10 mL) was added to a methanol solution (10 mL) containing 2-thioxo-3-formylquinoline (1 mmol). Added a drop of acetic acid and the reaction mixture was subsequently refluxed for 5 h, a yellow precipitate was formed. The yellow solid of ligand (L) was obtained from slow evaporation, washed with methanol and dried under *vacuum*. Yield: 90%; colour: pale yellow; m.p.: 240 ºC; Anal. calcd. (found) % for $C_{16}H_{12}N_2OS$: C, 68.55 (68.17); H, 4.31 (4.82); N, 9.99 (9.53); S, 11.44 (11.90). IR (KBr, ν_{max}, cm^{-1}): 3377 (O-H), 3148 (N-H), 1634 (CH=N), 1574 (C=S). UV-Vis (methanol, λ_{max}/nm): 302, 252. ^{1}H NMR (DMSO-d_6, δ ppm): 12.27 (s, -OH), 10.76 (s, -NH), 8.63 (s, -CH=N), 7.28-8.58 (m, aromatic-H).

Synthesis of metal complexes: A warm methanolic solution (10 mL) containing 2-thioxoquinoline aminophenol (1 mmol) was added to a 10 mL of methanolic solution of corresponding metal(II) nitrate (0.5 mmol) in 2:1 M ratio. The resulting reddish brown solution was refluxed for 5 h. A brown coloured crystalline powder was obtained on slow evaporation, washed with cold methanol and dried under vacuum (**Scheme-I**).

Co(II) complex, [Co(L)$_2$] (1): Yield: 87%; colour: brown; m.p.: 290 ºC. Anal. calcd. (found) % for $C_{32}H_{22}N_4O_2S_2Co$: C, 62.23 (62.82); H, 3.59 (3.97); N, 9.07 (9.49); S, 10.38 (10.66). IR (KBr, ν_{max}, cm^{-1}): 3180 (N-H), 1626 (-CH=N), 1582 (C=S), 502 (M-O), 468 (M-N). UV-Vis (methanol, λ_{max}/nm): 448, 351, 310, 260, 235. Molar conductivity Λ_M (1×10^{-3} M, DMSO): 8.3 Ω^{-1} cm^2 mol^{-1}. ESI-MS (*m/z*): calcd. 617.61; found: 617.44 $[M]^+$. ESR (g): 2.1.

Ni(II) complex, [Ni(L)$_2$] (2): Yield: 90%; colour: brown; m.p.: 295 ºC. Anal. calcd. (found) % for $C_{32}H_{22}N_4O_2S_2Ni$: C, 62.26 (62.78); H, 3.59 (3.30); N, 9.08 (9.45); S, 10.39 (10.75). IR (KBr, cm^{-1}): 3178 (N-H), 1626 (-CH=N), 1584 (C=S), 508



Scheme-I: Synthesis of complexes **1**, **2**, **3** and **4**

(M-O), 465 (M-N). UV-Vis (methanol, λ_{max}/nm): 465, 392, 303, 252. Molar conductivity Λ_M (1×10^{-3} M, DMSO): 4.8 Ω^{-1} cm^2 mol^{-1}. ^{1}H NMR (DMSO-d_6, ppm): 10.92 (s, -NH), 8.95 (s, -CH=N), 7.23-8.47 (m, aromatic-H). ESI-MS (*m/z*): calcd. 617.37; found: 617.19 $[M]^+$.

Cu(II) complex, $[Cu(L)_2]$ (3): Yield: 83%; colour: brown; m.p.: 310 ºC. Anal. calcd. (found) % for $C_{32}H_{22}N_4O_2S_2Cu$: C, 61.77 (61.32); H, 3.56 (3.97); N, 9.00 (9.51); S, 10.31 (10.87). IR (KBr, ν_{max}, cm^{-1}): 3141 (N-H), 1628 (-CH=N), 1577 (C=S), 547 (M-O), 470 (M-N). UV-Vis (methanol, λ_{max}/nm): 453, 360, 315, 230. Molar conductivity Λ_M (1×10^{-3} M, DMSO): 7.2 Ω^{-1} cm^2 mol^{-1}. ESI-MS (*m/z*): calcd. 622.22; found: 622.45 $[M]^+$. ESR (g): 2.3.

Zn(II) complex, $[Zn(L)_2]$ (4): Yield: 84%; colour: brown; m.p.: 298 ºC. Anal. calcd. (found) % for $C_{32}H_{22}N_4O_2S_2Zn$: C, 61.59 (61.87); H, 3.55 (3.98); N, 9.98 (9.31); S, 10.28 (10.79). IR (KBr, ν_{max}, cm^{-1}): 3206 (N-H), 1622 (-CH=N), 1590 (C=S), 535 (M-O), 466 (M-N). UV-Vis (methanol, λ_{max}/nm): 449, 382, 302, 240. Molar conductivity Λ_M (1×10^{-3} M, DMSO): 9.5 Ω^{-1} cm^2 mol^{-1}. ^{1}H NMR (DMSO-d_6, ppm): 10.81 (s, -NH), 8.81 (s, -CH=N), 6.64-8.54 (m, aromatic-H). ESI-MS (*m/z*): calcd. 624.05; found: 624.48 $[M]^+$.

Antimicrobial activity: The antimicrobial activity of the ligand and its metal(II) complexes (**1-4**) was determined by using the agar well diffusion method [31]. The compounds were studied for the inhibitory effect on the growth of different gram bacteria such as *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria). The 1 mg/mL concentration of the standard (streptomycin), ligand and its metal(II) complexes was prepared in DMSO for antibacterial and antifungal studies. The antifungal activity of the ligand and its metal(II) complexes were studied against *Candida albicans*. Each test bacterial were swabbed on sterile Muller-Hinton agar plates using a sterile cotton swab followed by punching wells of 6 mm diameter with the help of a sterile cork borer. The spore suspension of test fungi was swab inoculated aseptically on the sterile potato dextrose agar plates followed by making wells of 6 mm diameter using a sterile cork borer. The plates were incubated at 37 ºC overnight. After 24 h, the biological activities were expressed in terms of the diameter of the zone of inhibition (in mm) of each microbial species by different samples. Each of the above experiments was repeated thrice along with a control set using DMSO and the mean value was taken for comparison.

Anticancer activity: The MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide) method was employed to study the anticancer activities of the studied ligand and its metal(II) complexes (**1-4**) against the Hela cells (human cervical cancer cells) [32]. Cell lines were grown at 37 ºC with 95% and 5% air and CO_2, respectively, in an incubator (Thermo-Fisher). In DMSO, compounds were dissolved to acquire 10 mM stock solutions. The stock solutions were diluted in DMSO to < 0.1% concentration in the cell culture medium to prevent the influence of the solvent on cell proliferation. In 96-well plates, the cells were seeded and allowed overnight to adhere at 37 ºC in the incubator. Seeding density was 5×10^4 cells/well. Different ligand and metal(II) complex concentrations (1-500 µg/mL) were incorporated into the plates. These plates were incubated for 48 h at 37 ºC. To the cells, 20 µL of 5 mg/mL MTT was added, and the cells were incubated for 4 h followed by the addition of 100 µL of DMSO. The optical density of the living cells was measured at 570 nm. The number of viable cells was directly proportional to the formation of MTT colour, which validated its use. The half-maximum inhibitory concentration (IC_{50}) was analyzed based on GraphPad Pris, a non-linear multi-purpose curve fitting program.

RESULTS AND DISCUSSION

The reactions of $M(NO_3)_2{\cdot}6H_2O$ (M = Co^{2+}, Ni^{2+}, Cu^{2+} or Zn^{2+}) with 2-thioxoquinoline based NOS-tridentate Schiff base ligand were carried out in methanol with 1:1 molar ratio (**Scheme-I**). The new complexes obtained were of the type $[M(L)_2]$ (M = Co^{2+}, Ni^{2+}, Cu^{2+} or Zn^{2+}). The synthesized new complex is stable in air at room temperature, brown in colour, non-hydroscopic in nature and highly soluble in common organic solvents as dichloromethane, acetonitrile, chloroform, DMSO and methanol. The analytical data of all the synthesized complexes were agreed well with the proposed molecular formulae for 1:2 (metal:ligand) stoichiometric ratio of metal to the ligand.

FT-IR studies: The IR spectrum of the free ligand was compared with that of the synthesized metal complexes in order to confirm the coordination sites involved in chelation. The formation of Schiff base ligand and it's metal complexes has been confirmed by detecting the peaks of azomethine (>C=N) groups. The intense band at 1634 cm^{-1} that corresponds to azomethine group (-C=N) in the free ligand is shifted to the lower frequencies in the range 1628-1622 cm^{-1} in metal complexes, indicating the participation of azomethine group (-C=N) in the coordination sphere [33]. The broad band centered at 3148 cm^{-1} in the free ligand can be assigned to -N-H (ring) [34], which is slight altered in the complexes. This suggests that the non-participation of NH group in bonding. The ν(C=S) observed at 1574 cm^{-1} in the spectra of the ligand showed a higher shift in the region 1590-1577 cm^{-1} of the metal complexes indicates the coordination through the thionyl sulphur. The band due to ν(O-H) appeared at 3377 cm^{-1} in free ligand has disappeared on complexation, suggested that the ligand is coordinated to the metal ion through the phenolic oxygen atom [35]. The IR spectra of metal(II) complexes shows the band in the region 470-465 cm^{-1} and 548-502 cm^{-1} for ν(M-N) and ν(M-O) bond, respectively. Hence from the infrared spectroscopic data, inferred that the azomethine nitrogen, thionyl sulphur and phenolic oxygen atom of the ligand are involved in the coordination to the metal ion in the complexes.

Electronic studies: The electronic spectra of ligand and its metal(II) complexes have showed two to three bands in methanol solvent (Fig. 1). The bands obtained in the region 230-315 nm in both the ligand and the metal complexes can be attributed to the intra-ligand electronic transitions such as $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ of free azomethine and aromatic group, respectively. In the spectra of complexes, the bands that appeared around 351-392 nm have been assigned to a ligand-to-metal

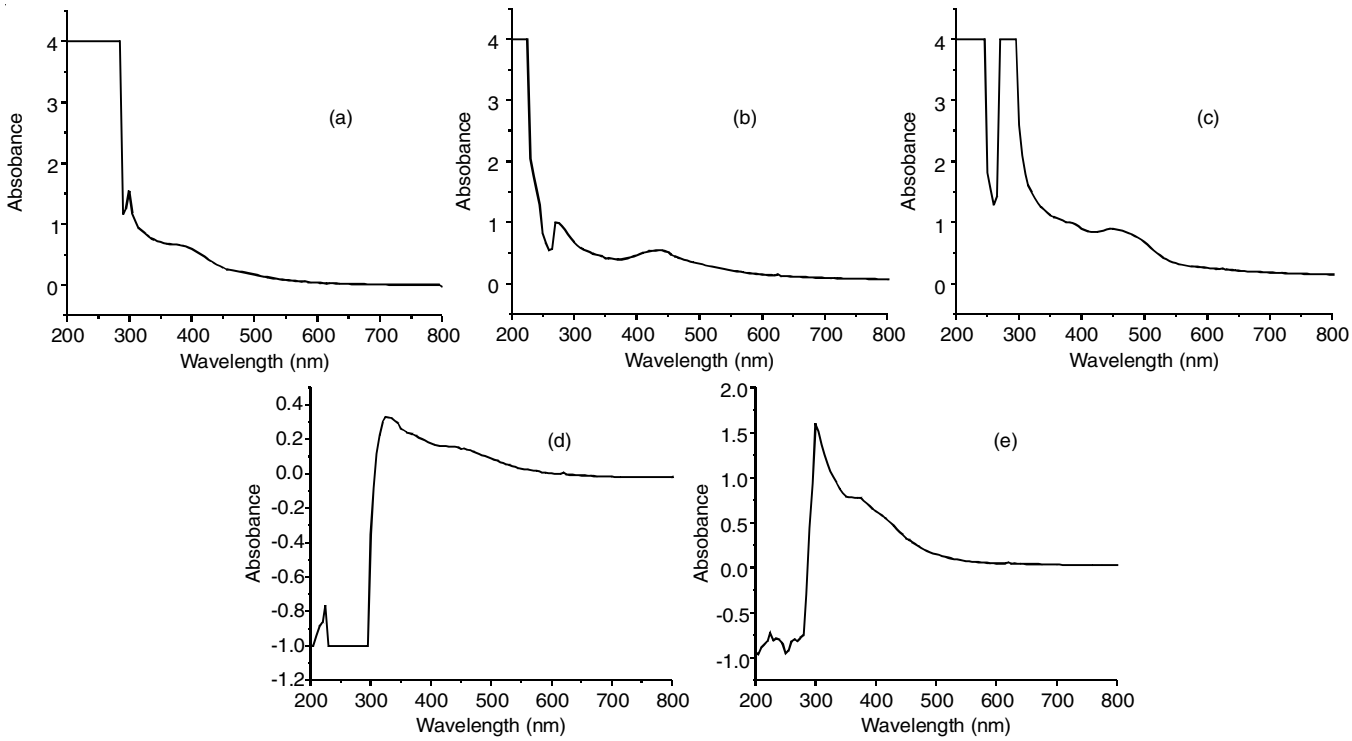


Fig. 1. Electronic spectra of ligand (a), Co(II) (b), Ni(II) (c), Cu(II) (d) and Zn(II) (e) complexes

charge transfer transitions [36]. Further, the band appeared at 449-465 nm region in the complexes have been assigned to *d-d* transitions [37,38].

Molar conductance: Molar conductivity of metal(II) complexes were measured at room temperature in DMSO solution. The values in the range 4.8-9.5 Ω^{-1} cm^2 mol^{-1} indicating that the non-electrolytic behaviour of the metal(II) complexes [39].

^{1}H NMR studies: ^{1}H NMR spectra of ligand and its Ni(II), Zn(II) complexes confirmed the metal-ligand binding modes in the complexes. Spectra of free ligand exhibit a peak at 12.27 ppm, which is characteristic of the phenolic O-H group [35]. This peak is disappeared in their corresponding complexes which confirmed that the binding of the ligand with metal ions *via* deprotonation of the phenolic oxygen atom. The azomethine proton of ligand exhibits a signal at 8.63 ppm, which undergoes a down field shift in its corresponding complexes (8.81 and 8.95 ppm). This confirms the binding of azomethine group with metal(II) ions through nitrogen atom. The peaks corresponding to the protons of aromatic moieties of the ligand and its complexes are observed as multiplets in the range of 6.64-8.58 ppm. Further, the signals of ligand and complexes appeared in the region 10.76-10.92 ppm has been assigned to the NH proton [35]. The presence of NH proton in the complexes clearly indicates that the coordination of sulphur to metal through the thionyl sulphur (C=S).

ESR studies: The ESR spectra of Co(II) and Cu(II) complexes were recorded at room temperature. The ESR spectra of the Co(II) and Cu(II) complexes (Fig. 2) exhibited a well-defined single isotropic line with g values of 2.1 and 2.3. This parameter is in good agreement with the values reported for other related octahedral Co(II) and Cu(II) systems [40,41].

ESI-mass studies: The stoichiometric composition of ligand and its metal(II) complexes were determined using ESI mass spectra. Complexes **1**, **2**, **3** and **4** provided good evidence for the molecular formulas from their highest mass peak at *m/z* 617.44, 617.19, 622.45 and 624.48, respectively (Fig. 3). The *m/z* of molecular ion peaks obtained for the complexes are in good agreement with the results of elemental analyses inferring

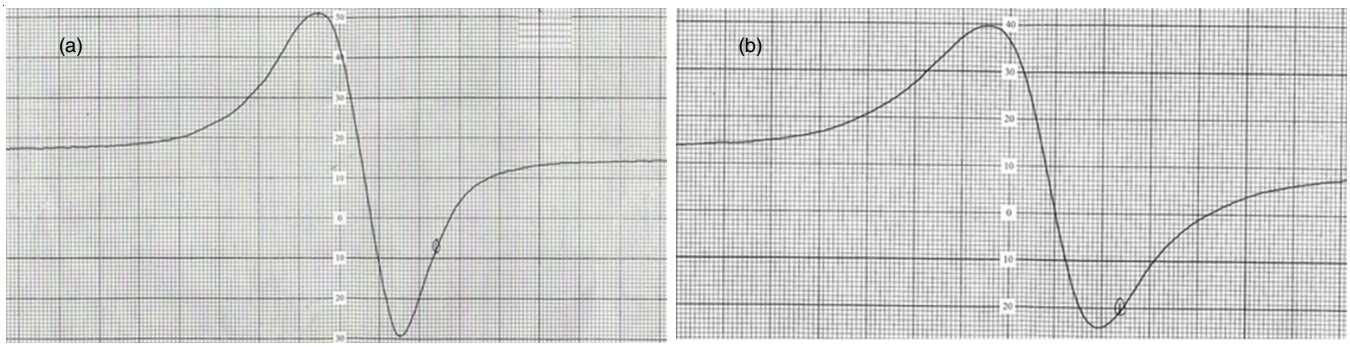


Fig. 2. EPR spectra of Co(II) complex (**1**) (a) and Cu(II) complex (**3**) (b)

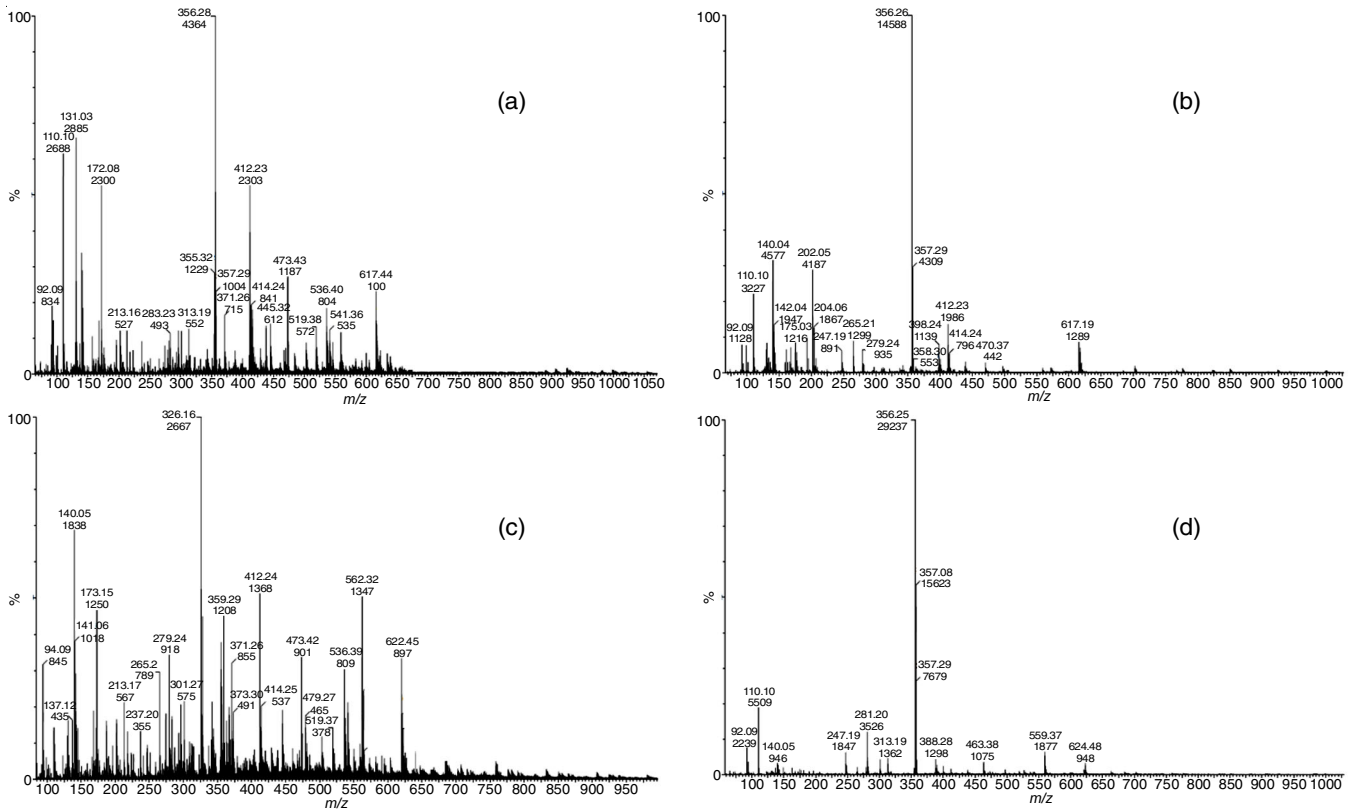


Fig. 3. ESI-mass spectrum of Co(II) (a), Ni(II) (b), Cu(II) (c) and Zn(II) (d) complexes

the formation of 1:2 (metal:ligand) metal(II) complexes in the respective system.

On the basis of experimental data, the octahedral structure has been tentatively proposed for all the metal(II) complexes containing 2-thioxoquinoline aminophenol based oxygen, nitrogen and sulfur donor tridentate Schiff base ligands.

Antimicrobial activity: The ligand and its metal(II) complexes were tested for antimicrobial activities against the bacteria (*Staphylococcus aureus*, *Escherichia coli*) and fungi (*Candida albicans*). The data of the antifungal and antibacterial activities of ligand, complexes and standard are given in Table-1. It is evident that the metal(II) complexes are most active than the parent ligand. On comparing the biological activity of the ligand and its metal complexes, it was found that the metal complexes are more effective against the bacteria and fungi. The higher activity of the metal(II) complexes, as compared to the free ligand is caused by the lipophilic nature of metal(II) complexes and explained on the basis of chelation theory [42]. Furthermore, chelation reduces the polarity of metal ion due to the sharing of positive charge metal to ligand donor atoms and causing π-electron delocalization over the complexes. The antimicrobial activity of the tested compounds follows the order $Cu^{2+} > Co^{2+} > Zn^{2+} > Ni^{2+} >$ ligand (Fig. 4). Most interestingly Cu^{2+} complex showed higher activity than other complexes.

Anticancer activity evaluation by MTT assay: For cytotoxicity in HeLa cells, the ligand and its metal(II) complexes were analyzed using the MTT assay. In DMSO, compounds were dissolved and the blank samples comprising the same DMSO volume were considered controls to determine the solvent activity.

TABLE-1
ANTIMICROBIAL ACTIVITY DATA OF LIGAND AND ITS METAL(II) COMPLEXES

Compound	Zone of inhibition in cm (Mean ± SD)		
	Bacteria		Fungi
	Staphylococcus aureus	*Escherichia coli*	*Candida albicans*
Ligand	1.00 ± 0.02	1.50 ± 0.05	1.80 ± 0.03
$[Co(L)_2]$	13.13 ± 0.05	17.22 ± 0.03	10.34 ± 0.04
$[Ni(L)_2]$	8.10 ± 0.04	13.25 ± 0.03	6.35 ± 0.05
$[Cu(L)_2]$	15.12 ± 0.02	18.23 ± 0.02	12.35 ± 0.04
$[Zn(L)_2]$	12.10 ± 0.03	16.23 ± 0.04	9.32 ± 0.02
Standard	5.56 ± 0.04	5.37 ± 0.05	5.64 ± 0.03

± Standard deviation

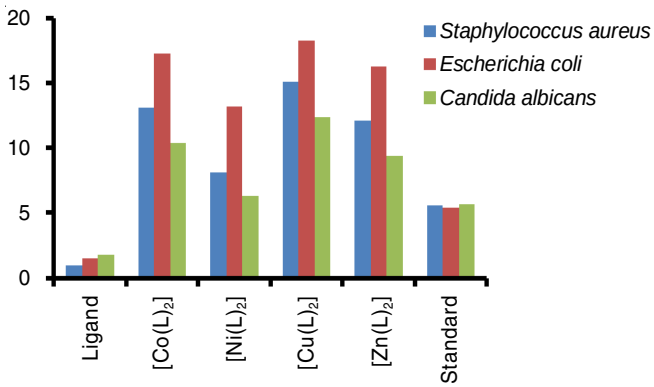


Fig. 4. Graphical representation of antimicrobial activity of ligand and its metal complexes

The standard used to explore compound cytotoxicity was *cis*-platin. The results were analyzed through cell inhibition expressed as IC_{50} (Table-2). The compounds exhibit anticancer activity at 1 µg/mL and higher concentration. Upon increasing the concentration of complexes from 1 to 500 µg/mL, the % cell inhibition also increased (Figs. 5 & 6). The IC_{50} values of compounds against HeLa cells were calculated and found to be 187.3 µg/mL for ligand and 24.51, 50.21, 52.35 and 54.99 µg/mL for complexes Co(II), Ni(II), Cu(II) and Zn(II), respectively. The observed IC_{50} values of synthesized complexes are significantly higher than standard *cis*-platin. The anticancer activity of the tested compounds against the HeLa cell line follows the order $Co^{2+} > Ni^{2+} > Cu^{2+} > Zn^{2+}$ > ligand. The Co(II) complex showed pronounced anticancer activity compared to all other complexes and ligand.

TABLE-2
IC_{50} (µg/mL) VALUE OF LIGAND AND ITS METAL(II) COMPLEXES AGAINST HELA CELLS (HUMAN CERVICAL CANCER CELLS)

Compound	IC_{50} (µg/mL)[a]
Ligand	187.3
$[Co(L)_2]$	24.51
$[Ni(L)_2]$	50.21
$[Cu(L)_2]$	52.35
$[Zn(L)_2]$	54.99
Cisplatin	12.33

[a]50% inhibitory concentration after exposure for 48 h in the MTT assay.

Conclusion

Newly synthesized 2-thioxoquinoline aminophenol ligand and its metal(II) complexes (**1-4**) were characterized by elem-

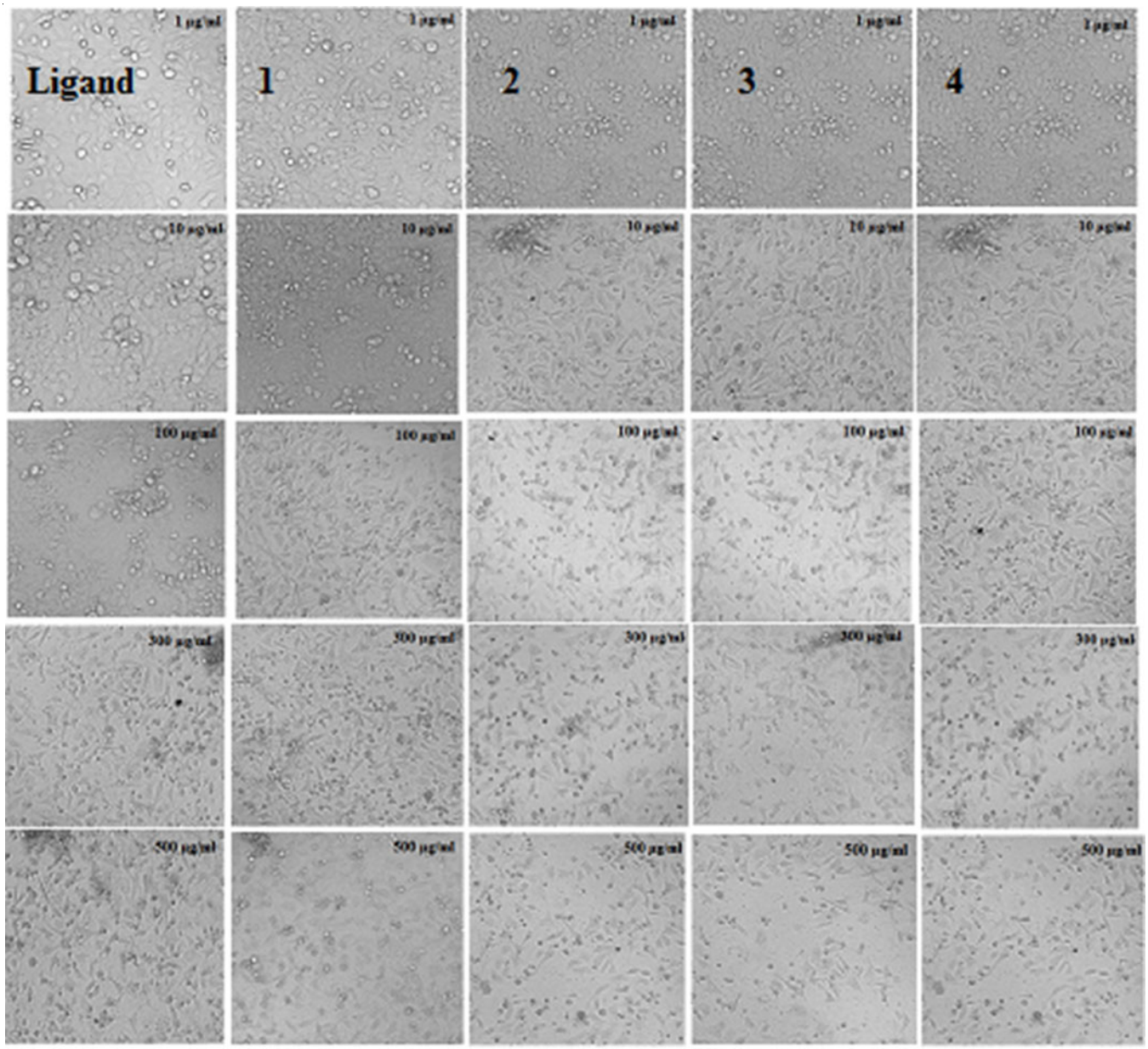


Fig. 5. Anticancer activity of HeLa cells (Human cervical cancer cells) after treated for 48 h in presence of different concentration of ligand and metal(II) complexes (**1-4**) (1-500 µg/mL)

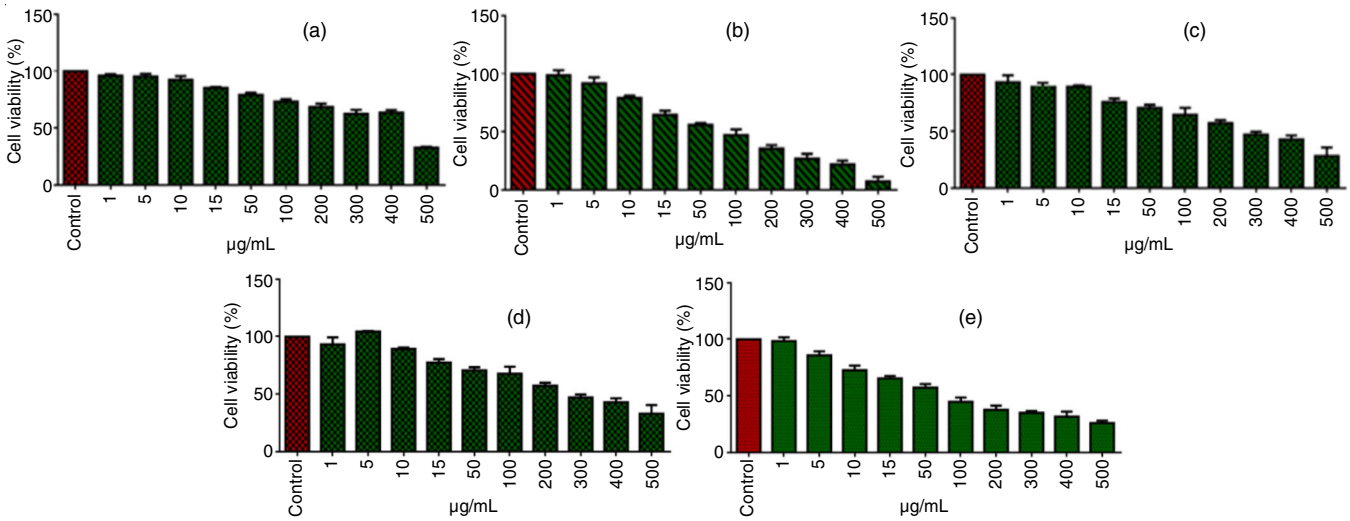


Fig. 6. Cell viability anticancer activity of (a) ligand, (b) Co(II), (c) Ni(II), (d) Cu(II) and (e) Zn(II) complexes against on HeLa cell line

ental analysis, spectral techniques such as FTIR, electronic, ^{1}H NMR, ESR and mass spectral studies. The spectral data of newly synthesized compounds are in the favour of an octahedral geometry of the complexes. The antimicrobial activity of Schiff base ligand and its metal(II) complexes have shown that they act as good antimicrobial agents against bacteria and fungi. Among the synthesized metal(II) complexes, Cu(II) complex shows the best antimicrobial activity against the tested microorganisms. The anticancer activity showed that all the synthesized metal(II) complexes exhibited greater activity as compared to Schiff base ligand.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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