Synthesis, spectroscopic characterization and DNA binding studies of Cu(II) complex of Schiff base containing benzothiazole moiety

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ABSTRACT
A Schiff base ligand L has been synthesized by the condensation of thiophene-2-carbaldehyde and 2-amino-6-methylbenzothiazole. It has been characterized by elemental analysis, Infrared (IR), 1H NMR and mass spectrometry. Copper (II) complex, ML2 has been synthesized by the reacting ligand L and Copper (II) acetate in 2:1 molar ratio. The Cu(II) complex was characterized by elemental analysis, molar conductance, electronic spectrum, IR and electronic paramagnetic resonance spectrum. TGA has been done to check the thermal stability of Cu(II) complex. Spectroscopic studies revealed that ligand L binds with the Cu(II) ion as bidentate fashion. On the basis of spectral studies, a distorted octahedral geometry has been assigned for Cu(II) complex of ligand L. The DNA binding studies of Cu(II) complex ML2 have been investigated by UV-vis absorption and fluorescence spectroscopy. The binding mode of ML2 with CT-DNA could be assigned as intercalation of the metal complex between DNA base pairs.

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1. Introduction
Schiff base and their metal complexes have been paid a huge attention all over the world due to their diverse biological applications [1]. Schiff bases contain azomethine group which was synthesized by the condensation of primary amines and carbonyl compounds. The azomethine group present in the Schiff base is generally responsible for the various therapeutic properties [2]. Schiff base bears potential sites for biologically active compounds that are linked to intermolecular H-bonding and proton transfer equilibrium [3]. Metal complexes of Schiff base have diverse applications such as clinical, pharmaceutical, biochemistry, agricultural and in other various fields. The variation of groups or atoms in the Schiff base ligand shows different electronic, geometric and biological properties upon complexation with metal ions [4].

Benzothiazole and its derivative are the significant class of compounds and easily found in nature [5]. 1,3-benzothiazole are well known to have diverse pharmacological properties and are used in different fields such as chemistry, biochemistry and pharmaceutical industry [6]. They have acted as anti-inflammatory, antipyretic, analgesic, anaesthetic and anticancer agents [7–10].

A number of available drugs like 2-(thiocyanomethylthio)benzothiazole(fungicide), methabenthiazuron (herbicides), riluzole(anticonvulsant), ethoxzolamide (used as diuretic), pramipexole (Parkinson’s disease), 2-(4-aminophenyl)benzothiazole(antitumor), 2-mercaptobenzothiazole used in rubber vulcanization; contain benzothiazole as the basic moiety [11]. The amino acid amides derivative containing the imidazol[2,1-b]benzothiazol-2-ylphenyl moiety act as an anticancer agents [12].
Copper(II) Schiff base complexes have diverse biological activities such as antioxidant, anticancer, antiproliferative and many chemotherapeutic properties [13,14]. They show different electrochemical properties depending upon moiety of the Schiff base ligand [15]. Keeping in mind the properties of copper complexes and benzothiazole moiety, we have synthesized the Schiff base ligand derived from benzothiazole and its Cu(II) complex. The DNA binding studies of ML2 has also been done by using absorbance and fluorescence spectroscopy and binding constant was calculated by plotting graph of log ([F0-F]/F) versus log [CT-DNA].

2. Experimental

2.1. Materials and methods

The chemicals thiophene-2-carbaldehyde and 2-amino-6-methylbenzothiazole used were of AR grade and received from Alfa Aesar (Heysham, England) and TCI (Toshima, Japan). Copper(II) acetate were purchased from Merck and used as received. All the solvents used were of the spectroscopic grade. Calf thymus DNA (CT-DNA) was acquired from Sigma-Aldrich Chemie (Steinheim Germany) and the stock solution was prepared by directly dissolving the lyophilized powder in MilliQ water. The concentration of DNA was procured by taking it UV absorbance at 260 nm with a known molar absorption coefficient value [16].

2.2. Instrumentation

The elemental analysis of the synthesized ligand and its metal complexes were recorded at ThermoFinnigan Flash EA 1112 series (Italy). IR spectra were recorded on FT-IR Shimadzu in the region 4000–400 cm$^{-1}$. Mass spectra were recorded on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS (USA). NMR spectrum was recorded on JNM-EXCP400 (JEOL, Japan) at 400 MHz using tetramethylsilane (TMS) as an internal standard. The electronic spectrum was recorded on Shimadzu UV mini-1240 spectrophotometer (Columbia, USA) using DMSO as a solvent. Thermogravimetric Analysis (TGA) was carried out in a dynamic nitrogen atmosphere with a heating rate of 10$^\circ$C/min using a Pyris diamond TGA (Perkin Elmer, USA). Molar conductance of the metal complex was measured in DMSO at room temperature on ELICO (CM82 T) Conductivity Bridge. The magnetic susceptibility of the metal complex was recorded on a Gouy balance using CuSO$_4$.5H$_2$O. EPR spectrum was recorded as a polycrystalline sample at room temperature on E4-EPR spectrometer (E-112 ESR spectrometer, Varian, USA) using the DPPH as the g-marker. The fluorescence spectra were recorded on Cary Eclipse spectrofluorometer (Varian, USA) equipped with a 150W Xenon lamp with a 1 cm quartz cuvette and a thermostat water bath. Fluorescence spectra of the metal complex were obtained at 25$^\circ$C in the range 290–550 nm at an excitation wavelength 270 nm, using a slit width of 5 nm.

2.3. General procedure for the synthesis of ligand L

Ligand L was synthesized by adding equimolar quantity of thiophene-2-carbaldehyde (0.01 mol, 1.12 g) and 2-amino-6-methylbenzothiazole (0.01 mol, 1.64 g) in dichloromethane (25 mL) and the mixture was allowed to magnetically stirred at room temperature for 6 h (Scheme 1). The reaction was monitored by thin-layer chromatography (TLC). After the completion of reaction, yellow coloured product was precipitated out. It was then filtered, washed with ethanol and dried. Yield: 75%, IR (cm$^{-1}$): 1693 $\nu$(HC=N), 3055 $\nu$(C–Haromatic), 815 $\nu$(S–C=S). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.15 (s, 1H, –CH$_2$imine), 7.82–7.80 (d, 1H, –CH benzothiazole), 7.65–7.63 (m, 2H, –CH benzothiazole), 7.58 (d, 1H, –CH$_2$imine), 7.82–7.80 (d, 1H, –CH benzothiazole), 7.25–7.24 (d, 1H, –CH thiophene), 7.17 (m, 1H, –CH$_2$thiophene), 7.15 (d, 1H, –CH$_2$thiophene), 2.45 (s, 3H, –CH$_3$). Anal. Calc. for C$_{13}$H$_{10}$S$_2$N$_2$ [258.03]: C: 60.43; H: 3.90; N: 10.84; Found: C: 60.03; H: 3.68; N: 10.95; Mass spectrum (ESI) [M+H]$^+$ = 259.03.

2.4. Preparation of Cu(II) complex of ligand L

The Cu(II) complex was synthesized by the dropwise addition of 1 mmol ethanolic solution of the copper(II) acetate (0.19 g) to the 2 mmol hot ethanolic solution of Schiff base ligand L (0.52 g) in round bottom flask. The resulting mixture was stirred at room temperature for 5–6 h and then refluxed it at 80$^\circ$C for 12–14 h. The solid was separated out, filtered off from the reaction mixture, rinsed with ethanol and dried under vacuum over P$_2$O$_5$. Yield: 72%, IR (KBr, cm$^{-1}$): 1625 $\nu$(HC=N), 802 $\nu$(C–Haromatic), 510 $\nu$(M–N), 494 $\nu$(M–S). Anal. Calc. for C$_{30}$H$_{26}$Cu$_2$N$_4$O$_4$S$_4$ [698.36]: C: 51.60; H: 3.75; N: 8.02; Found: C: 50.92; H: 3.67; N: 8.88; Mass spectrum (m/z) 697.03; Molar conductance $\Omega^{-1}$ cm$^2$ mol$^{-1}$; $\mu$ eff = 1.98 B.M.

Scheme 1. Synthesis of Schiff base ligand L.
3. Results and discussion

The ligand \( L \) and Cu(II) complex were successfully synthesized. Ligand \( L \) is highly soluble organic solvents such as ethanol, methanol, chloroform, acetonitrile, DMSO and insoluble in water. Cu(II) complex is soluble in dimethyl sulfoxide (DMSO), dimethylformamide (DMF) and insoluble in water, chloroform, Partially soluble in ethanol, methanol. Molar conductance of Cu(II) complex in DMF has been found to be 5.80 \( \Omega^{-1} \text{cm}^2 \text{mol}^{-1} \) corresponds to the non-electrolyte nature of the complex. The complex has been formulated as \([\text{CuL}_2(\text{OAc})_2]\).

3.1. Mass spectra

The proposed formula of ligand \( L \) found to be \( \text{C}_{13}\text{H}_{10}\text{N}_2\text{S}_2 \) having molecular ion peak at \( m/z = 259.03 \) corresponds to \([\text{M} + \text{H}]^+\) in the mass spectrum (Figure 1). The

mass spectrum of copper(II) complex of ligand \( L \) was given in Figure 2.

3.2. NMR spectra of ligand \( L \)

The \(^1\text{H}\) NMR spectrum of ligand \( L \) has been recorded in CDCl \(_3\) solvent at 400 MHz. The residual solvent peak of CDCl \(_3\) has been observed at \( \delta \) 7.26 ppm. The ligand \( L \) showed characteristic sharp singlet for azomethine proton (–HC = N) at \( \delta \) 9.15 ppm (Figure 3). The aromatic protons of substituted benzothiazole ring lies in the range of \( \delta \) 7.82–7.58 ppm and \( \delta \) 7.25–7.15 ppm of thiophene-2-carbaldehyde. The peak at \( \delta \) 2.45 ppm as singlet due to methyl hydrogens of substituted benzothiazole ring. The proton signals obtained for Schiff base ligand were in expected region \([17]\).

The \(^{13}\text{C}\) NMR of the ligand \( L_3 \) showing signals at 157 ppm of azomethine carbon and 146–120 ppm

![Figure 1. Mass spectrum of ligand \( L \).](image1)

![Figure 2. Mass spectrum of copper(II) complex of ligand, \([\text{CuL}_2(\text{OAc})_2]\).](image2)
Figure 3. $^1$H NMR spectrum of ligand L.

of aromatic carbon atoms. The peak at 23 ppm is associated to the carbon of the methyl group on substituted benzothiazole ring (Figure 4). The peak at 169 ppm is due to a carbon atom of the benzothiazole ring which is attached to two nitrogen atom and sulphur atom.

3.3. IR spectra of ligand L and its Cu(II) complex, $ML_2$

The IR spectral technique gave an idea of the functional group present on the schiff base ligand L. On comparison of IR data of the ligand L and its Cu(II)

Figure 4. $^{13}$C NMR spectrum of ligand L.
complex, **ML$_2$** indicates the binding sites of the ligand upon complexation (Figure 5). The IR spectrum of ligand **L** has frequency 1693 cm$^{-1}$ corresponds to the azomethine group ($\equiv$N = CH$\equiv$). This shifting of frequency to lower value 1630 cm$^{-1}$ proves the binding of azomethine nitrogen with the metal ion. The formation of bond M-N further supports by peak at frequency 510 cm$^{-1}$. There is a change in C=S-C frequency from 815 to 804 cm$^{-1}$ of the thiophene moiety. The band 494 cm$^{-1}$ confirms the bond formation between M-S of the thiophene moiety [18]. The binding of acetate group has been confirmed by the asymmetric and symmetric vibrations at 1458 and 1288 cm$^{-1}$, respectively. Difference between $\nu_{as}$(OAc) and $\nu_s$(OAc) stretching vibrations were found to be 170 cm$^{-1}$ which confirmed the monodentate binding nature of acetate group with the metal ion [19]. The IR spectra confirmed that Schiff base ligand **L** binds to the Cu(II) ion as a bidentate ligand.

### 3.4. Electronic spectrum of Cu(II) complex [CuL$_2$(OAc)$_2$]

The electronic spectrum of Cu(II) metal complex was recorded in DMSO at room temperature (Figure 6). The magnetic moment of the copper(II) complex was 1.98 B.M. correspond to the one unpaired electron. The transitions are $^{2}B_{1g} \rightarrow ^{2}A_{1g}$, $^{2}B_{1g} \rightarrow ^{2}B_{2g}$ and $^{2}B_{1g} \rightarrow ^{2}E_{g}$ has been observed but their energy levels will depends on the tetragonal distortion due to ligand-field and Jahn–Teller effects. The electronic spectrum of the Cu(II) complex have shown bands at 10,438 cm$^{-1}$ ($^{2}B_{1g} \rightarrow ^{2}A_{1g}$) and 12,376 cm$^{-1}$ ($^{2}B_{1g} \rightarrow ^{2}E_{g}$) [20]. This suggested distorted octahedral geometry of Cu(II) complex Schiff base ligand.

### 3.5. Electronic paramagnetic resonance spectrum of the Cu(II) complex

The EPR spectrum of Cu(II) complex was recorded as polycrystalline sample at room temperature under the magnetic field strength of 3000 G on X band at the frequency of 9.1 GHz. EPR spectrum of the copper(II) complex exhibited single line broad spectra and no characteristic features of dinuclear complexes (Figure 7). The values of $g_{\parallel}$ and $g_{\perp}$ were calculated by using the formula:

$$g = \frac{71.4484 \times \nu(\text{in GHz})}{B(\text{in mT})}$$

Figure 5. IR spectrum of ligand **L**. Inset, zoom IR spectrum of **ML$_2$**.

Figure 6. Electronic spectra of Cu(II) complex of Schiff base ligand **L** showing wide absorption upto 1100 nm.

Figure 7. EPR spectrum of Cu(II) complex showing single broad line spectrum.
where $g$ is proportionality factor, $\nu$ is frequency of the X-band (in GHz) and $B$ is magnetic field (in mT). The values of $g_\parallel$ and $g_\perp$ were found to be 2.249 and 2.019, respectively. The $g$-tensor value follows the rule: $g_\parallel > g_\perp > 2.0023$, indicates that the unpaired electron is localized in the $d_{x^2-y^2}$ orbital of the Cu(II) ion [21].

The $g_{iso}$ value has been calculated by using $g_{iso} = (g_\parallel + 2g_\perp)/3$ formula and found to be 2.154 which suggested the presence of elongated tetragonal axes [22]. The $G = (g_\parallel - 2)/g_\perp - 2)$ value for the Cu(II) complex was found to be 1.113 less than 4 indicating the exchange interaction is insignificant between the metal centres in the polycrystalline solids [23]. This suggests that the distorted octahedral geometry for Cu(II) complex of Schiff base ligand $L$.

3.6. TGA data of Cu(II) complex of Schiff base ligand $L$

Thermal analysis of the Cu(II) complex of the Schiff Base ligand has been done in N$_2$ atmosphere upto 900°C. The Thermogravimetric graph was redrawn as % weight loss versus temperature. Cu(II) complex [CuL$_2$(OAc)$_2$] shows two step decomposition and CuS and carbonaceous material is left as a residue. In the first step, the loss of coordinated anion, hydrazine takes place (calc. 19.08%, obs. 20.23%). In the second step, the loss of organic moiety and sulphur dioxide takes place (calc. 46.62%, obs. 46.10%) [24]. The decomposition analysis can be described as:

\[
\text{C}_{30}\text{H}_{26}\text{CuN}_4\text{O}_4\text{S}_4 \xrightarrow{37-260^\circ C} \text{C}_{25}\text{H}_{13}\text{CuN}_2\text{O}_2\text{S}_4
\]
\[
\xrightarrow{260-800^\circ C} \text{CuS} + 12\text{C}
\]

Based on above spectroscopic techniques, the proposed structure of Cu(II) complex of Schiff base ligand $L$ was given in Figure 8.

3.7. DNA binding studies of the Cu(II) complex of Schiff base ligand, ML$^2$

UV-visible absorption spectra studies

UV-vis absorption spectroscopy is effective tool to finding the binding mechanism of DNA with various ligands. The interactions studies between metal complexes and DNA is significant for the new drugs designing [25]. For this purpose, it becomes important to find out which type of interaction is present between metal complexes and DNA. Metal-based drugs can bind to DNA through covalent and non-covalent interactions [26,27]. The types of interactions between the DNA-drugs molecules are electrostatic binding, groove binding, intercalation-binding hydrophobic interactions and H-bonding [28]. When ligands are of proper size and fit itself chemically between the base pairs of the DNA then intercalation binding occurred while groove binders interact with the major and minor groove of the DNA. Electrostatic binding is the interaction between electrically charged
species with the phosphate backbone of the DNA double helix structure [29]. On DNA-ligand interactions; considerable changes are observed in the absorption spectrum of DNA. The hypochromic shift in the absorption spectrum of DNA along with redshift is attributed to intercalation of the ligand into the double helix of DNA [30,31]. Hyperchromic shift in the absorption spectrum of DNA is observed in the case of electrostatic binding between the ligand and DNA molecule [32,33]. The UV-vis absorption spectra were taken by keeping the constant concentration of metal complex 1-4 i.e. $1 \times 10^{-5}$ M and increasing the concentration of CT-DNA from zero to 120 µM in the presence of 20 mM Tris-HCl buffer containing 100 mM NaCl, (pH 7.4), where 5 min incubation time was given after each addition of CT-DNA. The characteristics bands at ca. 280 nm assigned to intra-ligand charge transfer transitions and the broadband occurs at ca. 383 nm is associated with $n-\pi^*$ transitions of the azomethine (–HC=N–) group [34]. Metal complex shows its absorption peak at 366 and 383 nm, which exhibited hypochromatism with red shift in the maximum absorption peak, on increasing concentration of CT-DNA, ranging from 30 to 120 µM (Figure 9). As bathochromic shift and hypochromism were seen hence, intercalation-binding mode has been assumed between Cu(II) complex with CT-DNA [35].

3.8. Fluorescence spectroscopy
To explore the binding mechanism of ML$_2$-DNA interaction, fluorescence spectroscopy technique was used. It is sensitive and selective method to determine the binding mode of interaction between DNA and ligand [36]. The experiment was performed by taking constant concentration of L and ML$_2$ (1 $\times$ 10$^{-5}$ M) and increasing the concentration of CT-DNA from zero to 100 µM in presence of 20 mM Tris- HCl buffer containing 100 mM NaCl, pH 7.4 (Figure 10). Fluorescence intensities of ML$_2$ samples were rectified for the respective absorbance of ML$_2$ at emission and excitation wavelengths of the fluorescence data. Corrections for the inner filter effect were made using the equation [37].

$$F_{cor} = F_{obsd}^{\frac{A_{em} + A_{ex}}{2}}$$

The fluorescence spectra of ligand L has shown no change in intensity upon addition of CT-DNA as shown in figure. The fluorescence spectra of ML$_2$ upon excitation at 270 nm wavelength exhibited a major peak at 339 nm along with a hump at 408 nm. With the increase in the concentration of CT-DNA, the intensity of ML$_2$ decreased regularly with a significant 15 nm red shift which is indication of shift to a more polar environment. This kind of phenomenon is known as fluorescence quenching. An increase in the fluorescence intensity of drug molecule indicates the groove binding while in the case of intercalation mode of binding, there is decrease in the fluorescence intensity [38]. Since there is a significant decrease in the intensity of ML$_2$, intercalation binding can be assumed as the probable mode of binding in this case.

The quenching of fluorescence intensity of ML$_2$ by binding with CT-DNA was further used to determine binding parameters like the binding constant ($K_b$), and number of binding sites (n) were calculated using following equation [39,40] and found to be
2.54 × 10^6 M^{-1} and 1.37 at 298 K respectively.

\[
\log \frac{F_0 - F}{F} = \log K_b + n \log [Q]
\]  

Values of \(K_b\) was determined by the intercept of the plot of \(\log (F_0 - F)/F\) versus \(\log [Q]\) (Figure 11). The values of \(n\) showed that there may be more than one independent class of binding sites for CT-DNA-ML2 interaction and \(K_b\) value suggests there is strong interaction between CT-DNA and ML2. The ethidium bromide and acridine orange are well known intercalator and have binding constant as reported in the literature are 2.6 × 10^6 and 4 × 10^5 M^{-1} [41]. The copper(II) complex have shown similar binding constant to ethidium bromide, the binding mode assumed for ML2-CTDNA might be intercalation mode [42].

It has been noticed that the emission intensity of ML2 gradually decreases with the increasing concentration of CT-DNA; it means CT-DNA could quench the intrinsic fluorescence of ML2. The fluorescence quenching constant at different temperatures was calculated using the

\[
F_0 = 1 + K_{SV}[Q] = 1 + k_q \tau_0[Q]
\]  

where \(F_0\) and \(F\) are the fluorescence intensities of ML2 in the absence and presence of the quencher, respectively, \(Q\) is the concentration of the quencher and \(K_{SV}\) is the Stern–Volmer quenching constant, which can be determined by the plot of \(F_0/F\) against \([Q]\), and \(\tau_0\) is the average fluorescence lifetime (10^{-8}s). The value of \(k_q\) was found to be 3.74 × 10^{11} M^{-1}s^{-1} at 298 K temperature. The maximum collisional quenching constant for dynamic quenching obtained for various quenchers is 2.0 × 10^{10} M^{-1}s^{-1} [44]. The calculated value is much larger than the suggested one, so one can conclude that the quenching of fluorescence intensity of ML2 is due the complex formation between ML2 and CT-DNA. The quenching process found in this study was static and not dynamic as the value of \(k_q\) is much larger than the limiting diffusion rate constant [45].

By taking advantage of the calculated binding constant, the standard free energy of the ML2-CT-DNA
interaction was also calculated using the following relation [46].

\[ \Delta G^0 = -RT \ln K_b \]  

(4)

where \( \Delta G^0 \) is the observed binding free energy, \( R \) is the gas constant (1.987 cal/K mol), \( T \) is the absolute temperature (298.15 K) and \( K_b \) is the binding constant. \( \Delta G^0 \) was calculated to a value of \(-8.74 \text{kcal mol}^{-1}\). The value of \( \Delta G^0 \) comes out to be negative revealed that the spontaneous binding process. Non-covalent interactions such as intercalation binding between the DNA base pairs and the Cu(II) complex \( ML_2 \) has been seen [47].

4. Conclusion

A Schiff base ligand \( L \) and its Cu(II) complex, \( ML_2 \) were successfully synthesized. The ligand \( L \) acts as bidentate ligand for Cu(II) complex \([CuL_2(OAc)_2]\). On the basis of spectral data, distorted octahedral geometry has been assigned for Cu(II) complex \([CuL_2(OAc)_2]\). The absence of water molecules coordinated with the metal has been justified by the TGA and IR data. The DNA binding studies of metal complex of synthesized ligand has shown affinity to bind with CT-DNA and revealed that intercalation binding of CT-DNA with Cu(II) complex, \( ML_2 \). The Gibbs free energy also suggested the same as it comes out to be negative. This finding suggests that transition metal-based drugs have potential applications; to design and improve the DNA targeted drugs and development of nucleic acid molecular probes.

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