



Synthesis, Spectral Characterization and Anticancer Studies of Some Metal(II) Complexes Derived from Imidazole-2-carboxaldehyde with 2-Amino-3-carboxyethyl-4,5-dimethylthiophene

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ABSTRACT

Imidazole-2-carboxaldehyde was condensed with 2-amino-3-carboxyethyl-4,5-dimethyl thiophene in 1:1 molar ratio yielded Schiff base ligand. Cobalt(II), nickel(II), copper(II) and zinc(II) complexes of the ligand were synthesized and characterized structurally using elemental analysis, molar conductance, magnetic moment, infrared and electronic spectra. The ligand structure was confirmed by proton nuclear magnetic resonance spectrum. The geometry exhibited by the complexes was proposed using magnetic and electronic spectral data. Thermal analysis was carried out to ascertain the thermal stability of the compounds. The fluorescence spectral analysis were investigated at different solvents for the ligand and copper(II) complex. Using powder X-ray diffraction measurements, the grain size was determined. The scanning electron microscope images indicate the surface morphology of the complexes. The antibacterial and antifungal activities were screened by disk diffusion method designed by Kirby-Bauer. *In vitro* anticancer studies were carried out, by MTT assay for human cervical carcinoma cell line.

Keywords: Schiff base, magnetic moment, infrared spectra, electronic, surface morphology, anticancer.

INTRODUCTION

Imidazole derivatives have wide biological and pharmaceutical applications such as antidiabetic, antihypertensive and anti-inflammatory activities¹.

Moreover, the substituted imidazoles are synthetically important for the use of synthetic intermediates such as, catalysts and asymmetric catalysis². Thiophene derivatives are one of the most extensive dynamic research areas and exist as natural and synthetic

pharmaceuticals³. Derivatives of thiophene play an active drug; therefore it is used in therapy and biodiagonostics⁴. Schiff base ligands prepared by the reaction between aldehydes and imines are considered to be "privileged ligands", because they can bind with diverse metals, stabilize them in various states. Schiff base and additional electron donor (nitrogen and oxygen) atoms are usually used as the ionophore in fluorescent sensor for determining several cations⁵⁻⁷. The novel nitrogen-containing heterocyclic compounds and their complexes may act as suitable catalysts in many chemical reactions⁸. Heterocyclic compounds containing amino or nitrogen atom of azomethine group and phenolic oxygen atoms that have rendered more interest to the research workers⁹⁻¹⁴. Schiff base complexes of various 3d metal ions have been investigated for their coordinating capability. Pharmacological⁶ and toxicological activities are shown by modified drugs when applied in the form of metal complex systems¹². The fluorescent sensors for metal ions have become globally used in recent years to the ease in handling and high sensitivity. In continuation of our research work^{15,16}, this article deals about the synthesis, structural elucidation and biological studies of Schiff base metal complexes. These synthesized metal complexes may be applied to pharmaceuticals and in drug designing applications.

MATERIALS AND METHODS

Analar grade solvents and chemicals were used for this study. Metal salts and ligands used were obtained from Merck. Microanalysis (C, H, N) was done using Carlo Erba EA1108 elemental analyzer. Molar conductance was measured with digital conductivity meter. The magnetic susceptibility measurements were made using Faraday balance method. Diamagnetic corrections were done by Pascal's constants and $\text{Hg}[\text{Co}(\text{SCN})_4]$ was used as calibrant. Infrared spectra of ligand and its complexes were recorded on a Shimadzu IR Affinity-1S FT-IR Spectrophotometer. UV-Visible spectra of the metal complexes were recorded on a Systronics double beam UV-VIS spectrophotometer. The ¹H-NMR spectrum of the ligand was recorded with BRUKER Avance -III 300 MHz NMR spectrometer, using internal standard tetramethylsilane and DMSO-d₆ as solvent. The thermogravimetric analysis was studied using Shimadzu TGA-50H thermal analyzer

in nitrogen atmosphere with 10 °C min⁻¹ heating rate. Fluorescence spectra of ligand and copper(II) complex was investigated by PTI QM-2000-4 Bench-Top model steady state spectrophotometer. Powder X-ray diffraction measurements were conducted using Rigaku D/Max-B X-ray diffractometer. Scanning electron microscope was recorded in Hitachi S5500 SEM instrument analyzer.

Synthesis of Schiff base ligand

The ligand precursor *2-amino-3-carboxyethyl-4,5-dimethylthiophene* was synthesized by Gewald synthesis¹⁷. The starting material *2-Amino-3-carboxyethyl-4,5-dimethylthio phene* (1 mmol) was dissolved with methanol. To this a solution of imidazole-2-carboxaldehyde (1 mmol) dissolved in methanol was added dropwise. The mixture was stirred magnetically and refluxed for 3 h. The resulting solutions volume was reduced in a boiling water bath, cooled at room temperature. The resulting compound was washed with ether, recrystallized using ethanol. Good yield of about 76% was obtained. The purity of the ligand was checked by thin layer chromatographic technique.

Synthesis of metal complexes

The ligand (1 mmol) was dissolved in methanol. To this, cobalt/ nickel/ copper/ zinc(II) chlorides (1 mmol) dissolved in methanol was added dropwise under magnetic stirring. The above mixture was refluxed for 2 h. The solid products was washed with ether, filtered, and dried in vacuum desiccator. Yield of about 66-72% was obtained for the metal complexes. Purity of the complexes was checked using thin layer chromatographic technique.

RESULTS AND DISCUSSION

The synthesized ligand and metal(II) complexes are found to be stable in air. Elemental analysis and physical parameters agree well with the calculated values in accordance with their formulae. Metal complexes was formulated as $[\text{MLX}_2]$, where M= Co^{II}/Ni^{II}/Cu^{II}/ Zn^{II}, L = Schiff base ligand, and X= Cl. The low molar conductance value determined in dimethylformamide falls in the range 10-19 ohm⁻¹ cm² mol⁻¹ suggesting the non-electrolytic nature¹⁸ of metal complexes. For the ligand the ultraviolet absorption band was observed at 354 nm, corresponds to n-π* transitions of aromatic ring and azomethine

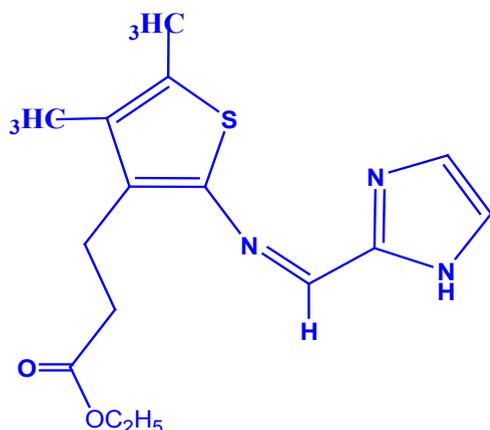
chromophore. The $^1\text{H-NMR}$ ligand spectrum exhibits the azomethine proton ($-\text{HC}=\text{N}-$) signal appeared at δ 8.4 ppm. The multiplet signals were also observed for aromatic protons ($-\text{CH}=\text{CH}-$) at δ 7.4-8.0 ppm and two methylene ($-\text{CH}_2-$) protons at δ 3.8-4.2 ppm. The assigned structure of ligand is displayed in Scheme 1.

Infrared spectra

The stretching frequency band of azomethine group ($-\text{HC}=\text{N}-$) occurred at 1618 cm^{-1} in the ligand. This band was shifted during complex formation to lower frequency region $1612 - 1609\text{ cm}^{-1}$ in the spectra of the complexes indicating coordination of azomethine nitrogen atom to the metal ion. The ester carbonyl ($\text{C}=\text{O}$) stretching frequency band appeared at 1640 cm^{-1} in the ligand was shifted down about 25 cm^{-1} in the metal complexes indicates the binding of ester carbonyl oxygen atom with the metal ion¹⁹. Also, the new stretching frequency bands were seen at $532-512\text{ cm}^{-1}$ $\nu(\text{M-O})$, $410-405\text{ cm}^{-1}$ $\nu(\text{M-N})$, and $295-245\text{ cm}^{-1}$ $\nu(\text{M-Cl})$ vibrations respectively. The infrared spectral results demonstrate that the ligand act as neutral bidentate manner.

Electronic spectra and magnetic measurements

Cobalt(II) complex displays an absorption band at 605 nm, corresponds to tetrahedral environment¹⁹ of ligand around metal ion, this corresponds to the transition $^4\text{A}_2(\text{F}) \rightarrow ^4\text{T}_1(\text{P})$. The cobalt(II) complex exhibits spin only magnetic moment value of 4.66 BM, corresponds to tetrahedral geometry. The nickel(II) complex displays only one



Scheme. 1

absorption peak at 482 nm, this is due to d-d transition of nickel(II) caused by square planar arrangement of ligand field. Hence square planar geometry was assigned to this complex. The electronic spectrum of copper(II) complex (Fig. 1) shows a broad absorption band at 661 nm, this band corresponds to the d-d transition of copper(II) complex in square planar geometry. Zinc(II) complex is diamagnetic, therefore this complex would have tetrahedral geometry as predicted.

Thermogravimetric analysis

The thermal decomposition and thermal stability of metal complexes were estimated by thermal studies. The thermogravimetric curve displays three stages of decomposition. First stage decomposition noticed may be due to loss of thiophene moiety. Second stage decomposition was seen above $200\text{ }^\circ\text{C}$ may be due to the loss of imidazole moiety. Above $500\text{ }^\circ\text{C}$ only the metal residue remain²⁰. The obtained results correlated well with theoretical formula calculation predicted from analytical data.

Fluorescence spectra

The photoluminescence studies of the Schiff base (Fig. 2a) and copper(II) complex (Fig. 2b) were investigated at room temperature for 10^{-4} M solution in various solvents. Excitation and emission slit widths were fixed at 10 nm with a scan speed of 500 nm/min . The excitation spectrum of Schiff base shows a maximum excitation at 490 nm with an emission band at 450 nm. Schiff base

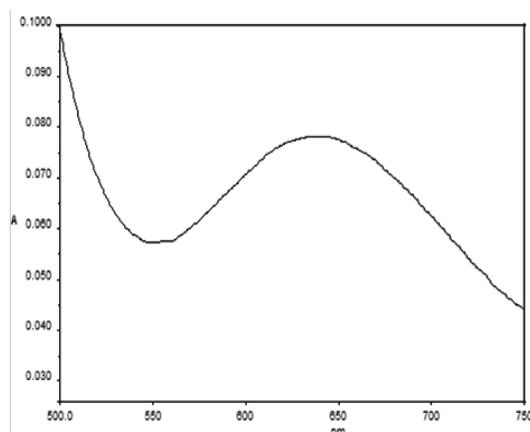


Fig. 1: The electronic absorption band spectrum of copper(II) complex

systems normally exhibit fluorescence spectrum due to intra-ligand transitions²¹. At the concentration of 10^{-4} M solution in methanol, acetonitrile and dimethylsulphoxide solvents shows an excitation bands observed at 475-500 nm in the fluorescence spectra. The quenching spectrum was seen for copper(II) complex at 450 nm. The results show that the ligand has potential activity than the complex. The strongest quenching has been obtained for copper(II) complex.

The powder X-ray diffraction were recorded at $2\theta = 10-80^\circ$ range. Sharp crystalline peaks were observed in the metal complexes, demonstrating the nanocrystalline behaviour²². From observed d_{XRD} patterns, the average grain sizes of the cobalt(II), nickel(II), copper(II), and zinc(II) complexes were determined using Scherer's formula. The grain size of the metal complexes was found to be 67, 77, 41 and 60 nm respectively suggest that metal complexes are in nanocrystalline phase.

For the metal complexes, the surface morphology was investigated by scanning electron microscope is shown in Fig. 3. The micrograph images showed irregularly shaped particles with micro crystalline structure for the metal complexes. Zinc(II) complex has cauliflower like morphological structure. Agglomerated size with controlled

morphological images was observed for cobalt(II), nickel(II), copper(II) and zinc (II) complexes. Powder X-ray diffraction patterns of the Schiff base complexes has grain size less than 77 nm with controlled morphology.

The bacterial and fungal species were tested by Kirby-Bauer disk diffusion method²³. *A. niger*, *C. albicans*, *S. aureus*, *P. aeruginosa*, *E. coli* and *K. pneumoniae* were used as fungal and bacterial strains. Nystatin and chloramphenicol were used as standards. The test solutions were prepared in dimethylformamide solvent, also used as control. The ligand and complex results were compared with the standards and the inhibition zone diagram is shown in Fig. 4. In the present investigation, the results indicate that the complexes depict more growth inhibition potential than the ligand. It has been observed that the metal complexes are biologically active and chelation enhances their activity. A possible mode of toxicity will be based on chelation theory²⁴. However, the zone of inhibition (mm) of ligand and its complexes varies with organisms as well as metal ions. Metal complexes moderately inhibited the growth of gram negative and positive bacterial strains and fungal activities.

Anticancer activity

Anticancer activity of the synthesized complexes was screened on the human cervical carcinoma (HeLa) cells by MTT assay. The results

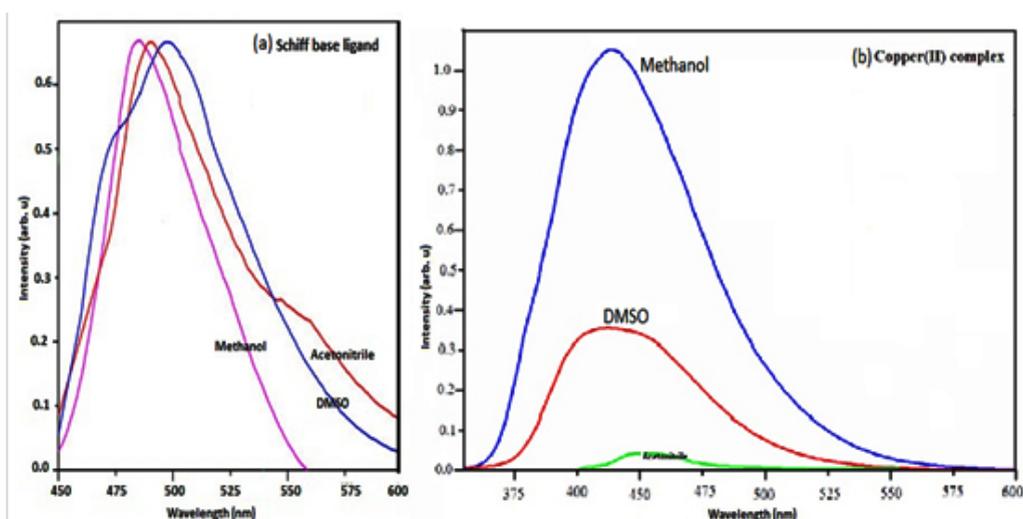


Fig. 2a,b: Fluorescence spectrum of (a) Schiff base, and (b) copper(II) complex at various solvents

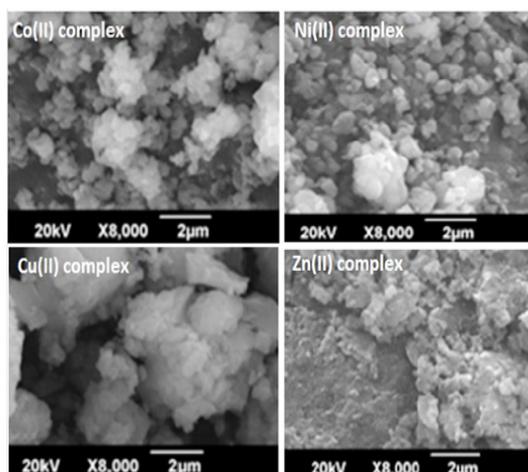


Fig. 3: SEM micrograph of metal(II) complexes

in terms of IC_{50} values were compared with the literature²⁵⁻²⁷ reports. The concentration range used was 0.1-100 μM for the complexes. MTT assay results clearly indicate that the copper(II) and zinc(II) complexes show very good inhibitory effect on the growth of HeLa cells. The lowest IC_{50} value of 7.35 μM was seen in copper(II) complex, zinc(II) complex also exhibits IC_{50} value of 8.33 μM and cobalt(II) complex has IC_{50} value of 8.35 μM . The ligand and its nickel(II) complex (8.39 μM) showed lowest growth inhibitory activity towards HeLa cells (>100 μM).

CONCLUSIONS

The synthesized metal complexes are non-electrolytes in nature. The infrared data indicate that the Schiff base behaves as bidentate manner and coordinating *via* nitrogen atom of azomethine group and ester carbonyl oxygen atom. Magnetic data and electronic spectral results reveal different coordination environments of metal ions (square planar geometry for nickel(II) and copper(II)

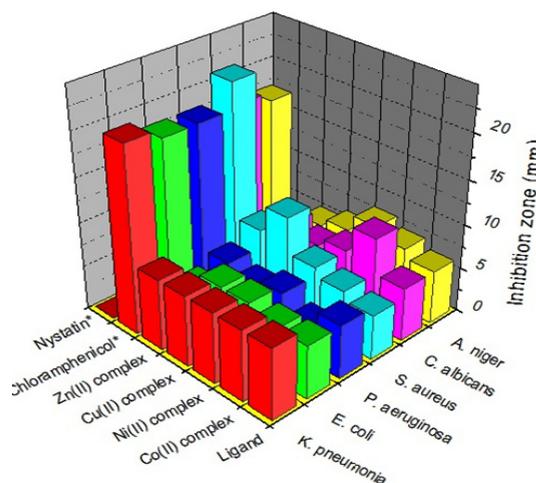


Fig. 4: Inhibition zone of ligand and its complexes

complexes, whereas tetrahedral geometry for cobalt(II) and zinc(II) complexes). Thermal results suggest that the metal complexes are thermally more stable than the ligand. The fluorescence spectral analysis of optical emission indicate that copper(II) complex exhibits strong fluorescence behaviour as compared with the ligand. Powder X-ray diffraction patterns pointed out the nanocrystalline nature of the metal complexes. SEM micrographs show agglomerated morphology for the metal complexes. Antimicrobial studies highlight more activity was present for metal complexes than the ligand. Except nickel(II) complex, all other metal complexes possess potent anticancer activity, whereas copper(II) complex exhibits maximum activity.

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